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KNEE SWELLING AND ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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King's College London

Centre for Human and Aerospace Physiological Sciences

KNEE SWELLING AND ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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CONTENTS

Table of Tables	14
Abstract.....	18
Acknowledgements.....	20
Table of Abbreviations	21
Chapter 1 Introduction	23
General Introduction.....	23
Anterior Cruciate Ligament reconstruction	23
Swelling Definitions.....	24
The effects and purpose of swelling	25
Background	27
Vascular Solute exchange and Microcirculation	27
Vascular physiology and swelling.....	27
Fluid exchange across Microvascular membranes	28
Factors affecting movement of Fluid across capillary membranes	35
The Starling Equation and ACute Inflammation (Vascular events).....	44
Endothelial gap formation	46
Fluid Exchange in the knee joint	46
Pathology Section	51
The Inflammatory process	51
Cellular and vascular events of inflammation.....	51
The inflammatory process after ACLR	53
The Effects of joint Swelling.....	56
Extra articular effects.....	56
Intra-articular effects	59
Interventions for swelling	60
RICE regimen and guidelines.....	60
Rationale for use	60
Physiological mechanisms of RICE regimens	63
Ice – Cooling/ physiology and mechanisms	63

Compression and Elevation -mechanisms- physiological effects	71
Optimum regimen for reducing swelling in the knee after ACLR	75
Reviews and Guidelines	75
Optimum regimen of application - Cold	77
Intensity (Temperature).....	79
Frequency.....	80
Duration (Time).....	81
Optimum regimen of application Compression and ElevationN	82
General Thesis Aims	83
Outline of chapters	85
Chapter 2 – The Measurement of Swelling in the Knee and after ACLR	87
Introduction	87
Methods to measure swelling – Intra-articular effusion	89
Extra articular – Volumetric measures.....	96
Aim	105
Methods.....	106
Results.....	112
Sample.....	112
Knee volume	114
Brush test results	115
Discussion.....	118
Perometer	118
Brush test.....	118
Limitations.....	120
Conclusions	120
Chapter 3-Intervention for control of swelling in ACLR.....	121
Background / Interventions for swelling.....	121
The Cryocuff.....	122
Aims	130
Hypotheses	130
Methods.....	131
Patients	131
Ethical Approval	131
Study Design and Randomisation	132
Preoperative Measurements	133

Operative Procedure.....	139
Cryocuff Intervention.....	142
Postoperative Measures	144
Data Analysis.....	145
Results.....	147
Discussion.....	163
Knee volume	163
Baseline data between groups.....	165
Pain.....	166
Medication use.....	166
Secondary Variables.....	167
Discharge time	167
Function	167
Study Limitations	170
Conclusions	172
Chapter 4 Correlates of Swelling in ACLR	173
Background	173
Factors that may relate to swelling in ACLR	174
Correlate Variables Summary	175
Aim	176
Hypothesis.....	176
METHODS.....	177
Sample / Patients	177
Study design and randomisation	177
Measured Variables	177
DATA ANALYSIS.....	179
Results.....	180
Subject Data	180
Discussion.....	196
Knee volume	196
Demographic correlates.....	197
Pathology data	197
Surgery data	198
Perioperative Iv Fluid given.....	200
Recovery room data.....	202

Home Diary correlates	203
Function correlates	207
Limitations.....	210
Recommendations for future work	211
Conclusions	213
Chapter 5– Measurement of Interface pressure in compression of the knee	214
Background	214
Compression effects	214
Fluid dynamics and posture	215
Quantity of Compression required for Occlusion.....	219
the Cryocuff-Compression and Elevation	220
Measurement of Interface pressure under bandages and the Cryocuff	222
Aims of the study	223
Methods	223
Measurement.....	223
Selection and recruitment	229
Measurement procedure.....	229
Intervention	233
Analysis	239
Ethics	240
Results.....	241
Sample.....	241
Interface pressure	243
Measurements on participants - Interface pressure in pads.....	254
Temperature	262
Discussion.....	263
Reliability and validity of interface pressure measurement.....	263
Interface pressure profiles.....	265
Considerations, Limitations, and ideas for further study	269
Conclusions	272
Chapter 6 General Summary.....	274
General Discussion – Thesis.....	274
Main findings and contribution of this body of work	274
Chapter 3.....	276
Chapter 4.....	277

Chapter 5.....	280
Clinical implications	281
future work	282
Conclusion.....	284
Appendices.....	285
Appendix 1 - Cryocuff operating instructions and CE compliance statements	285
Appendix 2 - ACLR rehabilitation protocol	290
Appendix 3 Ethical Approval letter	291
Appendix 4 Participant information leaflet	292
Appendix 5 Consent form	297
Appendix 6 Questionnaire - IKDC form.....	298
Appendix 7 Questionnaires - Tegner and Lysholm	299
Appendix 8 Questionnaire – Lower extremity Functional Scale	300
Appendix 9 – Diary Sheet.....	301
Appendix 10 Participant information leaflet and consent form.....	302
Appendix 11 University College London- Ethical approval letter	305
Appendix 12 Insurance form.....	306
Appendix 13 Pasco Quad Pressure sensor Instruction manual	307
References	309

TABLE OF FIGURES

Figure 1 the microcirculation from terminal arterioles to post capillary (pericyte) venules. See labels and text for description and function. (Modified from Levick J.R. An introduction to cardiovascular physiology 5 th edition Hodder Arnold 2010) ³²	28
Figure 2 Types of Capillary. (Modified from Levick an introduction to cardiovascular physiology 5th Edition Hodder Arnold 2010)	30
Figure 3 Intercellular cleft at the junction between capillary endothelial cells. Label = (Modified from Levick An introduction to cardiovascular physiology 5 th Edition Hodder Arnold 2010)	31
Figure 4 Glycocalyx layer of biopolymers inside the lumen of the endothelial cell capillary (Modified from Levick An introduction to cardiovascular physiology Hodder Arnold 2010).	32
Figure 5 pathways for transport of substances between the capillary and the interstitial space (Modified from Levick An introduction to cardiovascular physiology 5th Edition Hodder Arnold 2010)	34
Figure 6 Starling Equation for fluid exchange	37
Figure 7 - Diagrammatic outline of the Thesis aims and questions.....	84
Figure 8 Brush or stroke test- the examiners hand moves medially to “milk” effusion.....	90
Figure 9 Brush or stroke test- for the second part of the test the examiners hand moves laterally and the wave of fluid can be visualised under the skin coming back across to the medial side of the knee.....	91
Figure 10 Patella tap –the fluid in the knee causes the patella to “float” up off the trochlea of the femur	92
Figure 11 Patella tap- part 2 the patella is tapped. In high levels of joint effusion, the retropatella surface is felt to touch down or “tap” the femoral trochlea.	92
Figure 12 Knee radiograph - post ACLR patient with the suprapatella effusion outlined	94
Figure 13 Perometer set up for measurement of limb and knee volume	102
Figure 14 Perometer computer software screen	103

Figure 15 Recruitment and retention flow diagram summarising recruitment patients lost to follow up and DNA (did not attend) clinic appointments for the large ACLR clinical study.	113
Figure 16 Brush test grade (0-3) affected knee brush test examination from preoperative to 2 weeks versus the change in knee volume (ml) measured with the Perometer from preoperative to 2 weeks post ACLR (linear correlation trend line)	117
Figure 17 change of Brush test grade (-2 - 3) affected knee brush test examination from preoperative to 2 weeks versus the change in knee volume (ml) measured with the Perometer from preoperative to 2 weeks post ACLR (linear correlation trend line)	117
Figure 18 Cryocuff applied to the knee with container and connection hose	122
Figure 19 KT1000 dynamometer start position	137
Figure 20 KT1000 measurement dial zeroed prior to initial measurements	137
Figure 21 KT1000 Manual maximum test	138
Figure 22 Tourniquet applied prior to the surgery	139
Figure 23 Preparing the ACLR graft after the hamstring and gracilis harvest	140
Figure 24 Lateral radiograph of the knee after ACLR with fixation shown – the interference screw and the staple in the tibia and the endobutton sitting on the surface of the cortex of the femur in the lateral suprapatella area.....	140
Figure 25 Endobutton	141
Figure 26 Interference Screw	141
Figure 27 Metal staple onto tibia to hold final graft remnant down flush onto the tibia	141
Figure 28 Recruitment and retention flow diagram Summarising recruitment patients lost to follow up and DNA (did not attend) clinic appointments	148
Figure 29 Affected knee volume (ml) means Pre-operative time point and at 2 and 6 weeks post-operatively in the two groups. Measured with the Perometer (V) (Note that in all figures – error bars represent one standard deviation above and below the mean).	155

Figure 30 Unaffected knee volume (ml) means Pre-operative time point and at 2 and 6 weeks post-operatively in the two groups. Measured with the perometer	155
Figure 31 Mean knee pain before and after ACLR (Pain Frequency 0-10) from question 2 on IKDC subjective form (appendix 4).....	156
Figure 32 Mean knee pain before and after ACLR (Pain Severity 0-10) from question 3 on IKDC subjective form (Appendix 4)	156
Figure 33 Mean knee pain (0-3 likert score) from waking to 50 minutes post-operatively Recorded in recovery room.	157
Figure 34 International knee documentation committee subjective form (out of 87) (appendix 4) Mean score and post-operative week	159
Figure 35 Tegner activity scale (0-10) pre and post-operatively (appendix 5) (*= significant difference between groups $P<0.05$)	159
Figure 36 Lysholm score (0-150) pre and post-operatively (appendix 5)	160
Figure 37 Lower extremity functional scale (0-80) measured pre and post-operatively (appendix 6)	160
Figure 38 Range of motion loss (degrees) pre to post-ACLR (Note - Negative values indicate increased range compared to contralateral knee)	161
Figure 39 Anterior posterior knee laxity difference (millimetres) between affected and unaffected knee at 30 Pounds (lb) force measured by the KT1000 arthrometer	161
Figure 40 Summary of correlate variable data collection with possible relation to knee volume	175
Figure 41 Preoperative volume (ml) vs postoperative knee volume (ml) for the affected knee measured with the perometer	184
Figure 42 Preoperative volume (ml) vs change in knee volume pre to 2w postoperatively (ml) for the Affected knee measured with the perometer	185
Figure 43 Preoperative Affected knee volume (ml) vs height (cm)	186

Figure 44 Preoperative Affected knee volume (ml) vs weight (kg)	186
Figure 45 change in affected knee volume pre to 2w postoperatively (ml) vs Height (cm)..	187
Figure 46 change in affected knee volume pre to 2w postoperatively (ml) vs weight (kg)..	187
Figure 47 end recovery room blood pressure (mmHg) diastolic and systolic vs change in knee volume preoperatively to 2weeks postoperatively	188
Figure 48 AP Laxity KT1000 (mm) vs Volume difference pre to post op 2w (ml) Affected knee	189
Figure 49 AP Laxity KT1000 (mm) vs Volume difference pre to post op 2w (ml) Unaffected Knee	189
Figure 50 Preoperative Range of movement loss in degrees for both Extension and flexion vs the change in knee volume pre to 2 weeks postoperatively	190
Figure 51 Volume of IV fluid given intraoperatively vs Volume difference pre to post op 2w (ml)	191
Figure 52 Graph of IV fluid levels given perioperatively and change in knee volume pre to 2 weeks post operatively	191
Figure 53 Average daily elevation time in week 1 and 2 postoperatively graphed against the change in knee volume pre to postoperatively at 2weeks.	192
Figure 54 time from injury to surgery (months) vs the change in knee volume pre to 2weeks postoperatively	193
Figure 55 Tourniquet time (minutes) vs the change in affected knee volume preoperatively to 2 weeks postoperatively	194
Figure 56 Average daily cryotherapy (hrs/d) week 1-2 vs change in knee volume pre to 2 weeks postoperatively (ml)	194
Figure 57 Average daily standing or walking (hrs) for week 1 and 2 graphed against the change in knee volume from pre to 2 weeks postoperatively (ml)	195

Figure 58 Pasco Capstone 1.3.2 Pressure and Temperature traces of a typical 3 hour measurement session with a cryocuff and RJB knee. The four phases can be seen with each phase lasting 30 minutes. For this participant the phases were : - initial baseline + calibration 30 min , supine 30min , standing 30min , elevation 30 min, a final supine period 30 min and a final baseline phase 30 min.....	225
Figure 59 Reliability validity work used 2 round hard plastic pipes with the protocol repeated using the downpipes. Further pressure measurement devices were used to compare the capstone pressure measure	227
Figure 60 Reliability validity work also compared the Cryocuff and RJB in the different postures	228
Figure 61 Flow Diagram for the course of the study	230
Figure 62 interface pressure pads attached to participant and connected to the quad pressure sensors via plastic tubing	232
Figure 63 Supine position set with Cryocuff and RJB over respective knees on top of the pressure pads, with tubing connected to the Pasco quad pressure sensors and the Sparklink connecting them to the software on the laptop	234
Figure 64 Elevation with head of the plinth raised to maximum height and Cryocuff and RJB in place over the interface pressure measurement pads.....	236
Figure 65 standing phase 30 mins with Cryocuff and RJB and the interface pressure measurement pads visible posteriorly (posterior inferior and posterior superior pads	237
Figure 66 Correlation between the interface pressure measurements of the PicoPress and the Pasco quad sensor during the cylinder measurement session	247
Figure 67 Cylinder experiment Interface temperature between device and cylinder (°C) ..	249
Figure 68 Rate of change of temperature (°C/min x10 ⁻⁴) versus rate of change of pressure (mmHg/min x 10 ⁻⁴)	250

Figure 69 Mean Pad interface pressure (mmHg) on Cryocuff and RJB knee for initial supine posture	(NB for all figures Error bars are 1 Standard deviation above and below the mean).....	257
Figure 70 Mean interface pressures (mmHg) in each of the knee pads during Elevation and Standing		258
Figure 71 Mean standard deviations of the pressure measurement trace (mmHg) during each 30 min phase of the experiments.....		259
Figure 72 Mean Standard Deviation for pressure pad measures during the reliability experiment on 2 Cylinders for each knee and each 30 minute position (initial supine, elevation, standing, and final supine)		260
Figure 73 mean rate of change of the pressure trace for each knee and each position during the 30 min measurement of each phase		260
Figure 74 Mean interface pressures (mmHg) in each of the knee pads during Elevation and Standing – Standing first position		261
Figure 75 Mean interface pressures (mmHg) in each of the knee pads during Elevation and Standing – Elevation first position		261
Figure 76 Mean temperature participants for the sessions		262

TABLE OF TABLES

Table 1 Brush Test Classification (adapted from Magee and Sturgill et al)	111
Table 2 Perometer measured knee volume (ml) with 3 measures on each knee and means	114
Table 3 reliability and validity statistics for the Perometer measure of knee volume in both the affected and unaffected knees	115
Table 4 Brush / Ballottement test results number of subjects in each grade of effusion on brush (Grade 0-3)	115
Table 5 Pre to post-operative knee volume differences (ml) measured with the perometer versus the brush test grades at 2 weeks post op ACLR and the change, pre operatively to postoperatively, in brush test grade (-2-3)	116
Table 6 Summary of studies that have evaluated the effects of knee cooling on SWELLING after anterior cruciate ligament reconstruction	128
Table 7 Summary of studies that have evaluated the effects of knee cooling on PAIN after anterior cruciate ligament reconstruction	129
Table 8 Demographic and time to surgery data	149
Table 9 Knee pathology and surgical data with tunnel size (millimetres) and tourniquet time (minutes)	150
Table 10 Knee volume (millilitres) measured with the Perometer	151
Table 11 Intention to treat analysis 1 – preoperative knee volume brought forward for missing data	153
Table 12 Intention to treat analysis 2 – postoperative knee volume estimated from the percentage change in the sample as a whole	154
Table 13 Post-surgery to hospital discharge medication use	157
Table 14 Average daily time (hours) using cryotherapy on injured knee after surgery	162
Table 15 Average daily time (hours) in standing/walking and time with injured leg in elevation after knee surgery	162

Table 16 Number of post-operative home physiotherapy exercise sessions per day.....	162
Table 17 Demographic Variables Correlation analysis with correlation coefficient and P values for correlation with pre to 2 week post-operative change in knee volume (ml) measured by perometer	181
Table 18 Perioperative Variables Correlation analysis with correlation coefficient and P values for correlation with pre to 2 week post-operative change in knee volume (ml) measured by perometer	181
Table 19 Postoperative Variables Correlation analysis with correlation coefficient and P values for correlation with pre to 2 week post-operative change in knee volume (ml) measured by perometer	182
Table 20 Independent variables with significant correlation to knee volume change pre to two weeks post ACLR for multiple regression model	183
Table 21 the Three Independent variables with significant correlation to knee volume change pre to two weeks post ACLR for the final multiple regression model.....	184
Table 22 Baseline demographic, exercise, nutrition, body composition and Lab atmospheric data	241
Table 23 Baseline data for participants with means SD and CI	242
Table 24 Baseline leg data – circumference (cm) and Knee AP laxity measured with the KT1000 dynamometer (mm).....	243
Table 25 baseline Cylinder reliability measures with pads on desk (interface pressures in each pad pre and post session) (mmHg)	244
Table 26 baseline reliability/ Cylinder measures with devices applied in 4 positions (interface pressures in each pad (mmHg)	245
Table 27 Reliability - Response stability statistics for Cylinder measures initial vs final supine periods (mmHg)	246

Table 28 Final baseline pad pressure (mmHg) taken with the pads placed flat on a desk and off the participant	251
Table 29 Mean interface pressures (mmHg) in the knee pressure pads during initial and final baseline periods when the cryocuff was deflated	252
Table 30 Baseline initial supine and final supine postures with mean interface pressure (mmHg) of the participant cohort from each of the pads in both knees	253
Table 31 Initial and Final supine comparisons statistical tests of reliability.....	254
Table 32 Mean knee interface pressures (mmHg) in interface pads at 4 sites around the knee under RJB and Cryocuff.....	255

ABSTRACT

Swelling is universal after Anterior Cruciate Ligament Reconstruction (ACLR). Cooling compressive devices aim to treat swelling after surgery, but research has focussed more on pain than swelling.

The aims of this work were to measure knee swelling in ACLR with a perometer (an optoelectric volumeter) and to evaluate an intervention for knee swelling in ACLR which uses a cold compressive device.

The main outcome for the studies was knee volume measured using the perometer. Reliability was established and a randomised controlled trial was undertaken

The study aimed to compare the use of Cryocuff, and elevation, with standard treatment used post ACLR (compression bandage alone). Secondary outcomes were also measured to assess the correlates of knee swelling in ACLR.

The patients were randomised into a standard treatment group or into a Cryocuff and elevation group. Knee volume in both knees was measured pre-operatively and at two weeks post-operatively using the perometer. Secondary variables measured included: - range of movement, pain, knee laxity and function, medication use, tourniquet and discharge times, and operative factors.

There was with no significant difference between the groups ($p=0.977$). This study did not find Cryocuff and elevation to be more effective for minimising swelling at 2 weeks post-operatively, than a compression bandage alone. The perometer was reliable with Intra class correlation coefficient of 0.996.

Significant correlates of swelling post-ACLR were: blood pressure; knee joint laxity and extension loss, with daily elevation time and Intravenous fluid given intra operatively close to significance.

Further investigation outlined the level and profile of compression applied to the knee by the Cryocuff found that this device may have inherent features that could be provocative of swelling.

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TABLE OF ABBREVIATIONS

ACL = Anterior cruciate ligament

ACLR = Anterior cruciate ligament reconstruction

ANOVA = analysis of Variance

ANCOVA = Analysis of covariance

AP = Anteroposterior

BJH = Benign joint hypermobility

BMI = Body mass index

CV_{ME} = coefficient of variation of the method error

DBP = Diastolic Blood Pressure

DEXA = dual-energy x-ray absorptiometry

DSU = Day surgery unit

EDS = Ehler's Danlos Syndrome

ICC = inter-cellular cleft

ICN = intercondylar notch

IKDC = International knee documentation committee

ISF = interstitial fluid

ISS = interstitial space

IV = Intravenous

LEFS = Lower Extremity Functional score

MAP = Mean arterial pressure

ME = method error

mmHg = millimetres of mercury

MRI = Magnetic Resonance Imaging

NICE = National Institute for Clinical Excellence

NO = Nitrous Oxide,

(P)RICE = (Protection) Rest Ice Elevation

PVD = peripheral vascular disease

RBC = red blood cells

RJB = Robert Jones Bandage

ROM = Range of Movement

SBP = Systolic Blood Pressure

SD = Standard deviation

SPP = Suprapatella pouch

µm = micrometres

US = Ultrasound

VEGF = Vascular Endothelial Growth Factor

°C = degrees Celsius

CHAPTER 1 INTRODUCTION

GENERAL INTRODUCTION

ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

The anterior cruciate ligament (ACL) is one of the most commonly injured ligaments of the knee, with a reported incidence of 30 cases per 100,000 population¹ or 200,000 new cases per year in the United States of America² and incidences show signs of increasing³. Frequently the torn ligament does not heal but many patients rehabilitate and manage an adequate level of function^{4,5}, however many patients chose to have a reconstruction of the ligament with the aim of obtaining a greater level of stability and preventing later complications of reinjury and further damage, and arthritis⁶. The most common surgical procedure for the torn ACL is an anterior cruciate ligament reconstruction (ACLR), involving the harvest, insertion and fixation of an autologous replacement tissue (a graft), such as a hamstring or patella tendon, into the position in which the injured ligament attached. This allows a living graft, in which the body's own cells eventually inhabit and the graft is remodelled into a fibrous ligamentous like structure⁷, which aims to function similarly to the previously uninjured ACL.

Swelling tends to be a common feature after injury of the ACL – with an ACL partial or complete tear responsible for up to 70-86% of presentations with acute knee haemarthrosis⁸⁻¹¹. The level and speed of swelling are often used as strong diagnostic features. Knee swelling is also a very common (almost universal) feature following ACLR but it has been relatively uninvestigated. Immediately post ACLR, a haemarthrosis (blood in the joint) gathers. Drain studies after ACLR indicate a haemarthrosis volume of 120 to 150 ml in the first 1-2 days¹²⁻¹⁴.

There is also bleeding in the bony tunnels drilled in the femur and tibia, and outside the joint related to the harvest of the graft (patella tendon or anteromedial hamstring attachment). Swelling also occurs due to an inflammatory exudate released into the joint (effusion) and the tissues as part of the inflammatory process post ACLR. This exudate can persist throughout rehabilitation and many clinicians focus great efforts on preventing and treating swelling in both the early (in hospital stay) and late stages of the rehabilitation process.

SWELLING DEFINITIONS

SWELLING DEFINITION/ AETIOLOGY

Swelling is the extravasation or build-up of fluid into (in) the interstitial space and may be the result of multiple endogenous mechanisms. Acute swelling can relate to an inflammatory response following tissue damage or injury or from blood vessel damage and bleeding into the interstitial space. Chronic swelling may be caused by damage to lymphatic vessels and can lead to the swelling of lymphoedema.

Dependant postures such as prolonged standing (orthostasis) may lead to swelling in more dependant peripheral tissues and there is record of incidental swelling in some patient groups without a specific triggering event¹⁵. Swelling occurs in most body tissues following injury, however, in joints, the swelling is bound by a fibrous membrane, the joint capsule, and manifests as an effusion. This thesis will keep a broad based definition of swelling to include any of these mechanisms.

THE EFFECTS AND PURPOSE OF SWELLING

The physiological purpose for swelling varies depending on the tissue and mechanism of swelling, inflammatory responses assist the limitation of damage after injury and assist the process of repair and immune function, and together with the vascular components, are essential mechanisms of this response.

Swelling may provide a protective pressurised “cushion” that will limit further bleeding and damage and will immobilise the tissue. Swelling also provides a fluid medium through which immune and cells responsible for healing may be signalled, attracted and through which they can migrate to reach the damaged / infected tissue. Swelling may also dilute algogenic compounds. Swelling may be considered adaptive such as post injury or may be maladaptive, in conditions such as lymphoedema. There may be periods where swelling is desirable and helpful and speeds outcome, and others where swelling is unhelpful and will slow healing and improvement.

Knee haemarthrosis and swelling are considered maladaptive when they have detrimental effects on recovery. The deleterious effects of swelling and haemarthrosis in the knee include reduced collagen matrix turnover¹⁶, decreasing knee range of movement (ROM)¹⁷, and also a neurological muscle inhibition of the quadriceps femoris, with a possible nerve / reflex mediated pathway responsible¹⁷. In experimentally induced effusions, inhibition has been measured, with a change in motor neuron function to vastus medialis obliquus (VMO) alone for small effusions (30ml), and VMO, Vastus Lateralis (VL) and Rectus Femoris (RF) for larger effusions (60ml)¹⁸. Removal of an effusion has been found to reverse Quadriceps inhibition in both post-operative and induced effusions.^{19,20} The negative consequences of this inhibition on function, have been examined with gait²¹, running²², and deceleration type tasks, which are prevalent in sporting activity²³. The quadriceps are the primary knee extensors and are crucial for return to full knee function after anterior cruciate ligament reconstruction (ACLR)²⁴,

one of the main aims of early postsurgical treatment has been to limit or decrease knee swelling. It is not clear, however, from evidence that swelling can be effectively prevented or treated in ACLR.

It is important that clinical reasoning frameworks consider swelling as adaptive and beneficial, and it may not be desirable to decrease it. There is some literature suggesting that swelling may not be detrimental to the knee. Haemarthrosis will clear spontaneously in a closed joint, without clotting²⁵. Animal studies find that erythrocytes clear from a joint after autologous blood injections, with the joint clear of erythrocytes in 2-14 days²⁶, with synovium clearing erythrocytes even in 15 mins, and a canine knee joint was found to be 95% clear of erythrocytes in the first 48 hours²⁵. The conditions after injury or surgery may differ but the joint synovium has mechanisms for fluid exchange that can clear swelling²⁷. Likewise, quadriceps inhibition from knee swelling, may reduce with prolonged knee joint effusion²⁸ and with functional activities.^{29,30} This evidence may suggest that knee swelling can be left to clear spontaneously and does not require treatment. Swelling may also serve a beneficial purpose that will be compromised by its removal. It is not always clear whether swelling therefore, should be removed, permitted or even encouraged as a natural part of a joint's ability to heal.

BACKGROUND

VASCULAR SOLUTE EXCHANGE AND MICROCIRCULATION

VASCULAR PHYSIOLOGY AND SWELLING

The vascular system exists to transport materials around a large multicellular organism is vital for the organism to function. The circulation exists to transport and exchange of substances (cells, fluid and proteins) between the vessels and extracellular space. The exchange of materials occurs across blood vessel walls.

This exchange is important for protein / glucose / gas (oxygen or carbon dioxide) and cell transport and delivery to the tissues. Alteration to these exchange mechanisms is an important consideration during the inflammatory response and the effects on fluid exchange are important considerations when investigating swelling because swelling is heavily dependent on the vascular system and its response to injury. Several determining factors control the exchange of fluid and nutrients across (and through) the endothelial cells that form the capillary walls, including blood pressure and capillary pressures. These pressures are often recognised by clinicians as the only determinants of fluid/nutrient exchange but it essential to also understand the effects of colloid osmotic pressure (COP) and role of the Lymphatic system when attempting to understand swelling and its control.

FLUID EXCHANGE ACROSS MICROVASCULAR MEMBRANES

The exchange vessels relate mostly to the microcirculation structures – encompassing the terminal arterioles, capillaries and the pericytic (postcapillary) veins^{31,32}. Capillaries are responsible for most of the solute and fluid exchange. These vessels are made of epithelial cells – attached together like plates/ tiles to form a tube, with the cells performing multiple functions (see Figure 1).

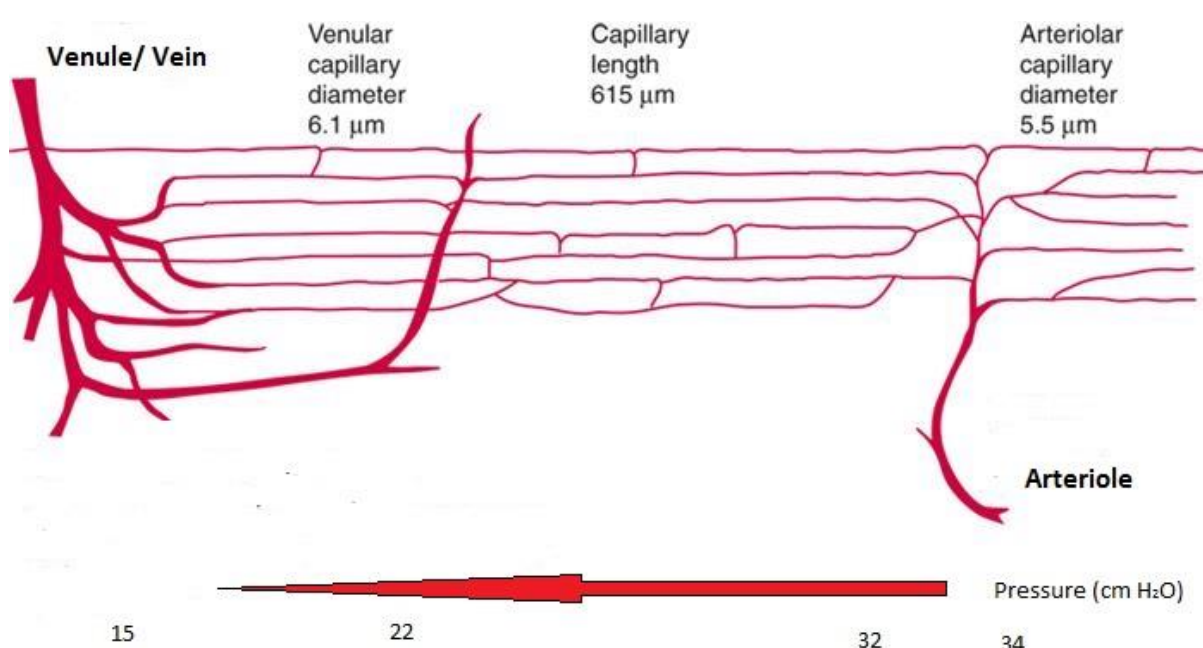


Figure 1 the microcirculation from terminal arterioles to post capillary (pericyte) venules. See labels and text for description and function. (Modified from Levick J.R. An introduction to cardiovascular physiology 5th edition Hodder Arnold 2010)³²

Terminal arterioles (diameter $5.5 \mu\text{m}$) normally divide and give rise to a cluster (module) of capillaries. Terminal arterioles have an additional layer of smooth muscle in the walls, which allows for opening and closure of the tube aperture as the muscle contracts and relaxes. This allows for alteration in perfusion of capillary modules, and heterogeneous perfusion between different body tissues at different times. This also allows a control mechanism for maintaining,

reducing or elevating perfusion to capillary modules. Terminal arterioles change their muscle tone constantly (with subsequent changes in perfusion) in a process called vasomotion³³.

Capillaries (4-8 μm diameter, 500-1000 μm length) form the main site for solute and fluid exchange to or from the tissues. They have a single monolayer of endothelial cells with junctions between the adjacent walls of each cell forming diagonal clefts (intercellular cleft) between the plate-like cells³⁴.

Pericytic venules (15 μm diameter) are formed when the downstream ends of the capillaries reunite. They have more breaks in the junctions between the endothelial cells and hence have a more permeable intercellular cleft. They are highly permeable to water and perform some diffusion functions for some solutes. They have a role in inflammation states, displaying alterations in function and permeability due to the effects of inflammatory mediators on gap junctions between the cells³⁴.

Arteriovenous anastomoses are microvessels (diameter 20-130 μm) with smooth muscle in their walls that bypass of the capillary bed and connect directly between terminal arterioles and venules. They are present in some extremities in skin to allow temperature regulation. They are important in the phenomenon of cold induced vasodilatation (CIVD) or the Huntington's response³⁵.

The type and density of capillaries varies between different tissues and gives tissues different exchange capability. Densities tend to be high in tissues that have high metabolic rates such as muscle (100 cm^2/g)³⁶, heart (500 cm^2/g)³⁷ and brain(500 cm^2/g)³⁸, or where large volumes of exchange are required , such as the lungs (3500 cm^2/g)³².

TYPES OF CAPILLARIES

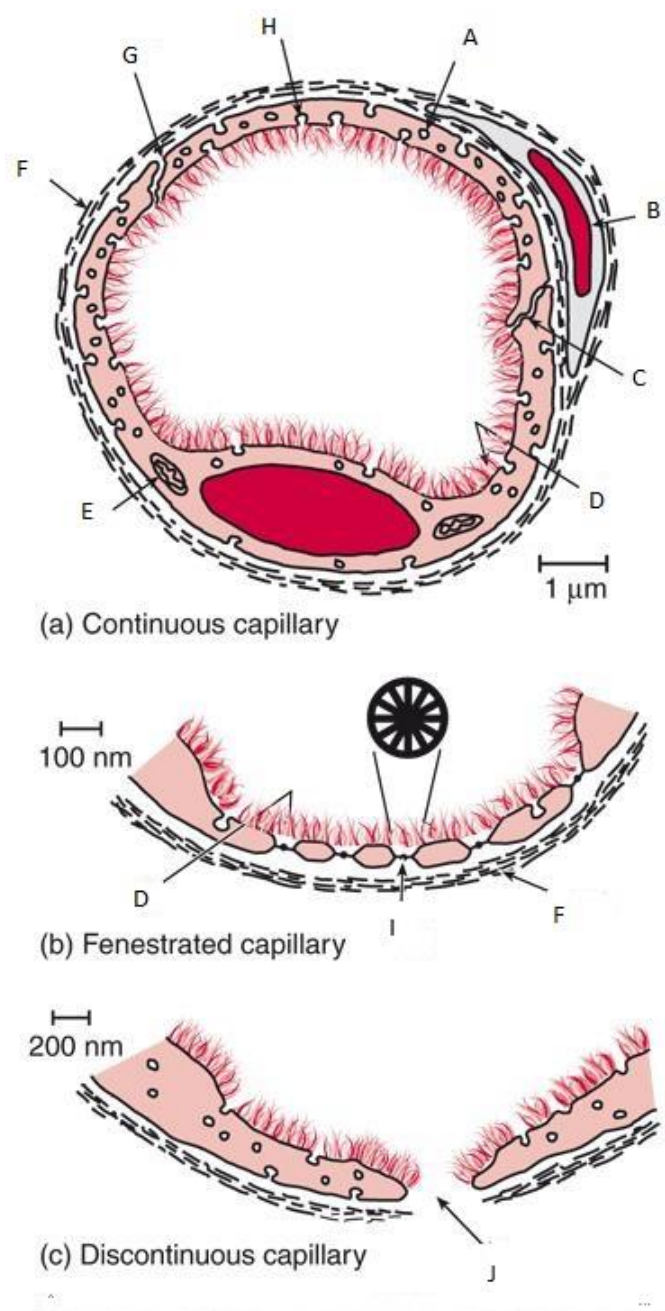


Figure 2 Types of Capillary. (Modified from Levick an introduction to cardiovascular physiology 5th Edition Hodder Arnold 2010)

Different types of capillaries allow for differences in fluid / solute exchange behaviour

Continuous capillaries see label (a) in figure 2, are found in muscle, lung, skin, connective tissue and fat. They have a Continuous ring of 1-3 endothelial cells ($0.3\ \mu\text{m}$ thick) surrounded by basement membrane. The Inter cellular clefts (see figure 3) – between endothelial cells (with some junctional strands holding the cells together) allow for solute or fluid exchange, and water and small lipid insoluble solutes (ie glucose) can move through the clefts between the strands³⁹.

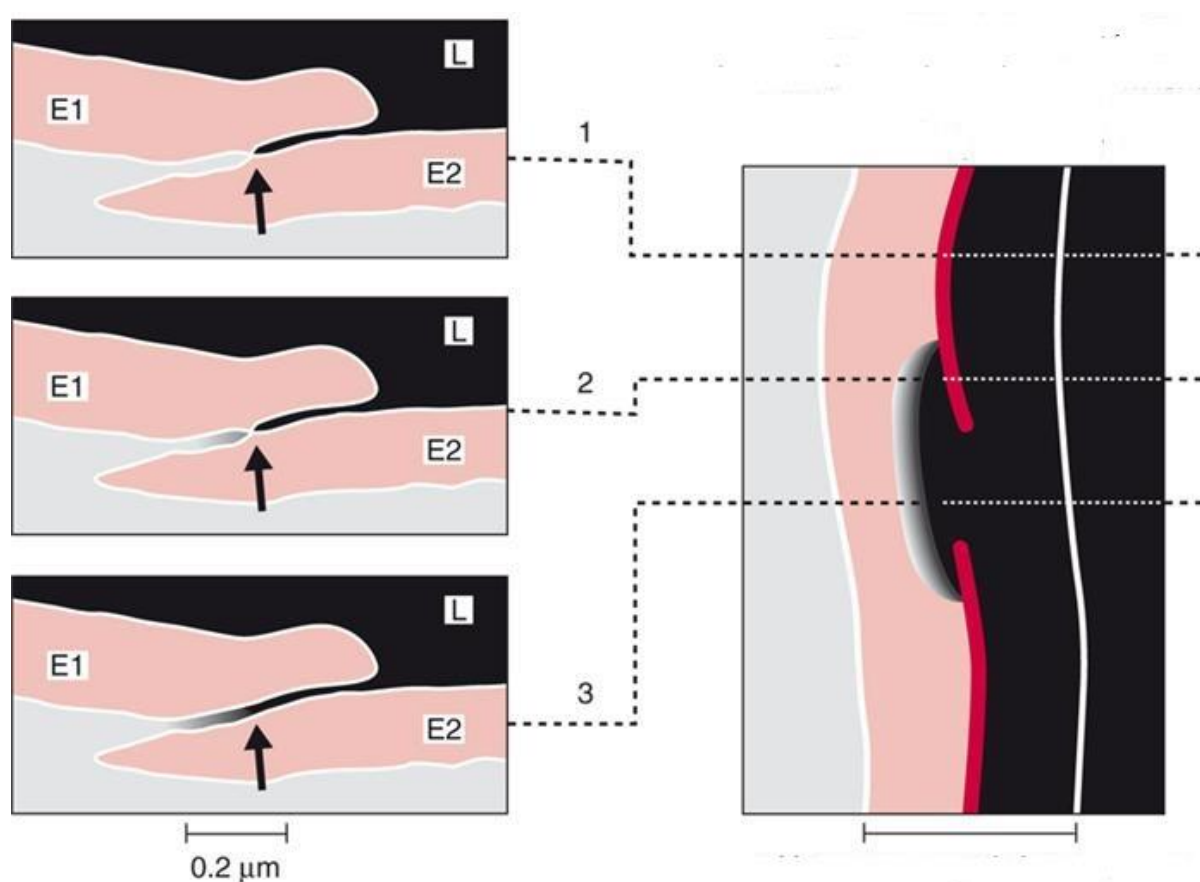


Figure 3 Inter cellular cleft at the junction between capillary endothelial cells. Label = (Modified from Levick An introduction to cardiovascular physiology 5th Edition Hodder Arnold 2010)

Lining the walls of the lumen of the capillary there is a layer called the Glycocalyx (see figure 4 label C and D). This is a hydrated Gel of negatively charged carbohydrate polymers attached to a core protein, which are attached intracellularly to the actin cytoskeleton at $100\ \mu\text{m}$ intervals. The glycocalyx protrudes into the lumen of the vessel in tufts like brushes ($60\text{-}570\ \text{nm}$ thick)⁴⁰. The glycocalyx and the junctional strands in the intercellular clefts determine the

permeability of a capillary to solutes and water. The glycocalyx acts as a filter or sieve to exclude large plasma proteins from access to the cleft but is permeable to water or small solutes. The glycocalyx mechanically senses changes in blood flow and allows for flow sensitive NO secretion, and it lubricates the large deformed red blood cells (RBC) as they move along the capillary. The glycocalyx may be degraded or shed, leading to negative effects including hyper-permeability, oedema, leaked proteins, leukocyte adhesion and changes to RBC transport across capillaries⁴¹.

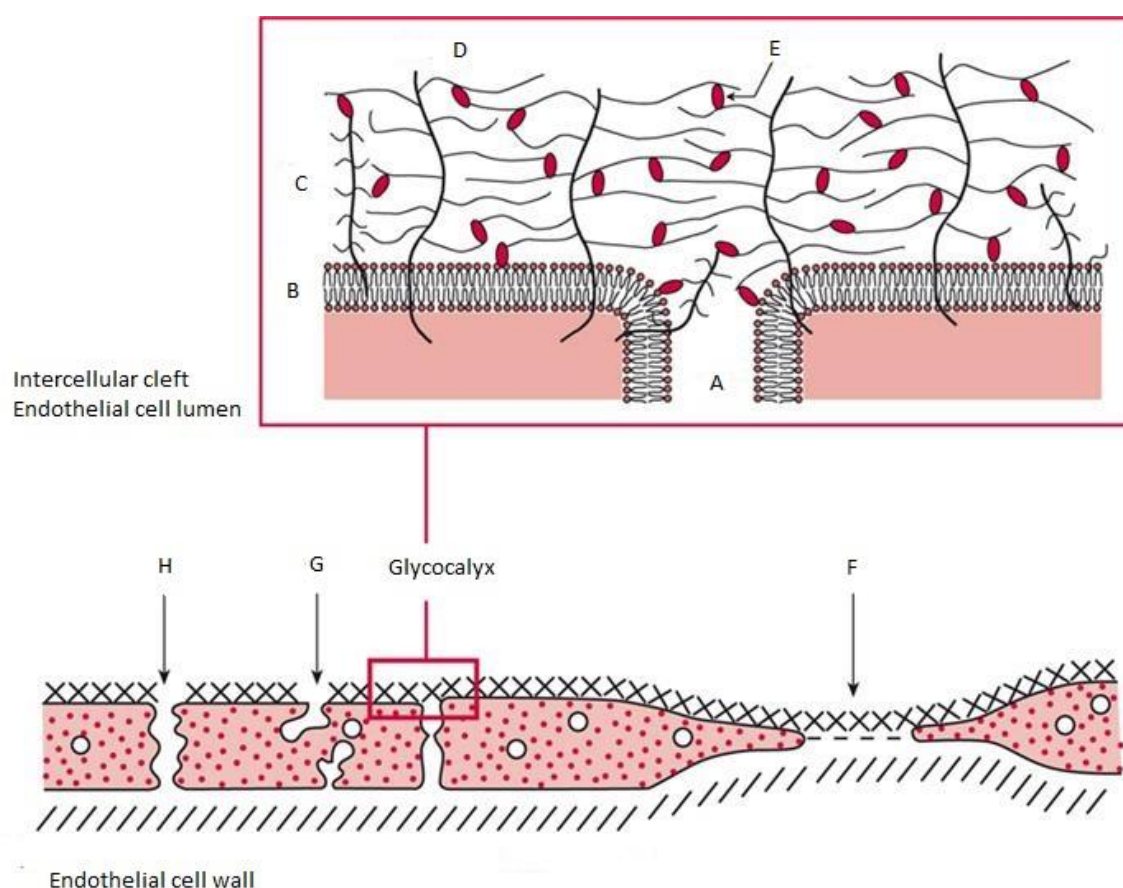


Figure 4 Glycocalyx layer of biopolymers inside the lumen of the endothelial cell capillary (Modified from Levick An introduction to cardiovascular physiology Hodder Arnold 2010)

Fenestrated capillaries see label (b) in Figure 2, are found in tissues that specialise in fluid exchange, including synovial joints, kidneys, intestinal mucosa, exocrine glands, and the ciliary body of the eye³². They are much more permeable to solutes and water than continuous capillaries and are characterised by small circular window perforations of endothelium or fenestrae, which are 50-60nm in diameter. Each fenestra has a type of diaphragm (4-5nm thick) bridging the fenestration, which is shaped like a cartwheel with spokes⁴². This allows water, hormones or solutes to pass quickly between the spokes. Fenestrae develop when intra and extra luminal membranes of the epithelial cell are brought together. Vascular endothelial growth factor (VEGF) has a role in the development of fenestrae⁴³ and this process may also be important for angiogenesis (the sprouting of new endothelial cell tubes or vessels) during inflammation and tissue healing⁴⁴.

Lymphatic capillaries form a network of anastomosing tubes (diameter 10-50 μ m) with endothelial cell walls, which are tethered to surrounding tissue by microfibrils (fibrillin). The basement membrane is incomplete and the intercellular clefts are wide (14nm +)⁴⁵. The clefts are diagonal and can act as a flap valve, allowing entry but not exit. This gives them the property of allowing entry to interstitial proteins and fine particles, providing a mechanism for return of these substances back into the vascular system.

Discontinuous Capillaries see label (c) in figure 2 exist in bone marrow, spleen and liver, which allows migration of large cells between blood and tissues⁴⁶. The endothelial cell gap junctions are very wide and the cells are discontinuous with their basal lamina. They are highly permeable, even to large diameter plasma proteins

MAIN TRANSPORT PATHWAYS ACROSS CAPILLARY WALLS

The permeability of capillaries and microcirculatory vessels to fluids and solutes is achieved via several pathways relating to the endothelial cells and their walls and intercellular clefts (see figure 5).

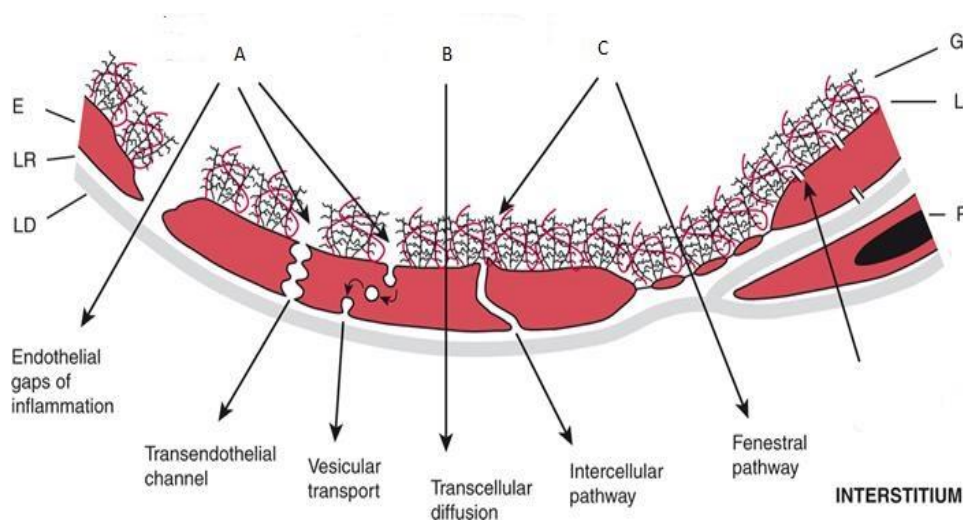


Figure 5 pathways for transport of substances between the capillary and the interstitial space (Modified from Levick An introduction to cardiovascular physiology 5th Edition Hodder Arnold 2010)

Lipid soluble substances such as oxygen (O_2) and carbon dioxide (CO_2) (see Label B figure 5) diffuse through the endothelial cell lipid membrane, allowing for a large surface area for diffusion and very rapid diffusion. Permeability is so high to these substances that some exchange occurs through the walls of terminal arterioles and post capillary venules (O_2 Counter current shunting).^{47,48}

Water and small lipophobic (hydrophilic) substances such as plasma electrolytes, glucose, lactate, amino acids, vitamins and hormones insulin and adrenaline (see figure 5, label C) cannot diffuse through the lipid endothelial cell membrane. They must diffuse through the water filled pathways of the intercellular clefts and the fenestrae (fenestrated capillaries only). The intercellular clefts make up only a small proportion of the surface area of the

capillary wall and hence the permeability is much lower for these substances than for the lipophilic substances⁴⁹.

Permeability of continuous and fenestrated capillaries to large lipophobic (hydrophilic) solutes and plasma proteins (see figure 5 Label A) is very low but some concentration of these substances (such as :- Immunoglobulins, albumin, fibrinogen, and protein bound substances such as vitamin A, thyroxine, testosterone and oestradiol) is needed in interstitial fluid and the concentration of plasma proteins in lymph can reach 20-70% of that of the plasma concentration⁵⁰. Grotte in 1956 proposed an exchange through a “large pore” pathway for these substances⁵¹. This may be accounted for by a vesicular system across the endothelial cell, with transcellular channels or vesicles that allow for transport of larger lipophobic substances through the endothelial cell, from the lumen, to the interstitial space.

Blood is not static in capillaries and blood flow can affect capillary exchange but this depends on the solute concentration profile across the capillary wall. There is a spectrum of solute exchange. For Lipophilic solutes like O₂ and CO₂ the concentration gradient equalises before the blood flow has reached the end of the capillary. Increasing blood flow results in more exchange and the velocity of the blood flow is the factor that limits the rate of exchange. This is called flow limited exchange. At the opposite end of the spectrum, it is diffusion that is the rate limiting step to the exchange of larger lipophobic solutes – even if the blood flow increases (diffusion limited exchange)⁴⁹.

FACTORS AFFECTING MOVEMENT OF FLUID ACROSS CAPILLARY MEMBRANES

Fluid in the body is constantly exchanged between the intravascular plasma the interstitial fluid in the tissue. Even at rest, the fluid turnover, while slow, is extensive and the entire plasma volume can do an extravascular circulation each day (up to 50ml/minute of plasma ultrafiltrate moves to the ISF at rest)⁵². During exercise or standing, more fluid is passed out

into the interstitial fluid (i.e. into exercising muscle) and the plasma volume can drop up to 15%⁵³ but can increase by 4.5% after an intense bout of exercise. Fluid movement across the capillary wall (semipermeable membrane) is a process of filtration, governed by the glycocalyx biopolymer endothelium coating and the intercellular clefts. This size allows passage of water and small size solutes, pores in fenestrated and discontinuous capillaries allow more fluid movement, and movement of larger size solutes and proteins into the interstitial space.

The main force driving filtration is the capillary blood pressure (pushing force), and the main force opposing filtration is the osmotic pressure from the plasma proteins (pulling / sucking force). Osmotic pressure or Colloid osmotic pressure (COP), in a solute, is the pressure exerted as water moves from an area of high solute concentration to an area of low concentration and is the main force holding water in the plasma / intravascular compartment.

The rate at which fluids filter across capillary membranes is proportional to the hydraulic push of the blood pressure minus the Osmotic suction of the plasma proteins⁵⁴. Normally the net hydraulic push is greater than the net osmotic pressure of the plasma and fluid filters from the bloodstream into the tissues. But in conditions such as hypovolemia or haemorrhagic shock the capillary pressure drops and fluid and solutes can move from the interstitium back into the blood stream⁵⁵.

STARLING EQUATION

The Starling equation for fluid filtration, which allows for quantification of transcapillary filtration rates. When considering swelling or oedema it is important to understand the Starling equation as it explains the factors underlying tissue (interstitial swelling) in many states such as oedema, inflammation and haemorrhage^{52,56,57}.

Equation 1 Starling Equation for Fluid Filtration

$$J_v = L_p S [(P_c - P_i) - \sigma(\pi_p - \pi_i)]$$

Equation 2 Starling Equation for Fluid Filtration with Glycocalyx Cleft (Michel Weinbaum) theory of fluid Exchange

$$J_v = L_p S [(P_c - P_i) - \sigma(\pi_p - \pi_g)]$$

Where:-

J_v = Volume filtered / unit time – the filtration rate.

$(P_c - P_i)$ = the net hydraulic push, which equals the capillary blood pressure, P_c , minus the interstitial fluid pressure, P_i .

$(\pi_p - \pi_i)$ = the net osmotic suction, which equals the plasma COP, π_p , minus the interstitial COP, π_i .

Nb. π_i (COP of the interstitial fluid) is used, but it is a substitute for the exact COP at the immediate outer (downstream) end of the glycocalyx (π_g) or Intercellular cleft, which cannot be measured. This may actually differ from the interstitial space COP (π_i). I.e. the COP within the ICC (π_g) is more important than the COP force of the rest of the ISS (π_i). This gives Equation 2 model, which may explain why the net filtration rate in capillaries can be different from expected, when measured using COP force of the rest of the ISS (π_i).

L_p = the hydraulic conductance of the capillary wall

S = the capillary surface area

σ = the Osmotic Reflection Coefficient. The capillary wall is an imperfect semi permeable membrane and thus exerts only a proportion of its effective osmotic pressure. σ indicates the effective proportion of the COP that is exerted at the capillary wall, and it differs for different substances (i.e. for plasma proteins $\sigma = 0.8-0.95$).

Figure 6 Starling Equation for fluid exchange

It is worth considering each aspect of the Starling equation sequentially, particularly the pressures in the above equation. This is important for swelling ACLR because the forces in this equation govern the microcirculation fluid exchange around the knee (intra and extra-articular) and hence how much fluid extravasates or re-enters the plasma in normal fluid exchange but also in post injury or surgery conditions.

CAPILLARY BLOOD PRESSURE (P_c)

Capillary blood pressure (P_c) at heart level is approximately 32-36 mmHg at the arteriole end, with pressure falling along the length of the capillary to 12-25mmHg at the venous end (skin). Different tissues have varied capillary pressures allowing different filtration and fluid exchange levels and functions. The filtration rates for capillaries increase with increases in capillary pressure⁵⁴.

There are several factors that can influence capillary pressure including arterial and venous pressures (blood pressure), vascular resistance (including tone in arteriolar smooth muscle), gravity and posture and distance along the capillary axis. Capillary pressure is influenced by the amount of resistance both upstream and downstream i.e. precapillary arteriolar resistance and post capillary venous resistance.

This ratio of arteriolar to venous resistance controls the capillary pressure. If this ratio is high (as in vasoconstriction, haemorrhage), it gives a lower capillary pressure and if the ratio is low (as in inflammation) the capillary pressure is higher. Therefore, the tone in the smooth muscle in arteriolar walls at a local level controls the capillary pressure.

If a cuff is placed around a limb, thus raising venous pressure, the capillary pressure rises and the limb starts to swell as the capillaries filter fluid (this is the same reason that the leg swells

with a Deep vein thrombosis (DVT)). The swelling rate increases linearly with vascular (&capillary) pressure. This has been measured, even with a cuff pressure of 40mmHg⁵⁸. This has relevance for therapeutic devices used to apply a compression around the limb with the aim of reducing swelling. Even small amounts of cuff pressure, may actually cause increases rather than decreases in swelling.

In standing when the limb is below heart level, the pressures in the arterioles and veins of the foot can reach 180 and 90mmHg – respectively, with capillary pressures of 95mmHg⁵⁹. This is why the feet and ankles can swell with prolonged standing. Capillary pressure, however, does not increase as rapidly as arteriolar or venous pressure because there is a local arteriolar vasoconstriction (the veni-arteriolar response)⁵⁹. This can attenuate the pressure rise in the dependant limb capillaries, and prevent postural oedema.

PLASMA COLLOID OSMOTIC PRESSURE (π_p)

Osmosis is the flow of water molecules across a semipermeable membrane from a dilute to a more concentrated solution. Osmotic pressure is defined as the hydrostatic pressure that will stop the osmotic flow from pure solvent into a solution. It is expressed as a pressure but is actually a suction effect. Osmosis may be more responsible for net water movement than diffusion.

This force is often not sufficiently considered in swelling, and it can be substantial. If plasma proteins collect in the ISF and the concentration raises sufficiently, this will give a net suction force moving fluid from the vessels into the ISS.

The plasma colloid osmotic pressure (COP) (π_p) is the main force opposing capillary filtration. Osmotic pressure is exerted by proteins such as Albumin, but also by Crystalloids such as Sodium Chloride. Plasma proteins, such as Albumin, exist within the vessels but also in some concentration in the interstitial space. They exert an osmotic suction force (approximately

25mmHg)⁵² across the capillary wall to maintain fluid volume within the vascular system. In bleeding and extravasation during inflammation there is a very large efflux of plasma proteins to the ISS which changes the COP of both the intra and extravascular spaces, further driving more fluid out to the ISS until the homeostasis is returned.

THE EXTRAVASCULAR (INTERSTITIAL) COP (π_i)

The extravascular/ interstitial space also contains plasma proteins (around 20-30g/L), and over half of the entire plasma protein mass is extravascular. The protein concentration however can differ greatly between the intra and extravascular spaces. Proteins can pass into the ISS via the “large pore”, or vesicular system. Movement of fluid (small pore system) between capillary and ISS will change the ISS plasma protein concentration, and capillary filtration therefore can alter the COP of the interstitial space. In inflammation, for example, the protein concentrations change between the intra and extravascular spaces, as proteins leak out of the vascular system into the ISS. This changes the protein concentration gradients and hence COP. Therefore, while capillary blood pressure may suggest that the capillary is in a strong state of filtration, the COP balance may mean that the capillary is in a much lower (or non-existent) state of filtration.

INTERSTITIAL FLUID PRESSURE (P_i)

Interstitium is made up of a three dimensional matrix of negatively charged biopolymer fibres (Collagen / proteoglycan/ Glycosaminoglycans (GAG) and other glycoproteins) (solid) as well as a solution of electrolytes and escaped plasma proteins (fluid). The negatively charged matrix (GAG) tends to attract water and electrolytes (particularly sodium) and the water stabilises the tissue shape. Interstitium therefore exerts a negative pressure – the gel swelling pressure. This structure exists in many connective and interstitial tissues with variable space between the GAG matrix. This means the matrix and GAG exert a negative or subatmospheric

pressure in tissues. In tissues like skin, the fibroblasts cells and fibres to which they connect exert a mild compressive force which counteracts the gel swelling pressure of the matrix⁶⁰.

LYMPHATIC SYSTEM

The lymphatic system also affects the ISS fluid balance but is not usually considered in studies relating to swelling. It provides the main pathway for capillary ultrafiltrate and ISS plasma proteins to return to the bloodstream. Conditions such as post mastectomy lymphoedema show the swelling effects in a limb when the lymphatic vessels are removed or blocked.

It has also been previously thought that capillaries filter fluid, but that post capillary venules or venous ends of capillaries absorb it. A well perfused capillary, however, is normally in a state of filtration along its entire length and dropping capillary blood pressure to the venous pressure only produces a very transient absorption before returning to capillary state of filtration. Venous ends of capillaries or post capillary venules actually show a normal small net filtration rather than absorption. This is due to the COP of the interstitial fluid π_i as well as the interstitial force P_i .

Electrolytes and nutrients filter from the plasma to the tissues, but a volume homeostasis must be maintained so that the ISS does not over accumulate plasma filtrate. This balance is achieved by the lymphatic system, which provides the main mechanism for plasma proteins and fluid to return to the vascular system.

The Lymphatic system comprises a network of absorption vessels that cover the body, which function like veins (ie they drain). The system has roles in nutrition and immunity as well as preservation of fluid balance. Lymph provides the main pathway for capillary ultrafiltrate and ISS plasma proteins to return to the bloodstream. Lymphatic capillaries as previously described, have wide epithelial cell clefts, producing flap type valves that allow a one way

passage of fluid and plasma proteins into the vessel. Lymph vessels fill with a squeeze recoil system and lymph flow varies with capillary filtration rate.

Lymph vessels take up only a small fraction of the fluid filtered from the plasma into the ISS. (0.1-0.3% in most tissues) but approximately 4000 L of plasma pass through the microcirculation per day, which generates 4-8 L of lymph per day. At rest, in humans, approximately 100ml per hour of lymph flows through the thoracic duct and 20 ml per hour re-enters the circulation through other channels³¹.

Lymph cannot passively drain but must be pumped. Either extrinsically – from tissue movement, distortion, contraction (muscle) or intrinsically from smooth muscle contractions. The initial lymph collecting capillaries do not have smooth muscle in their walls but the second order lymphatic vessels have semilunar valves and smooth muscle in their walls. These work in contractile segments like a cardiac ventricle and, in the limb, can pump at pressures up to 40-50mmHg against resistance⁶¹. A cuff or tourniquet that is applied at this pressure in a limb will affect not just venular or arterial flow but also lymphatic flow.

STARLING PRESSURES DURING SWELLING AND OEDEMA

Normally, the body maintains a fluid balance between ISS (10-12Litres) and plasma fluid (3L). If plasma volume drops (haemorrhage) a net absorption of fluid ensues to restore the plasma volume. During plasma volume expansion (renal fluid retention /over transfusion) fluid is moved to ISS. At normal hydration the ISS pressure P_i is subatmospheric, but with oedema, P_i rises. The pressure volume curve is relatively flat in tissues like skin (stretchable) but rises much faster in tissues with a capsular surround, like muscles or synovial joints. Oedema in a limb will follow the path of least resistance and gather in the subcutaneous space⁶².

RAISED CAPILLARY PRESSURE $\uparrow P_c$

Capillary pressure can rise when venous pressure is chronically raised in:-

- over transfusion
- deep vein thrombosis (DVT)
- Dependant or recumbent tissues.

INCREASED CAPILLARY PERMEABILITY $\uparrow L_p$, $\downarrow \sigma$, $\uparrow P_{protein}$

In inflammation, the capillary barrier breaks down with holes within, and gap formation between epithelial cells and this allows a large efflux of fluid and proteins out of the vascular system to the ISS. Therefore the hydraulic conductance L_p and the permeability to proteins $P_{protein}$ increase. The protein reflection coefficient σ falls. This oedema has a raised plasma protein (>30g/L) and cellular content.

LYMPHATIC INSUFFICIENCY

Impairment of Lymph results in impaired return of escaped plasma proteins to the vascular system. This allows both water and plasma proteins to accumulate in the ISS. Lymphoedema has high protein content (>30g/L). Chronic Lymphoedema can result in deposition of fibrous adipose tissue in the ISS – resulting in a non “pitting” type of oedema. This occurs in conditions such as:-

- Damage of lymph nodes in cancer surgery or radiotherapy
- Hereditary Lymphoedema (inadequate lymph development)
- Filariasis

THE STARLING EQUATION AND ACUTE INFLAMMATION (VASCULAR EVENTS)

During acute inflammation, such as post injury or postsurgery, the key change bringing on swelling in the vascular system is formation of gaps in the endothelial barrier. The initial trigger such as: - trauma, infection, ischaemia, or allergy triggers release of pro inflammatory chemicals by the tissue cells.

Most chemical mediators of inflammation act on receptors in the post capillary venule and cause gaps to form through and between the endothelial cells. This also creates holes in the glycocalyx coating of biopolymers within the lumen, causing a disruption to the semipermeable membrane, and allowing rapid leakage of plasma proteins and water.

Cytokines such as interleukin-1 β , tumour necrosis factor α (TNF α) are secreted by cells (monocytes/ fibroblasts/endothelial cells) to induce Leukocyte adhesion and migration.

Leukocytes are large compared to the vessel diameter, and marginate to the vessel walls and adhere and eventually migrate (squeeze) out to the tissues through the gaps in the endothelium.

The inflammatory response often shows 2 phases. An initial phase (10-30minutes) large but transient rise in permeability which then reduces, and a more sustained increase in permeability lasting hours^{63 64}.

Different pro inflammatory chemicals have differing effects on the endothelium. Histamine, Serotonin, and bradykinin cause a transient rise in permeability whereas Thrombin and vascular endothelial growth factor (VEGF) cause more prolonged rises.

The oedema caused is called an “exudate” as it is a high protein concentration >30g/L.

The chemical cascade alters almost every factor in the Starling equation see Figure 6.

RAISED CAPILLARY PRESSURE $\uparrow P_c$

Inflammatory chemicals cause arteriolar vasodilatation giving redness and heat in inflamed tissues, and raising the pressure on the arterial side of the capillary, causing an increase in filtration pressure.

INTERSTITIAL FLUID PRESSURE P_i

Interstitial fluid pressure falls initially in skin and submucosa to a more subatmospheric level, which is caused by fibroblasts releasing some of their integrin link to the collagen fibres around them. This reduces the compressive (anti-swelling) effect the fibroblasts and integrins exert on the ISS. As the oedema fluid accumulates in the ISS, P_i rises to 2mmHg (supra-atmospheric) and this serves eventually as a minor check on filtration.

EXTRAVASCULAR OSMOTIC PRESSURE $\pi_i \pi_g$

The protein concentration in the ISS increases as the proteins leak out of the gaps in the endothelium. This reduces the difference between the capillary and ISS plasma COPs in favour of further increase in filtration rate.

OSMOTIC REFLECTION COEFFICIENT σ

With gap formation and the loss of the glycocalyx barrier, the osmotic reflection coefficient falls (to 0.4), as the plasma proteins are unable to exert their full osmotic potential.

HYDRAULIC CONDUCTANCE OF THE EPITHELIAL CELL WALL $L_p, \uparrow P_{Protein}$

The gap formation in the endothelial cell walls, causes the hydraulic conductance to increase by around seven times. The changes in P_c, P_i, π_i and σ all greatly increase the net filtration force across the venules. All of these factors combine to give a 50-100 fold increase in the fluid extravasation rate.

ENDOTHELIAL GAP FORMATION

Endothelial cells in the post capillary venules form gaps (both inter and transcellular) during acute inflammation facilitating the passage of fluid. Histamine, substance P, serotonin, and platelet activating factor induce intercellular gaps whereas VEGF, heat shock proteins and direct pressure overload or vessel injury, result in more transcellular gaps⁶³.

Influx of Calcium ions through ion channels in endothelial cells, in combination with higher levels of nitric oxide cause an activation of actin and myosin complexes within the endothelial cell formation of the gaps. In small amounts, nitric oxide can lower permeability, but high levels, NO is pro-inflammatory, and increases endothelial gap formation⁶⁴.

FLUID EXCHANGE IN THE KNEE JOINT

It is important to contextualise the above physiology to the knee joint in order to understand the potential impact of ACLR on fluid exchange. The main tissue controlling fluid exchange in the synovial joint is the synovial membrane. Synovium produces synovial fluid that acts as a lubricating fluid to facilitate friction-free surface movement, and helps to aid oxygen and nutrition exchange to intra-articular tissues, including cartilage. Synovium achieves this through its circulation with sinuous micro vessels. It's total volume in the human knee is about 1.6 cm³ with a thickness of 60 µm, ^{65-68 69} thus producing an extremely dense capillary microcirculation network with an area of approximately 240 vessel profiles / mm² for comparison this is 3 times the density of muscle). The capillary network is situated close to the joint cavity with a very small mean capillary depth (approximately 35 µm). Close to half the capillaries are fenestrated, with a greater density on their joint cavity side, ensuring a short direct diffusion pathway between capillary and joint cavity.

Beneath synovium is a layer of loose connective tissue and fat tissue called subsynovium with terminal vessels and a lymphatic plexus that drains away fluid and other molecules and proteins that pass out through the synovium. Many of these molecules are large and cannot re-enter the circulation via the synovial capillaries and they require the lymphatic system to remove them from the joint and return them to the circulation⁶¹. The lymphatic system is the only transport system in the joint that can perform this function. Lymphatic openings or stomata exist between some types of synoviocytes and may be open or closed⁷⁰. There is some evidence that more of the stomata open during inflammation. The terminal lymph vessels have a role in moving fluid and escaped proteins away from the joint. Terminal vessels feed into larger vessels and eventually the popliteal lymph nodes (PLN), which have been found to enlarge with inflammation. If this system is blocked (including at the PLN level), there is evidence that knee effusions are larger⁷¹. Highlighting the importance of this system for oedema resolution.

Synovial cells have almost no intercellular junctions, allowing a discontinuous lining which is open and very permeable. Collagen micro fibrils and other proteins hold the cells together but their composition and concentration differs in different depths, creating a hydraulic drag, and setting up a negative pressure hydraulic gradient, also moving fluid through the cellular layer toward the joint cavity, and helping to retain fluid in the joint cavity.

SYNOVIAL PERFUSION

The result of these synovial and vascular features create a huge perfusion (1 ml / min for the human knee). This equates to 0.63ml/min for each 1ml of Synovium which is high for such a small volume of tissue (1.6cm³), and it is thought that this flow aids cartilage (volume 37cm³), as well as synovial nutrition⁷². Fluid exchange is vital for this nutrition because both cartilage and synovium consume oxygen and glucose. There is also evidence of knee joint effusions in static patients such as, spinal cord injured and Intensive care patients.^{15,73-77} There may be factors responsible for these, such as trauma, sepsis, pseudogout, and over giving of IV fluid, but this raises the possibility of stasis as a cause of effusions.

SYNOVIAL FLUID

The amount of synovial fluid within the joint after the synovial diffusion is normally small (0.5ml in the knee) and spread thinly and unevenly. It functions for lubrication, providing a cleavage plane and fluid transport medium for both nutrition and removal of debris and wastes.

Synovial fluid is composed of plasma electrolytes and proteins, as it formed from capillary exudate flowing through the fenestrations in the synovial vessels. Plasma protein concentration in synovial fluid is 25-58% of that in plasma. Synoviocytes secrete lubricating macromolecules such as Lubricin (glycoprotein) and Hyaluronan (Glycosaminoglycan) (concentration of 2-4g/L). Hyaluronan helps to keep out larger plasma proteins, hence the lower concentration than capillary plasma⁷⁸.

It is continually being turned over by synovium⁷⁸ and turnover time for synovial fluid is about 1 hr. Hyaluronan turnover time is much longer as there is a selective retention of hyaluronan within the joint cavity.

Synovium generates its own weight in fluid in 0.5-2 hrs. Plasma proteins and fluids that are not able to diffuse back through the synovial membrane enter the sub synovial lymph system.

INTRA-ARTICULAR PRESSURE

Normal knee intra-articular pressure is sub atmospheric , typically around -3 to -6 cmH₂O , and stays negative, even with walking and weight bearing (between 1 and -25mmHg⁷⁹ with quadriceps contraction also causing a drop in pressure⁷⁹. Joint angle does not influence pressure a great deal, but changes to be above atmospheric pressure at some angles and below at others. Trans-synovial flow therefore may change direction during normal joint movement – presenting a possible further mechanism for replenishing synovial fluid.

In Joints with effusions, intra-articular pressure is greater than atmospheric pressure and joint angle has a larger effect on pressure, with an angle of ease often adopted by a patient¹⁷. Nade and Newbold found that movement affected the fluid exchange and pressure in canine joints, with the major determinants of intra-articular pressure including: - joint size, synovial fluid volume, position of joint, peri-articular tissue and joint anatomy, membrane permeability and capsular compliance⁸⁰

As intra-articular pressure rises with a large effusion, trans-synovial (joint to synovium) flow will normally increase. Flow happens through synovium interstitium but fluid can also be absorbed by the synovial microcirculation. The relation is not linear, and some studies suggest a change pressure of about 9cm H₂O beyond which flow rates more rapidly change⁸¹

,although another study suggests that rises in IAP as much as 20mmHg may reduce synovial blood flow which have implications for nutrition and hypoxia of joint ⁸². In this situation, it may actually be the lymphatics that act to drain fluid.

COLLOID OSMOTIC PRESSURE (COP)

The fenestrations in synovial capillaries, allow some of the plasma proteins to exit and cross and move through the extracellular synovial spaces to enter the joint cavity. The proteins are cleared from the joint via the synovial lymphatic flow, which sets up a turnover system for proteins. Across the synovial membrane there is a protein concentration gradient set up by the synovial fluid with a plasma protein concentration of 19-30g/L⁸³. This gradient sets up a COP gradient.

Hyaluronan gives synovial fluid viscosity- it is a large glycoprotein with a concentration of 2-4g/L in synovial fluid. It is less important than plasma proteins for COP and is retained in the joint. It may be too large to filter through the synovial membrane and seems to limit flow ⁸⁴.

Effusions may be affected by protein concentrations. Elevations in inflammatory mediators, increased capillary permeability, generalized fluid or albumin derangements and disruption of lymphatic drainage channels can all cause abnormal fluid levels. These factors impact intra-articular pressure and colloid osmotic pressure respectively per the Starling equation discussed previously.

PATHOLOGY SECTION

THE INFLAMMATORY PROCESS

Inflammation as a result of tissue damage also contributes significantly to swelling. Inflammation involves a series of cellular, vascular and fluid exchange events that require a dynamic interplay between the circulation and the ISS in injured tissue. The body mounts a local inflammatory response to any injury, causing the changes in the circulation and fluid exchange which lead to swelling and oedema. Much has been written on the inflammatory process with a brief summary below in light of this current study

The process initiated by specific factors linked to cellular damage or blood loss from vessels into the tissues and proceeds as a series of chemically mediated events that involve specific cells and mediators. Inflammation is likely to occur twice in the knees of patients undergoing ACLR. Once at the time of initial injury and secondly following the reconstruction surgery. ACLR surgery involves the drilling of bone tunnels, breach of the joint capsule by the arthroscope and probe, and the harvest of the graft. All are associated with damage, subsequent bleeding and activation of the inflammatory pathway.

CELLULAR AND VASCULAR EVENTS OF INFLAMMATION

Cells and chemical mediators are responsible for not only the initiation but also the maintenance and resolution of this process. The effects on the local vascularity and fluid are key to the inflammatory process.

Tissue damage causes chemical release from cells such as interleukin and TNF that attract cells, most notably macrophages. These also release multiple inflammatory mediator chemicals, which have many different actions on a variety of tissues. Blood vessels are affected with release of vasodilatory agents such as histamine, nitric oxide and substance P from arteriole to capillaries. They widen the gap junctions between the endothelial cell walls, particularly of the post capillary venules. This causes a plasma exudate out of the blood vessels and into the tissues and ISS. The plasma exudate allows specialist cells such as leukocytes (neutrophils) to migrate to the injured/ infected area, via chemotaxis along diffusion gradients of chemokine mediators.

Oedema / swelling is caused by the plasma exudate into the tissues. Eventually this exudate fills the ISS, creating pressure, which may build to a point where fluid exudate slows and a stasis is reached, this static fluid environment allows the relevant cells (particularly leukocytes) to migrate to the appropriate site to initiate the process of repair.^{85,86}

Various chemical release systems and chemicals maintain, heighten or reduce the response. These systems relate to plasma cascade systems with plasma chemical mediators that work to initiate/prolong vasodilation, coagulation and removal of pathogens (phagocytosis). Chemicals such as bradykinin, and thrombin participate in this process.

Cellular systems with chemicals released from damaged cells and migrated leukocytes, also play a role in heightening the inflammatory response with chemicals such as histamine, prostaglandins. Several anti-inflammatory mediators are release in a sequential fashion which help to damp down and control the response such as Nitric oxide and IL-10, giving a system of checks and balances on this process. This allows a return to normal flow mechanics.

DURATION OF RESPONSE

Mediators heighten the response from the initial cell damage and bleeding / extravasation, depending on the type of tissue and size of damaged area. In connective tissue this process starts in the first one to two hours and comes to maximum at two to three days, with resolution over several weeks as mediators gradually reduce.^{87,88}

Acute inflammation gradually gives way to a proliferation phase, as connective tissue cells become more active and commence the process of repair by proliferating. This second phase starts as early as 24-48 hours post injury with peak activity at around 2-3 weeks and gradually decreases over several months as the cells elevate production of collagen and matrix

The final phase is remodelling, with matrix deposition and fibrosis continuing and collagen laying down aligned in response to tissue forces. The onset peak remodelling phase is around 2-3 weeks but probably starts earlier at 1-2 weeks. This may be altered by activity but may actually require activity for the tissue to reach maximum strength.^{85,89}

THE INFLAMMATORY PROCESS AFTER ACLR

Much literature concerning inflammation and altered fluid mechanics in joints is based on arthropathies such as rheumatoid arthritis. Much information on inflammation in damaged / operated joints comes mainly from animal studies. Swelling and oedema formation after ACLR was examined, however more attention has been made to the healing process of the graft and its attachments than to vascular aspects of the initial inflammatory process⁷. There has, however, been research into aspects the articular inflammatory response in ACLR^{90,91}

There are 4 areas of surgical intervention in the ACLR procedure, associated with bleeding, inflammation and healing:- the graft harvest site adjacent the pes anserine hamstring or patella tendon attachments (extra articular) , the graft (semitendinosus and gracilis tendon) tissue itself, the bony tunnels drilled into the tibia and femur to contain the graft and, finally, via the arthroscopy, the knee joint itself.

Normal cruciates have a surrounding synovium layer which helps to deliver the cruciate blood supply and bath them in synovial fluid. This is sacrificed in the surgery, although this may be damaged in the initial ACL injury. It has been found to re-establish by 6 weeks post ACLR in dogs.

After the semitendinosus and gracilis or patella tendon are harvested, the graft is prepared outside the joint, while the bony tunnels are measured and drilled with arthroscopic visualisation. Finally, prior to closing the joint an injection of intra-articular morphine and local anaesthetic is delivered into the joint cavity.⁹²

INITIAL ARTICULAR RESPONSE – HAEMARTHROSIS

A tourniquet is applied during the surgery, influencing the knee vascular and capillary pressure, and limiting the intra-articular bleeding. The average tourniquet time (i.e. approximate measure of operation time) will depend on the surgeon and level of knee pathology but is approximately one hour. Post operatively, once the tourniquet is released, the operated tissues bleed, and a haemarthrosis gathers during the initial minutes and hours, the volume of this varies between patients, however, drain studies indicate a volume in the first 1-2 days of 152ml ¹², 146.9ml ¹³ and mean 120ml ¹⁴. The duration of haemarthrosis response is variable. Animal studies with autologous injections of blood into the canine knee showed a very rapid clearance of red blood cells (RBC) ²⁵ – with synovium containing large

loads of RBC even within 15 mins. At 48hrs there was only 5% of intra-articular erythrocytes remaining, but almost none in the synovial tissue. They also found no sign of clotting in any of their joints. Synovial fluid exchange may present a clearance/ filtration system not just for replenishing synovial fluid, but also for resolving haemarthrosis in the closed joint⁹³. Another study using radiation to track Erythrocytes in carrageenan-injected joint effusion in rabbits found a 3-14 day period to clear erythrocytes.^{26,94}

The lymphatic system has been more extensively investigated in Lymphoedema and tumour metastasis, but surprisingly has been little investigated in joint function. There is some investigation in inflammatory arthropathy and Rheumatoid arthritis but not in acute inflammation and injury. The lymphatic system assists with clearance of effusions and large molecules, and may be the joint's main clearance system (possibly through the lymphatic stomata). Osteoarthritic joints show greater lymph vessel density than age matched controls, and effusions in osteoarthritic joints show negative correlation with the lymph vessel density, but no histological association with synovitis⁹⁵. This may indicate that in synovitic joints, a reduced lymph vessel density reduces clearance rate and that may increase effusion size. Studies in mice indicate that blockage of the lymph pathway during inflammation may affect the resolution of effusion. This may indicate blockage at the stomata level and/or further along the vessels, even as far along the pathway as the popliteal lymph node.^{71,96} The lymphatic contraction (the so called "lymph pulse") may also be inhibited, reducing clearance rates.

In a study on the tendon / bone tunnel in ACL reconstructed rats Kawamura et al (2005) found neutrophil numbers present in the tendon bone interface had increased by 4 days post ACLR but were shown to have dropped again at 7 days post ACLR. Within the core of the tendon graft there were no neutrophils found. Macrophages were present at 10 days, and peak at 14-21 days in the tendon bone interface. They were found to show and peak later in the inner

tendon. Neutrophils and macrophages (as well as platelets) release growth factors such as TGF B, which stimulate scar fibrosis and healing. Healing therefore probably progresses from the tendon bone interface, inwards. There may be a difference in the inflammatory response within the tendon vs the tendon bone interface. Angiogenesis was found to accelerate up to 14 days post op, and then to plateau both within the tendon and within the tendon bone interface.⁹⁷

This literature indicates that the inflammatory response (including swelling and oedema) is a necessary precursor to healing and fibrosis, and by inhibiting the response it may be detrimental to healing progression.⁹⁸

THE EFFECTS OF JOINT SWELLING

Whilst joint swelling may be considered adaptive, there may be maladaptive effects on adjacent structures. An effusion within a joint has a direct effect on the mechanics of the joint, but also on the joint's metabolism and the activity in the sensory and motor neurons around the joint.

EXTRA ARTICULAR EFFECTS

ARTHROGENIC MUSCLE INHIBITION

An effusion in a knee joint causes some neurological effect, with a muscle inhibition around the joint, particularly of the quadriceps. In an early study on muscle inhibition using plasma to distend the knee, De Andrade et al (1965) showed loss of straight leg raise ability with an induced effusion to the knee. As the intra-articular pressure (IAP) increased, pain was demonstrated, however, a sensation of heaviness and loss of straight leg raise occurred (IAP

18-330 mm mercury) prior to onset of pain. Both a denervated Joint (Charcot joint) and an anaesthetised joint blunted this effect, with onset of heaviness requiring greater IAP. IAP was increased by knee Extension and SLR, with the lowest pressure in a position of slight Flexion¹⁷. In other studies inhibition has been found to vary with different knee angles⁹⁹, however normal motor pool activity alters at different knee angles¹⁰⁰. Electromyographic (EMG) activity in quadriceps Vastus lateralis was reduced in both amplitude and muscle action potentials as IAP increased. Deandrade et al concluded that the loss of function related to muscle weakness rather than mechanical effect, with a possible nerve / reflex mediated pathway responsible.¹⁷

In experimentally induced effusions, inhibition has been measured, with a decrease in motor neuron excitability to vastus medialis obliquus (VMO) alone for small effusions (30ml) and VMO, Vastus lateralis (VL) and Rectus Femoris (RF) for larger effusions (60ml)¹⁰¹. Other studies have demonstrated an increase in soleus activity, even with a 30ml experimentally induced effusion¹⁰². Removal of an effusion has been found to reverse Quadriceps inhibition in both postoperative and induced effusions^{19,20,103} and can increase both the quadriceps maximum strength, and its EMG activity¹⁰⁴, again supporting a neural mechanism. Interestingly there may be some pre synaptic contribution to inhibition with experimentally induced effusions, leaving open the possibility of the placebo effect¹⁰⁵.

The mechanism for Quadriceps inhibition is complex. There are afferent, sensory nerve endings/ receptors in many joint tissues including the ligaments, joint capsules that monitor tension, for example Ruffini-like receptors in the cat have been found to respond to changes in capsule tension¹⁰⁶. Tendons and muscle also contain nerve endings with tendon organs and muscle spindles all having effects on the motor pool. For example, stimulation of the ACL and PCL both induce changes in motor activity in quadriceps and hamstrings¹⁰⁷.

There may be a change in inhibition over time with longer lasting effusions, with some studies showing that the inhibition is reduced with chronic effusion²⁸. There may be some accommodation of the joint capsule with time, for example up to 37% change in pressure with the rabbit knee¹⁰⁸, or of the stretch receptors in the joint capsule.

Synovium dependent fluid exchange mechanisms may operate to filter the effusion and reduce the IAP. Inhibition, however, may persist, and result in a loss of quadriceps strength. The consequences of this on function, have been examined with gait²¹, running²², and deceleration type tasks, which are prevalent in sporting activity²³. Palmieri-Smith et al demonstrated altered knee kinetics and kinematics with induced effusions during single leg drop landing tasks. They found that with high grade, induced effusions (60ml), subjects landed with a more extended knee and reduced ability to absorb shock. A low grade effusion (30ml), while reducing EMG activity, did not alter kinematics. From these studies, there may be some implications for the Quadriceps rehabilitation exercise necessary post ACLR. Effusions may be detrimental to the optimal performance and effectiveness of these exercises. However, there is some evidence above suggesting that short lasting inhibition may not have effects on quadriceps rehabilitation, even with a maintained effusion. Supporting this, a further study by Coughlan et al, did not show significant change in running kinematics with induced effusion¹⁰⁹. Likewise, McNair et al showed that isokinetic quadriceps strength reduced immediately after an experimentally induced effusion, but that this effect was cleared after 2-4 mins of submaximal exercise¹¹⁰.

Inhibition has been demonstrated post knee arthroscopic ACLR surgery and one main aim of reducing a post-operative effusion is to increase Quadriceps activation and speed of muscle return and strengthening. Conversely a large and persistent effusion post operatively has implications for strengthening and hence gait and functional tasks. This may be one reason for trying to prevent or reduce effusions post ACLR surgery.

INTRA-ARTICULAR EFFECTS

METABOLISM OF CARTILAGE

A further effect of even short lasting effusions and haemarthrosis, relates to the effect on articular hyaline cartilage in the knee. Several studies have found that exposure of hyaline cartilage to blood can be detrimental to chondrocyte function. This has been found in vitro with long lasting effects on cartilage matrix production after only 4 days exposure¹⁶. While cartilage may behave very differently in vivo, chondrocyte change has been found in even short lasting haemarthrosis in dogs²⁵ and metabolic and oxidative stress may affect how cartilage matrix protein production¹¹¹. This is also demonstrated most clearly by Haemophilia patients, where marked osteoarthritis as the main sequela of knee articular bleeds, although altered muscle function may also be a factor in these patients¹¹².

RANGE OF MOVEMENT

De Andrade found that the knee adopted a position of comfort which was slightly flexed from full extension with a large effusion¹⁷. Extension loss after ACLR can greatly affect long term outcome¹¹³ and incidence of Osteoarthritis¹¹⁴. Maintaining and regaining hyperextension for normal gait is considered a priority, particularly in the very early stage of rehabilitation after ACLR. Flexion range of movement can also be limited in large effusions with subsequent effects on patellofemoral stiffness and quadriceps muscle tightness. This restriction in range of movement may have a helpful function. Rest and immobilisation, or restricting range of movement (bracing) are often used early after injury or surgery to protect injured tissues in the early stage of healing. The restriction in range of movement caused by swelling, may perform this function.

PAIN

The relationship between knee swelling and pain is not clear, and frequently knee effusions and swelling are pain free. Possible mechanisms for pain production relate to the pressure of swelling with stimulation of articular nociceptors or chemical sensitization of nerve endings from the composites of exudate and cells in the swollen tissue.

INTERVENTIONS FOR SWELLING

RICE REGIMEN AND GUIDELINES

There have been many methods employed to reduce intra-articular knee effusion postoperatively, including aspiration and articular drainage. This body of work has focused on physical modalities rather than invasive intra-articular procedures to reduce effusion.

Much research has been done on physical modalities to reduce pain and inflammation (and swelling or oedema). A RICE (Rest, Ice, Compression, and Elevation) regimen has been synthesised from evidence, recommendations were made by a panel of experts based on the available evidence. This has been popularised and is used (or encouraged) almost universally post injury and surgery¹¹⁵. The rationale and evidence behind its use is discussed below.

RATIONALE FOR USE

Ice is a simple modality that has been used for centuries in the treatment of injury and inflammation after surgery. It is thought that reducing temperature will result in less pain, inflammation, tissue damage and thereby improve and speed healing and recovery. The methods of action are thought to involve an initial decrease in bleeding and blood flow (vasoconstriction), a decreased oedema (swelling), a decreased inflammatory response, a decrease in cellular metabolism, preventing secondary hypoxic injury, and finally, a reduction in pain by reducing nerve conduction and receptor firing.^{116 117}

Compression is used after acute injury to stop bleeding. It is also used to increase the hydrostatic pressure in the interstitial space (ISS) (P_i) and to inhibit extravasation of fluid from the microcirculation, which is proposed to reverse the flow of fluid by pushing extracellular fluid and exudate back into the vascular system. In a joint, compression is supposed to increase intra-articular pressure to prevent bleeding into the joint and extravasation of fluid through the synovial membrane, and again to attempt to push this fluid back into the circulation.

Regarding the rationale for elevation, normal body tissue maintains perfusion with blood pressure via cardiac pumping. When a body part is above heart height, blood must be actively moved against gravity and the work of perfusion increases, with potential reductions in local capillary pressures. Elevation proposes to decrease blood flow by decreasing the vascular perfusion pressure. Elevation will also improve venous return from a body part with gravity acting to help the returning venous blood. These two components of elevation aim to decrease the vascular congestion in a body part, thus preventing bleeding and extravasation of fluid into the interstitial space, plus moving fluid out of the interstitial space back into the circulation.

Many textbooks give conflicting advice and optimum regimens for application of P(RICE)¹¹⁸. There is conflicting evidence concerning the optimum dose of Cooling, Elevation or Compression for maximum effects on inflammation. This body of work focusses on Ice Compression and Elevation as modalities. The Rest or immobilisation component of the regimen has not been investigated in this work. In light of this it is worthwhile reviewing the physiological effects of cryotherapy, elevation and compression and some of the guidelines that have been produced. Considering the effects of PRICE on swelling, it is relevant to reconsider the Starling equation and the rationale for PRICE in view of the Starling fluid exchange variables.

THE STARLING EQUATION AND THE RATIONALE FOR RICE

It may be useful to review aspects of the Starling equation that may be influenced by the above modalities. Capillary pressure (P_c) may reduce, with a reduction in blood flow by using ice or compression. Elevation of a body segment above heart level will also reduce P_c , by elevating a body segment above the heart, also aims to assist the venous drainage. The interstitial fluid pressure (P_i) will be raised by compression, which also aims to reduce the extravasation of fluid and plasma from the postcapillary venules. A reduced plasma proteins extravasation to the ISS should presumably reduce the Interstitial COP (π_i). The plasma COP (π_p), however, may also change during the inflammatory response, given the change in the composition of plasma during inflammation. The other factor that may be influenced by RICE is the lymphatic flow to return fluid and extravasated proteins to the circulation. High levels compression may reduce lymphatic flow and compromise the ability of the lymphatics to help resolve oedema in inflammation. It should be noted however, that almost no studies measure or even consider the effect of the RICE regimen on COP or Lymph flow. When considering swelling and oedema formation, the RICE regimen may actually be detrimental to these Starling pressures.

PHYSIOLOGICAL MECHANISMS OF RICE REGIMENS

ICE – COOLING/ PHYSIOLOGY AND MECHANISMS

COLD - TEMPERATURE EFFECTS AROUND THE KNEE

During cooling, the temperature changes in tissues due to conduction, as heat moves from tissues to the cooling apparatus/ice. There are many factors that affect temperature conduction in tissues, including the ambient temperature, the presence of overlying dressings¹¹⁹, the temperature of the rest of the body and the thickness / depth of the tissue plus the presence of subcutaneous adipose tissue¹²⁰. Skin cools and heats to a greater extent than the underlying tissue.^{121,122} Skin temperature is affected by cooling more than other body tissues, with normal skin temperature around 29.5°C near the knee, and knee intra-articular temperature (suprapatella pouch) 33.7/33.4°C¹²³. Warren et al, in this cryotherapy study, found that skin temperature dropped further and faster than intra-articular temperature. A Japanese study¹²⁴, investigating intra-articular temperature post ACL reconstruction found that the suprapatella pouch temperature dropped further than the intercondylar notch temperature by approximately 3°C in the initial phase. They divided temperature readings with time into 3 phases with a “low temperature phase” where the temperature dropped, a “temperature rising phase” when the temperature started to rise and a “thermostatic phase, where temperature plateaued. In the control group without cooling the temperature started to rise post-surgery and eventually plateaued after 2.9 hrs on average. The plateau occurred much later in the 2 cooling groups, however the plateau or thermostatic phase was reached sooner in the intercondylar notch than in the suprapatella pouch. It occurred after 5.1 / 6.8hrs respectively for the 5°C cooling group and 4.9 / 6.1 hrs in the 10°C group.

COOLING - VASCULAR EFFECTS

One of the primary effects of cooling is thought to be a change in blood flow. Cold application initially results in vasoconstriction of blood vessels, and it is thought that this reduces haemorrhage and perfusion, and thus decreasing oedema¹²⁵. A vasoconstriction response in microcirculation is shown in the skin around the knee with cooling by commercially available devices¹²⁶ and this vasoconstriction and reduced blood flow lasts for a period even after the cooling device is removed. Blood flow reduction was also demonstrated by Abramson et al in the upper limb¹²⁷, with a study using plethysmography. Ho et al used bone scan scintigraphy to measure knee blood flow in deeper tissue, with a finding of reduction in blood flow of by 19% for a 20 min ice application.^{128,129} It is important to note however that many of these studies did not measure ISS volume. They do not split blood flow response between microcirculation and arteries and arterioles and it is not fully clear which vessels contribute most to this response. They did not measure during a post-injury or surgery inflammatory response when vessels are more likely to extravasate fluid to the ISS. A reduction in blood flow may not necessarily signify a reduction in extravasation of fluid from plasma volume and may not hence signify a reduction in swelling or oedema. For example, if arteriolar blood flow is reduced, there may also be a reduction in lymphatic flow, which may mean that fluid balance may remain static and ISS volume does not change. It should be noted that there are multiple control mechanisms to maintain microcirculation in many states of heat and cold.

Some studies, however, have shown a return of blood flow with more prolonged cooling (30 minutes+) even in an inflammatory situation like an induced burn¹³⁰. A vasodilation response to prolonged cooling is shown in some body tissues. This may be related to a reactive hyperaemia¹³¹, and has been termed the “hunting response”, and “cold induced Vasodilation (CIVD)”. This response was thought to occur after 5-10 mins, and at temperatures below 15°C¹³¹. It was thought that this response was consistent with all cooling, in all tissues, and it is one

of the main justifications for recommending the intermittent rather than continuous use of cooling for tissues. This response has also been used to justify the timing (dose) of cooling applications. Not every person responds in this way¹³² and many studies have failed to show a Hunting response. Including for knee, and in spite of using cooling times longer than 30 mins¹²³. This leads some authors to question the existence of the hunting's response. It has been found, however, that the response is confined to extremity areas of the skin¹³³ and that other areas of skin or deeper tissues in the body respond to cold without this vasodilatation CVD, although this has been investigated very little in deep tissue post injury.

Some authors suggest the mechanism for CVD relates to the flow of circulation through arteriovenous anastomoses present in these skin areas. The CVD mechanism may be to prevent cold induced injury in more exposed skin areas¹³⁴. Many studies have investigated Upper limb – hands and fingers / extremities as these are more convenient to examine.

COOLING- NEURAL EFFECTS

There is a large body of evidence to support a reduction in pain with cooling of body tissues¹³⁵¹³⁶¹³⁷, including arthroplasty¹³⁸, arthroscopy^{139,140} and ACLR¹⁴¹. It may be pertinent to note, however, that many factors influence pain levels and it is well known that pain is particularly susceptible to the placebo effect¹⁴².

Cooling has an effect on nerve conduction, with a change in nerve conduction as the cooling affected the nerve fibre membranes¹⁴³. Nerve conduction velocity is reduced more in more superficial nerves, and sensory nerve fibres seem to be affected before motor nerve fibres¹⁴⁴. Small myelinated fibres are affected before large myelinated fibres and unmyelinated fibres are affected last. Nociception is predominantly conveyed by unmyelinated C fibres, suggesting it may take longer exposure to reduce their firing and potentially modulate pain.

Studies show variable response of the effect of cooling on pain and conduction levels. The magnitude of this response has been reported at 18.3% reduction in conduction velocity after 16 mins of ice therapy to ulnar nerve at the medial elbow.¹⁴⁴ Stillwell quantified this response at 0.4mm/s reduction in conduction velocity for every 1° C of cooling.¹⁴⁵

The threshold required for effects on conduction was 27°C¹⁴⁶ and analgesia started at 13.6°C¹⁴⁷. De Jong et al reports that nerve conduction ceases between 9-18°C^{143,148}, and the time required to reach this temperature was found to be 9 minutes with an ice pack^{148 149} and 12-15 mins of intense cold therapy after injury^{150,151}. Vangaard found that the threshold for nerve conduction effects was 7–8°C¹⁵².

The temperature required for return of conduction was found to be at 15.6 °C¹⁴⁷, with a residual nerve effect lasting up to 30 mins¹⁴⁴. Different modalities of cooling also have different effects on nerve conduction velocity, with cold water immersion found to have the greatest reduction in conduction velocity¹⁵³.

Some cold applications can be painful. Abramson hypothesises a possible vascular mechanism for increased pain with cooling¹⁵⁴, however, this may relate more to skin tissue, possibly related to anastomoses, and vasoconstriction.

Arthrogenic muscle inhibition is also thought to involve a neural mechanism and there is evidence for cryotherapy reversing the Quadriceps inhibition found with effusions¹⁵⁵⁻¹⁵⁷.

COOLING - CELLULAR / METABOLISM EFFECTS

A further claim of cooling in injured tissues relates to a reduction in cellular metabolism to decrease the secondary ischaemic damage to cells.^{158,159} Cooling may slow or shut down the metabolic processes in a cell to decrease its energy demand during damage and inflammation.^{150,160}

Cooling is used to preserve and assist cellular recovery with cryogenics in cryopreservation for reproductive medicine or allograft tissue¹⁶¹, and cooling during cardiac surgery to minimise the body's cellular demand, with the reduction in cardiac output during surgery. This has been used in head injury and cardiac arrest to minimize cellular death^{162,163}

Zachariassen, quantified the reduction in enzyme activity with cooling, finding a 50% reduction in enzyme activity with a 10°C drop in temperature¹⁶⁴. Adenosine Triphosphate (ATP) demand has also been found to decrease with cooling¹⁶⁵

Abramson noted a decrease in oxygen transport in areas treated with ice¹⁶⁶. Olsen and Stravinho in a study on brain blood flow found that venous blood had higher O2 saturation after cooling¹⁶⁷. To quantify the effect on cellular metabolism, Sapega found that the tissue temperature had to be around 10°C.¹⁴⁹

Other studies, however, suggested it took some time to reduce temperature sufficiently for cellular metabolism effects.^{147,148} It should also be noted that there is also a risk of cold injury or damage if cells are exposed to cold for too prolonged a period or too low a temperature, for example frostbite. There are multiple reports of this in the literature with cold induced injury produced by therapeutic application¹⁶⁸⁻¹⁷². This cold injury may actually cause damage inflammation and oedema – particularly in skin and subcutaneous tissue.¹⁷³

COOLING – EFFECTS ON JOINTS

Several studies have looked at blood flow effects in joints with cooling. In an animal study, Cobbold et al investigated knee blood flow and temperature in dogs, with finding of vasoconstriction and decrease in the intra-articular temperature.¹⁷⁴

In an ACLR drain study, using cooling pads inside knee dressings, Okhoshi et al found that pad temperatures of 5°C and 10°C produced different amounts of blood loss post operatively, with the 10°C group showing no significant difference from control (non-cooled) group.¹²⁴ The numbers in this study (n=7) for each group may however present too low a sample size to draw full conclusions.

Ho et al used tripple-phase technetium scintigraphy to investigate knee blood flow during cooling, using a 20 min ice application via a 0-1°C wrap and using the contralateral knee as a control¹²⁸. They found vasoconstriction in both the joint and the subcutaneous soft tissue, with no evidence of cold induced vasodilation. Arterial blood flow decreased by $38.4\% \pm 4.97$ (8.0% to 73.0%). Soft tissue blood flow decreased $25.8\% \pm 2.04$ SEM, (7.2% to 44.7%) and bone uptake reduced by $19.3\% \pm 2.0$ SEM (4.0%-37.9%). A further study by Ho et al investigated the optimum cold regimen for lowering knee temperature¹²⁸. They found that at lower temp there was less blood flow on all 3 phases of the bone scan with bone phase blood flow less at 5 and 10°C. It was not clear, however, if this changed lymph flow, ISS volume or fluid exchange. It was also not clear if the reduction in blood flow related to the microcirculation or higher order vessels (i.e. arterioles). It should be noted that there are multiple control mechanisms to maintain microcirculation in many states of heat and cold.

The Vascular response in a limb may relate to alterations in central blood flow and core temperature. In another study Abramson warmed the body (central) with heat packs during cold application in the forearm (peripheral), and found the blood flow was not as effected by

the cold application.¹⁷⁵ Body exercise and movement also had a positive effect, with faster recovery of blood flow after cooling (peripheral) if the subject exercised the body (central).¹⁷⁶

SAFETY REGIMEN OF APPLICATION OF COOLING

There is some evidence of detrimental effects of cooling. To obtain greater cooling of deep tissue means that skin and more superficial tissue is cooled to a greater level. Several authors report clinical incidences of skin ice burns or frostbite injury from ice or ice packs^{168,172,177-181}, even with as little as 30 minutes of application.¹⁷¹ Lower temperature cooling, therefore, may help deeper injured tissue, but may produce cold injury to more superficial structures that are cooled to a greater degree.

Matsen et al used an animal study on rabbits with hind limb tibial plateau fractures. They cooled to much lower temperatures, and showed that, while deeper tissue showed improvements the superficial tissues and the limb as a whole showed increased oedema. This occurred in temperature ranges from 5-15°C¹⁷³. Parry and Prentice et al reported a similar finding with injured radiocarpal ligaments in pigs, finding that the ice compression treated limbs had more swelling generally, but better microscopic ligament status¹⁸².

Several authors report injuries to nerves with cooling in temperatures from 0-8°C, with motor function dropping prior to sensory functions and superficial nerves are more susceptible where subcutaneous fat levels are low. There are several reports of injury to common peroneal nerve after cryotherapy to the knee at temperature of °C.^{183,184} Bassett describes several cases with nerve injury taking several months to recover, with an average threshold cooling time of about 20 mins¹⁸⁵ and there is report of nerve enlargement (oedema) even after a single upper limb application of 15 minutes cooling¹⁸⁶.

There is a risk that this may occur following ACLR. To obtain a deep tissue/ intra-articular cooling of 10-15°C would require cooling of the skin, to temperatures of approximately 5 °C,

or possibly lower, according to Warren et al's data, with subsequent risk to skin and common peroneal nerve¹²³. Optimum temperatures for safety and effectiveness would seem to be not less than 15°C at the skin to avoid injury, but with intra-articular temperature as close to the 10- 15°C as possible.

Warren et al, used an ice bag and Cryocuff on normal knees, they found that after just more than a 1 hour application, the ice bag knees had an intra-articular temperature of around 20°C but a skin temperature of below 5°C which may put the tissues or superficial nerves at risk¹²³. The Cryocuff knees had an intra-articular temperature of around 25°C with a corresponding skin temperature of 15°C. This may represent a safer situation for knee cooling, particularly in those who have little subcutaneous fat.

Wound infection may be a further risk with cryotherapy postsurgery, where there are surgical skin wounds. This has been reported as a risk with cryotherapy in total knee replacement¹⁸⁷ and abdominal surgical wounds¹⁸⁸⁻¹⁹⁰. The application of wet cooling, is normally avoided, as dressings can moisten and the risk of transfer of infection can increase. Dry methods of cooling with closed cooling devices are often preferable when cooling over surgical wounds. It may also be noted that capillary microcirculation and partial oxygen pressure in subcutaneous bed can relate to occurrence of postoperative wound infections.^{191,192} Cryotherapy to reduce capillary circulation may have a detrimental effect on the partial pressure of oxygen, and negative effects on wound healing.

Cooling may also adversely affect the function of platelets possibly compromising clotting and haemostasis. There has been some debate about the appropriate level of cooling after acute bleeds in literature related to Haemophilia¹⁹³⁻¹⁹⁶. This is important post ACLR when there is an initial haemarthrosis and postoperative bleeding into both the joint and extraarticular spaces.

COMPRESSION AND ELEVATION -MECHANISMS- PHYSIOLOGICAL EFFECTS

Normal capillary and perfusion pressure in microcirculation depends on blood pressure with normal resting diastolic Blood pressure between 60-80mmHg and 90mmHg and systolic pressure between 90mmHg and 120mmHg¹⁹⁷. Blood Pressure varies considerably, even from heart beat to heart beat, and is influenced by many factors including age, sex, activity, posture, mental state, gravity, temperature, nutrition, obesity, medication and trauma.¹⁹⁸⁻²⁰¹ Physical factors include: - Heart rate, stroke volume, vascular or tissue resistance, blood volume and viscosity. Vascular pressure in arteries reduces with distance from the heart, and further reduces through the smaller arterioles and capillaries. Capillary pressure varies through a capillary and has been found to vary at different ends of the capillary from 45-35mmHg at arteriole end to 12-15mmHg at the venule end of the capillary loop for a heart level finger capillary.^{202,203} These pressures increase with lowering below heart but not as much as the arterial pressure, indicating some modulation of pressure effects with gravity i.e. collateral circulation, or control of flow to ensure tissue perfusion²⁰⁴. The arteriolar tone increases or decreases to counteract the gravity effect and maintain microcirculation perfusion.

It is possible to compromise microcirculation however, and Some studies, have found that an external pressure of 10-25 mmHg is sufficient to cause venous occlusion in deeper tissue such as muscle ²⁰⁵. Elastic leggings can exert a greater occlusion effect when a person is in lying, with a finding of pressure >20mmHg causing occlusion.²⁰⁶ Tourniquet type compression in a limb is known to cause filtration more distally and this can occur at pressures as low as 40cmH₂O for an upper limb. The rate of swelling in the forearm at this pressure was found to be 0.003ml/min/100ml volume (capillary filtration capacity)⁵⁸

The amount of capillary absorption versus filtration to the interstitial space (ISS) varies in different tissues and this flow is also influenced by the protein concentration and COP in the plasma and ISS and these are rarely measured or even taken into account in many studies investigating swelling. Note that, in a steady state, there is normally no absorption of fluid back into the venule side of the capillary, although, this varies in some tissues including synovium. This may be due to differences in the fenestrations in the capillary walls in these tissues.^{57,204} Approximately half of the capillaries in synovium have fenestrations on the intra-articular side of the capillary, allowing for a different response to compression in synovial joint cavity than the extra articular tissue.

In a rabbit knee study, Levick et al investigated the pressure effects of intra-articular infusion ofringer solution into the synovium of a rabbit knee. They found no consistent relationship between the synovial volume and the articular pressure, indicating some fluid exchange mechanism to reduce pressure over time. Capsular hysteresis may be one explanation for this, with capsular and connective tissue compliance partly responsible for intra-articular pressure over time, however, Synovium may have tissue exchange capabilities that alter at different intra-articular pressures.

Another factor which is often not considered in most RICE studies is lymphatic flow. If compression is sufficient to block lymphatic flow, the compression may compromise the ability to resolve the swelling in the ISS. Meussen et al investigated lymph flow at the ankle in healthy volunteers with Lymphoscintigraphy and flow of a colloid tracer with labelled albumin²⁰⁷. They used a Cryocuff to apply compression and cooling, and investigated different temperatures and amounts of compression. They found that lymph flow increased with the application of cold and pressure. They measured pressure however at the lateral malleolus and the pressure did not exceed 25mmHg. It is therefore not be possible to extrapolate these results to other joints or situation post injury or surgery.

There are some mechanisms whereby compression may actually increase swelling²⁰⁸. There is a known “rebound phenomenon” in lower limbs where swelling increases as a person goes from recumbent to upright. Some guidelines have suggested that combining compression and elevation can cause this effect (PRICE guidelines for treatment of soft tissue injury)¹¹⁵. In the “rebound effect” the microcirculation dilates in elevation when the articular pressure in the limb drops, to ensure sufficient tissue perfusion.^{209,210} Nielsen et al found that 40–50mmHg pressure with an intermittent compression device caused arteriolar dilatation under the area of compression²⁰⁹. They found that a proximal pressure of 66-70mmHg (i.e. up to diastolic pressure) had a further effect on distal blood flow. 10-40mmHg resulted in significant ($p<0.005$) decrease in blood flow, but they found a compensatory arteriolar dilatation, pointing to an autoregulation of blood flow.^{155,156} Guidelines, therefore, recommend avoiding high proximal-distal pressure gradients. Many compression bandages or devices such as the Cryocuff may apply proximal-distal pressure gradients, thereby causing a tourniquet effect. The amount of proximal-distal compression applied by many devices has not been measured.

On standing, vascular pressure in the limbs increases, and vascular pooling results. This arteriolar dilatation has been documented in muscle by Murthi et al²¹¹. In a clinic study on treatment with elevation post ankle sprain, ankles were found to return to a swollen state within 5 mins after returning to the dependent position²¹².

Guidelines place a lot of weight on the recommendation to avoid combining compression and elevation based on one study in particular by Rucinski et al²⁰⁸. They investigated the application of compression in lateral ankle sprains, using 3 (n=10) groups with 30 minutes of :- elevation 45° + elastic bandage, elevation 45° + intermittent compression device, or elevation 45° alone. They measured swelling with water volumetry and found an increase in oedema in both of the compression groups, with the intermittent pressure pump group having the greatest increase in volume. There were several methodological limitations,

however, suggesting the groups may not have been equivalent at baseline, and great variability between subject responses. Measuring with water volumetry may be a better measure of volume than skin girth, but it may not be appropriate to apply this as the gold standard measure for volume and this measure comprises some error²¹³. Kerr et al, suggest, from the results of this study, that elevation and compression should not be applied together. They suggested that compression has its most beneficial effect when the limb is not elevated¹¹⁵.

Airaksinen et al, investigating post ankle sprain, found that a sustained compression group had less oedema at 1 and 4 weeks post sprain, than a once daily intermittent compression group²¹⁴. The acute situation post injury may produce different responses than a sub-acute or chronic phase.

There were very few studies to investigate the effect of compression on the knee, especially with an acute injury and haemarthrosis. In a muscle study Thorsson et al investigated 40 athletes, with immediate (within 5 minutes of injury) compression onto an acute muscle injury vs rest and elevation only. They found no difference in range of motion, serum Creatine Kinase, and ultrasonic scan outcomes²¹⁵.

This literature may have implications for my work, as cold compression devices (like the Cryocuff), when filled, exert some external pressure on the knee cavity. There is currently no study that has quantified the pressure exerted on the joint by these cold compressive devices such as the Cryocuff. This may vary in different parts /compartments of the knee. If this pressure is beyond 25 mm Hg there may be some implication for compromise of tissue microcirculation and perfusion. If the Cryocuff is used in elevation, there also may be an implication for collateral circulation and a possible “rebound effect” may be set up, actually causing more swelling!

OPTIMUM REGIMEN FOR REDUCING SWELLING IN THE KNEE AFTER ACLR

REVIEWS AND GUIDELINES

Many reviews of the literature have been performed relating to components (or combinations of components) of RICE in the treatment of inflammation in various clinical populations after injury or surgery^{118,150,165,216-228}. Most reviews relate generically to soft tissue injury, but there are also several reviews specific to knee surgery, and more specifically total knee arthroplasty^{187,229} and ACLR²³⁰⁻²³². They have more frequently focussed on the use of Ice and cooling after injury or surgery.

Most reviews have investigated the use of ice but few have reviewed the use of compression or elevation alone, and where they have, Compression and elevation are usually investigated in combined with cooling in many reviews and their individual effects are not clarified or examined.

The reviewed studies comment on multiple outcomes but the most frequent are;- pain , range of movement, speed of recovery, function, medication use, blood loss, and swelling or oedema.

Only several reviews or meta-analyses have used methods to evaluate the quality of the studies they review. Some use a measurement tool of quality such as the PEDro score²³³ or the Cochrane Risk of bias tool²³⁴. In these reviews, there were many methodological limitations found in the studies. The most common were: - poor supply of baseline subject data, poorly concealed allocation during recruitment, inadequate randomisation processes, insufficient blinding of subjects or therapists or raters, lack of information on subject drop out or lack of appropriate methods to deal with missing outcomes.

With respect to ACLR, often the subject sample numbers were small and some studies were underpowered. For outcome data, few studies had longer term follow up beyond 6 weeks. Pain was the most frequent measure, with very few studies measuring swelling or oedema. When swelling was measured, the method for measuring swelling was almost universally a limb girth measure using a tape measure and this was never normalised to leg or body size. It is not clear that limb girth relates to intra-articular effusion. Surgical outcomes were frequently not provided, and anaesthetic outcomes such as blood pressure, IV fluid given or the status of hydration of the subjects were not given in any study. For the interventions applied, the temperatures and pressures that the ice or cooling devices delivered to the tissues (superficial or deep) were rarely measured or reported.

Many reviews aim to synthesise an optimum regimen for the use of ice compression and elevation (dosage) but frequently the authors recommend very different modes, durations and frequencies (dosages) of use (particularly of ice)^{118,235,236}.

Guidelines have also been developed based on expert consensus after study of the available literature evidence. Initial guidelines were produced in 1998¹¹⁵. Due to the conflicting evidence, they give recommendations based on general principles rather than specific optimal dosages. Several caveats are given for safety or application of ice and compression, including that compression and elevation not be combined- as one study in the ankle found that this increased swelling. Due to evidence of a “rebound effect” they also recommended that the limb be gradually lowered to a dependant position after elevation. Many of the recommendations, however, relate to consensus statements where the literature evidence is sparse. They state in their conclusion that “in view of the surprisingly limited amount of evidence in the literature to support definitive guidelines for the PRICE regimen, it is apparent that further research is necessary to provide that evidence.”

A further guideline was produced in 2010 with an updated review of literature published since the initial guideline²³⁷. The strength of the working group's recommendation was graded based on the strength of evidence for each component of the RICE regimen. A GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach was followed to obtain consensus²³⁸⁻²⁴⁰, and the studies selected were evaluated with the Cochrane risk of bias tool²³⁴. In the panel consensus, they were able to make definite recommendations on levels of protection/ rest and mobilisation. They reported the literature was strong on ice and cooling having and analgesic effect, but reported the literature was only moderate to weak on the effect of ice, compression and elevation to reduce swelling and oedema. With low quality evidence only, and a high risk of bias in the studies reviewed.

Many of the reviews and guidelines do not address swelling specifically but address it as one of the overall aims of the PRICE regimen.

Very few of these reviews consider vascular physiology of fluid exchange, in spite of this being integral to swelling and the inflammatory response.

OPTIMUM REGIMEN OF APPLICATION - COLD

It would be useful to have recommendations on specific optimum dosages for cold application, however trying to synthesise these from available literature has proved difficult. Optimum dosage will vary depending on body area/ tissue / general state of body – temperature / movement, / depth of treatment, and status of tissue or stage post injury / surgery. It will also vary depending on the aim of cooling. This study focuses on the knee joint, specifically post ACLR surgery, with both articular and bony components to the surgery

requiring a deep cooling effect. There is insufficient evidence to outline an optimum cooling regimen generally post injury, however there less sufficient evidence relating to the knee and specifically post ACLR. The below sections summarise literature findings for effects of cold generally and that of the knee post ACLR specifically.

There are many methods used to apply cooling / ice to a joint or limb. Ice towels/ cold water / cold sprays /. Ice may be crushed or whole, with or without a barrier between ice and the skin. Merrick et al assessed temperature at the thigh after application of crushed ice bags vs commercial ice packs and gel packs with a 30 min application¹²⁰. There was only a small difference found between skin temperature with ice packs and gel packs. A further study compared Gel packs with frozen peas with a 20 min application²⁴¹. The frozen peas were found to be more effective with the skin temp of 10.8 °C vs 14.4 °C for the gel pack.

Warren et al studied knee skin and intra-articular temperatures in normal subjects using an Ice bag on one knee vs a Cryocuff device on the other knee¹²³. They used a one hour application and continued measuring temperature for one hour after removal. They found skin temperature to be consistently lower than intra-articular temperature. The ice bag cooled faster and to a lower temperature than the Cryocuff. While the knees rewarmed after removal of the cooling, the cooling effect from both the ice and the Cryocuff lasted for greater than an hour after removal.

Moisture in the barrier between ice and skin lowers temperature faster due to conduction. Lavelle and Snyder compared ice application with wet and dry towels on skin versus ice applied directly to skin. Ice applied with a wet cloth and applied directly were found to be most effective methods for cooling tissues. Ice with wet towel produced slightly lower temperatures but these were not found to be significant²⁴².

Dykstra et al used different states of ice to compare a 20 minute application, measuring every 30 seconds, and found that wet ice lowered temperature more than cubed or crushed ice²⁴³.

Barriers between ice and skin will also have an effect to protect against infection and damage of frostbite or ice burn, but they may also decrease the effectiveness of the cooling¹¹⁹. Maximum cooling, therefore, takes place with crushed or wet ice applied directly to skin, which more effectively lowers skin and subcutaneous temperature than gel or ice packs, or cryotherapy devices, however in a postsurgical model dry cooling may be more appropriate, as wet cooling may carry risk of infection to surgical wounds.

INTENSITY (TEMPERATURE)

In a review of the literature on cold effects, Greenstein suggests some target temperatures for the effects of cold, based on available physiological evidence. Normal skin temperature is 29.4°C. Normal joint temperature is 33°C¹²³, with knee intra-articular temperature 37.3°C²⁴⁴. For pain relief, nerve conduction velocity starts to reduce at skin temperatures of 27°C, and complete analgesia is produced at 13.6°C¹⁴⁷. Blood flow was found to reduce at 17°C in skin²⁴⁵, with temperatures of 5- 10 °C sufficient to cause changes in bone blood flow in the knee.¹²⁸ Limb oedema was found to reduce when local temperatures were lowered to between 12.8°C and 15.6°C after hind limb injury in rats¹²⁵, but was found to increase in limbs cooled to 5°C¹⁷³. Cellular metabolism was reduced at temperatures between 10-15°C in a review on limb transplantation¹⁴⁹. Enzyme activity was found to reduce at 30C²⁴⁶

TARGET TEMPERATURES SPECIFIC TO THE KNEE JOINT

There are few studies that address threshold levels of cooling at the knee for analgesic effects post ACLR surgery. Analgesic effects however may be expected to occur at the above threshold temperatures of 27°C (intra-articular knee joint) and 13.6°C (skin). Blood flow has been investigated specifically for the knee²⁴⁷, with reduction on blood flow found even as deep as bone, with corresponding lateral retinaculum skin temperatures of

between 9 and 20 °C. Cellular metabolism would seem to reduce at 10-15°C, however target cells are deep in the knee (including bone, as the surgery involves both tibial and femoral bone tunnels). Enzyme activity would also reduce at 30°C. While evidence for optimal dose of cooling is insufficient, available literature would suggest that a decrease inflammatory response would require intra-articular temperatures of between 10°C and 15°C. Ohkoshi et al, in a study investigated a Japanese cooling device post ACLR, with cooling pads in the dressings around the knee, measured immediately post tourniquet release and over an applied elastic bandage. They found that the application pad temperatures of 5° C and 10°C (corresponding to Supra patella pouch (SPP) / intercondylar notch (ICN) temperatures of 30.9°C/33.9°C and 32.1°C/34.3°C(respectively), and produced significantly different amounts of blood loss in the initial 48hrs post ACLR. The 10°C group showing no significant difference from control (non-cooled) group (SPP and ICN temp of 37.3°C/37.3°C. This would suggest that a lower temperature for cooling has a greater effect on blood loss post ACLR, and that intra-articular cooling post ACLR must go at least beyond 32.1°C/34.3°C for SPP and ICN respectively to have an effect on blood flow. The cooling effect prior to plateau temperature lasted >6 hrs for SPP and 5hrs for ICN for cooling groups with control group reaching plateau temperature in 2.9 hrs , however it was unclear whether cooling liquid was changed in the equipment. The numbers in this study (n=7) for each group are quite low.

FREQUENCY

There is some debate about whether cold should be applied continuously or intermittently. There has also been some concern about possible detrimental effects of sustained cold on tissues. Per the safety section above, intermittent application would seem more appropriate considering that many of the applications causing ice burns were longer than 30 mins.

DURATION (TIME)

Merrick et al, looking at thigh skin temperature, found that it only took 10-15 mins for ice to cool skin to 10 °C¹²⁰. Hocutt et al looking at skin temperature at the ankle describes timings for cooling with 1-3 minutes for the sensation of cold, 2-7 minutes with an aching burning feeling. After 5-12 minutes, a local numbness was experienced, and finally a deep dilation of blood vessels²⁴⁸. A cooling time of at least 12 mins would seem appropriate.

The hunting response (CIVD) was found to begin at 20 – 30 mins post start of cooling. This has typically been one argument for not extending cooling beyond 20-30 minutes, as it was felt that cooling would be less effective when CIVD occurs at 20-30 mins. These CIVD studies relate to skin but not to knee cooling, however, and it is not possible to extrapolate these recommendations to the knee joint. Warren et al found the drop in intra-articular knee temperature to occur rapidly with use of both ice bag and Cryocuff device. The cooling effect showed no CIVD rewarming effect and cooling continued to increase through the one hour application, with the effect continued to last, even one hour post removal ¹²³

OPTIMUM DOSE COOLING – SUMMARY

Optimum temperatures for safety and effectiveness would seem to be not less than 5 - 10°C at the skin to avoid injury but with intra-articular temperature as close to the 10 - 15°C as possible.

To be safe cooling over superficial nerves should avoided or kept to mild levels of cooling. Wet cooling should be avoided post surgically, and a barrier should be used to keep wounds from infection risk. Intermittent application should be considered for safety but continuous application may not risk causing a CIVD response in the joint.

OPTIMUM REGIMEN OF APPLICATION COMPRESSION AND ELEVATION

There are many methods used to apply compression to the knee. A Robert Jones bandage is used commonly, immediately after knee surgery as a simple non expensive way to control swelling.²⁴⁹ The Cryocuff will also apply some compression, however, the levels of pressure applied to the knee by these bandages and devices have not been quantified, and may vary between applications. A study by Gibbons et al, looking at 2 groups post total knee replacement, found no difference in range of movement, pain scores and need for analgesia between a Robert Jones group and a Cryocuff group. They did, however find a significant difference in the knee drained blood volumes, with the Cryocuff group less²⁵⁰.

Based on the literature reviewed, in an optimal regimen to manage swelling post ACLR, Elevation should be as far above heart level as possible but it is unclear if it should be intermittent or continuous. Compression should probably not be used with elevation. Compression should not be applied proximally to distally, and not applied for long periods. Due to the “rebound phenomenon”, lowering the limb after elevation and removing compression should be done gradually to avoid an increase in swelling. Compression to the treated tissues should probably not exceed 20-25mmHg, as amounts beyond this may compromise venous return and cause a possible ischaemia, but even pressures lower than this may cause venous occlusion in certain positions or tissues. Venous occlusion applied to a limb via a cuff or tourniquet may also be detrimental as this will increase capillary filtration distal to the applied compression and increase swelling. Therefore the optimum amount of compression post-surgery to minimise or treat knee swelling after ACLR (or indeed any other soft tissue injury) cannot be elucidated from current literature. There is sufficient evidence to suggest that if compression is applied incorrectly it may cause an increase in swelling, which raises the question of whether compression should be used at all to treat swelling. Vascular physiology of Starling pressures should be taken into account – particularly colloid osmotic

pressure. The role of the lymphatic system should also be taken into account, as compression may have a role in clearance of lymph. Further research is required before being able to give recommendations on optimal compression for managing lymphatic clearance and colloid osmotic pressure.

GENERAL THESIS AIMS

This body of work aimed to measure knee swelling, pre and post-operatively, after ACLR, using a Perometer (an infrared volumetric device, found to be valid and reliable for measuring knee volume), and a clinical knee swelling test – the stroke test. The initial studies aimed to compare the use of Cryocuff, and elevation, with standard treatment used at an NHS knee unit (compression bandage with no elevation, no cooling).

Secondary outcomes were also measured to assess the correlates of knee swelling in ACLR, and the relationship of swelling to outcome after ACLR

Further work aimed to measure and quantify the amount and distribution of interface pressure around the Cryocuff device and to ascertain its relationship to physiological variables in the limb (blood flow/ blood pressure) in postures of standing, elevation and supine lying. A schematic diagrammatic overview of the work is outlined in Figure 7.

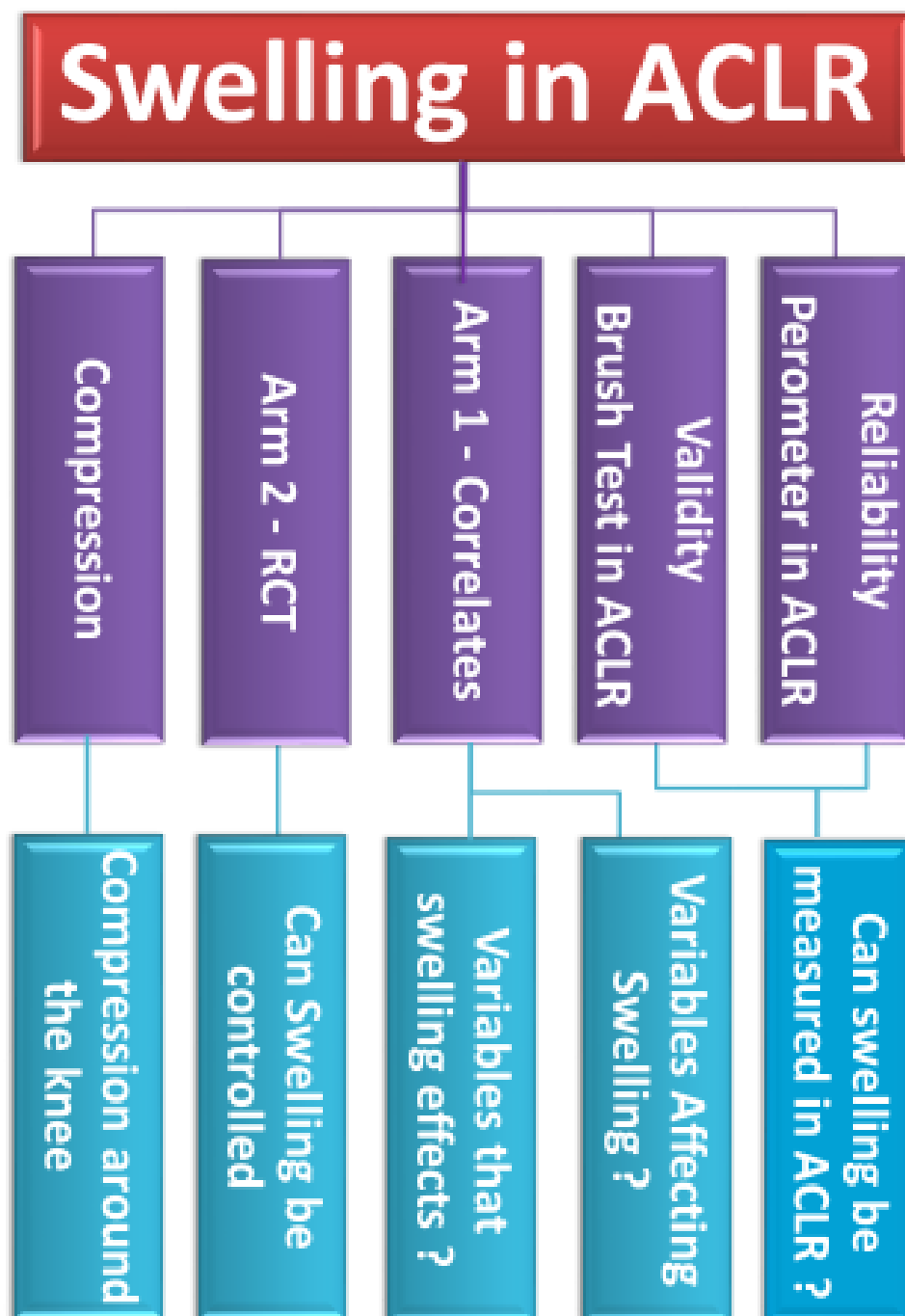


Figure 7 - Diagrammatic outline of the Thesis aims and questions

OUTLINE OF CHAPTERS

This thesis therefore commenced with assessing measurement of swelling in the knee after ACLR and refined a measurement reliable measurement method. This work is reported in Chapter 2 , which also reviews available methods of measuring swelling, and considers the reliability and validity of the device chosen for measurement of knee volume and swelling in this body of work (the Perometer (350S, Pero-System, Wuppertal, Germany)). Both instrumented and clinical methods are discussed and investigated.

The question of intervention to prevent or treat swelling in ACLR, is dealt with in Chapter 3 which reports a study investigating a commonly used intervention for swelling after ACLR. The chapter covers the methodology, sample and the variables measured in the clinical study on a sample of ACLR patients. With description of the primary and secondary measured variables and the methods utilised to measure them. The interventions used in the randomised controlled trial are also outlined.

Chapter 4 covers the results of a further study, on the same sample of ACLR patients, investigating a series of pre, peri, postoperative and outcome factors that were predicted to associate with knee swelling in ACLR. The chapter discusses some of the possible mechanisms behind the associations (or non-associations) found.

Chapter 5 outlines a mechanism based study on Healthy volunteers investigating the levels of compression delivered to the knee by two devices that are commonly and globally used in ACLR. The study investigates compression and evaluates the level and profile of the interface pressure that these devices actually deliver to the knee. It also investigates some of the associations found in chapter 5 and some of the potential underlying mechanisms.

Chapter 6 gives summary discussion and final conclusions to the body of work.

This work was originally undertaken solely for the degree of Masters in Philosophy. The initial bodies of research and clinical trial work in Chapters 2-4 were undertaken for that degree as a final end-point. After Thesis submission, viva examination and award of the degree of MPhil, and after formal review, an offer and decision was made to carry the work on and enrol for the degree of Doctor of Philosophy. The fifth Chapter forms, in large part, the follow on work for this higher degree. The thesis should be read with the understanding that initially, it was undertaken for the degree of MPhil alone. This is why the larger clinical trial was undertaken first rather than a series of mechanism based or methodological research studies prior to the clinical trial work. The enrolment into the degree of Dr of Philosophy allowed follow up work to investigate the findings in the clinical studies and to investigate several possible mechanisms and explanations for the results.

INTRODUCTION

Swelling is one of the key components of the inflammatory response to injury or surgery, and any measurement of inflammation should encompass a method of measuring swelling and oedema. Clinically it should be monitored throughout rehabilitation in order to dose progression in rehabilitation loads correctly. For research purposes it should be measured accurately to determine the effectiveness of treatments aimed at reducing inflammation. It is important, therefore, to have an accurate measure of the volume of oedema or exudate, both in the early stage post-operative or in the later stage throughout rehabilitation. This allows accurate quantification of the effectiveness of interventions to limit or treat swelling, but also allow a method for pacing or dosing levels of rehabilitation based on inflammatory swelling or effusion in the knee. It may also allow safer progression of treatment as there can be negative effect of knee joint effusion on quadriceps inhibition. Progressions could be modified based on the effusion size and the presence of quadriceps inhibition. It would therefore be valuable to have precise measures of swelling or knee effusion but it is important to correlate “high-tech” measures with “low-tech” clinically applicable tests that are simple and easy to apply whilst remaining accurate.

It has proved difficult to find a valid and reliable method of measurement of knee swelling and oedema. Much of the literature on limb volume measurement has come from Lymphoedema research with whole limb volume measures²⁵¹. Swelling and oedema have often been measured after lower limb orthopaedic surgery but only one review has commented on the validity or reliability of the measurement swelling and oedema of the knee after ACLR²³⁰.

The most commonly (only) reported measures in the literature after ACLR (see table 1) have been : - the use of either tape measurement of knee girth ^{140,252,253}, or blood and fluid volume loss from intra-articular drainage ²⁵⁴⁻²⁵⁶ or a combination of both²⁵⁷. The insertion of a drain, however, increases the risk of infection and is limited in use to in-patient surgical based settings only. Additionally the insertion of a drain may also impact on normal post-operative intra-articular pressure gradients, and hence affect fluid exchange, across the synovium. It should also be noted that blood loss has not been normalised to body or knee size in any study. Pragmatically, intra-articular drainage is not used for ACLR in our facility, as drains have been found to delay recovery, increase pain and add infection risk for no greater benefit to recovery^{12,258}, and drains were, therefore, not an option in this thesis.

A major problem with measuring swelling in the knee is the evaluation of the contribution to the total volume from within the joint capsule (intra-capsular) compared to extra-capsular swelling. After ACLR, intra-capsular fluid is due to effusion and/or haemarthrosis within the synovial membrane, in addition extra-capsular parts of the knee such as the graft harvest sites of the pes anserine or patella tendon also swell. A whole knee volume measure will encompass both the intra and extra-capsular volume and will not discriminate as muscle and subcutaneous compartments will be included in the measurement. The fluid exchange behaviour postoperatively may differ greatly in each of these tissue compartments. Volumetry will evaluate whole limb volume and aspiration will evaluate intra-capsular volume only, state of the art imaging modalities such as Magnetic Resonance Imaging (MRI) allow differentiation of the intra and extra-capsular spaces. Instrumented measures of effusion can be utilised when reliability is paramount but have the disadvantages of expense and demand based accessibility.

It would, therefore, be useful to have a rapid, convenient measure that could be used clinically to detect intra-articular effusion. There are several tests for swelling that have been described

in knee examination literature This chapter will review the methods of measurement of limb and knee swelling and the method employed in this thesis to measure knee volume will be detailed. The results of a reliability study on a clinical cohort of patients will be outlined and discussed.

METHODS TO MEASURE SWELLING – INTRA-ARTICULAR EFFUSION

CLINICAL INTRA-ARTICULAR TESTS – EXAMINATION TESTS

Clinical tests to detect and grade intra-articular effusion have been described^{259,260} and widely used clinically over many years, however there is little literature on their origin or literature on their validity and reliability. There are many names and variations of these tests: - brush test, stroke test, ballottement test, peripatella fluctuation test, patella tap. They involve various methods of manipulating the skin and linings around the knee, and observing fluid movement under the skin^{261,262}. A brush test, stroke test, or peripatella fluctuation test aims to detect the presence of intra-articular / intra-capsular knee effusion. It involves brushing the anteromedial aspect of the knee (medial to the patella) in a distal to proximal direction from the area of the pes anserine, up to the area of the knee superomedially to the patella (see figure 7).



Figure 8 Brush or stroke test- the examiner's hand moves medially to "milk" effusion

It is important to brush sufficiently superior to encompass the superior extension of the knee joint capsule above the patella. Sufficient pressure is exerted by the examiners hand and fingers with the aim of "milking" the effusion from the medial to the lateral side of the compartments of the knee. The second phase of the test involves a second "brush" or "stroke" lateral to the patella from the distal to the proximal lateral part of the knee (see figure 8).

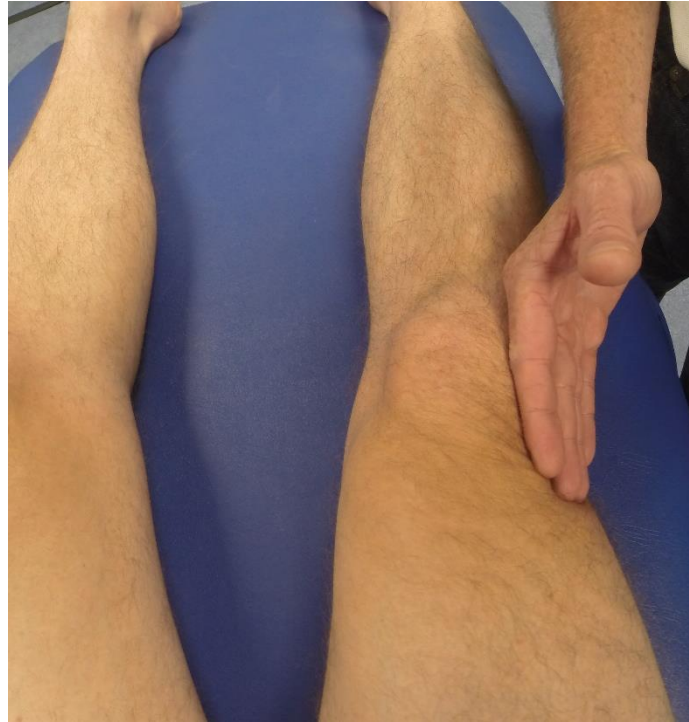


Figure 9 Brush or stroke test- for the second part of the test the examiners hand moves laterally and the wave of fluid can be visualised returning to the medial side of the knee

As the examiners hand passes the lateral superior capsule, if there is sufficient volume of effusion in the knee, a “wave” of fluid can be visualised under the skin, passing across the knee from lateral to medial, with a bulge of the medial capsule (medial to patella). The ballottement or patella tap, involves the examiner compressing the superior capsule above the patella with their hand. In the presence of a larger effusion the fluid passing into the lower portion of the capsule causes the patella to “float” or lift up off the trochlea (see figure 10).



Figure 10 Patella tap –the fluid in the knee causes the patella to “float” up off the trochlea of the femur

When the patella is “tapped” it is possible to feel a soft then a hard sensation as the retropatella surface touches down on the femoral trochlea surface (see figure 11).



Figure 11 Patella tap- part 2 the patella is tapped. In high levels of joint effusion, the retropatella surface is felt to touch down or “tap” the femoral trochlea.

With normal amounts of joint fluid and very small effusions the retro patella surface will normally remain in contact with the trochlea, it is only with larger effusions that the examiner will feel the patella “tap” of the trochlea and retropatella contact.

The advantage of these tests is ease and speed in the clinical setting, however, they rely on subjective judgement. There may also be difficulty detecting synovitis using these tests and the presence of synovitis or synovial swelling may not necessarily correlate with a positive finding on examination. These tests can be very hard to perform accurately in some patients, as well as being hard to grade and their validity has not been investigated.

Sturgill et al²⁶³ assessed a stroke test, adapted from Magee²⁵⁹. They evaluated the inter rater reliability of a 5 point grading system, using 9 trained raters. The kappa value was 0.61 (0.54, 0.81) with 73% agreement between raters. They found a lack of specific objectivity between 2 of the grades, the “trace”, and Grade 1.

Kastelein et al²⁶⁴ evaluated patients presenting to their GP with a traumatic knee injury. Using an MRI and examination study, they found good association between the patient’s subjective report of knee swelling, the ballottement test and the MRI presence of an effusion. Interestingly 31 out of 42 patients with an effusion had an internal derangement of the knee and they showed a positive association with internal derangement of the knee (chi-square 9.5). There were 11 patients having an occult or non-visualised cause of the effusion.

These tests have advantage to rapidly detect the presence of an intra-articular effusion but they cannot give an accurate quantification of volume. Other tests will be more useful for quantifying volume.

ASPIRATION

Whilst aspiration has been used as a clinical measure of intra-articular effusion, it is more typically used for diagnosis and treatment of effusions. The amounts aspirated, often underestimate the true intra-capsular swelling, as it is difficult to clear all the synovial compartment areas of the knee.^{93,265} Aspiration is invasive and often painful and puts the knee under risk of infection. In a normal knee joint it is only possible to aspirate a few millilitres of fluid. Hall et al in a radiographic study, measured the suprapatella knee distance on a lateral knee arthrogram. They measured from the anteroposterior distance from the posterior edge of the suprapatella fat pad to the posterior edge of the prefemoral fat pad (see arrows figure 12)



Figure 12 Knee radiograph - post ACLR patient with the suprapatella effusion outlined

They found that a distance of 10mm corresponded to the presence of an intra-articular effusion on aspiration but where measurements were 5mm or less, there was only a few drops of fluid obtainable on aspiration. Measures of between 5 and 10mm corresponded to more variable levels of fluid aspirated, and it may be that insufficient effort was made to

obtain fluid from other parts of the knee, giving a non-complete volume. Effusions have been found to gather more in the lateral suprapatella pouch on MRI²⁶⁶ and measurements lateral may be more valid than midline measures used by Hall. Aspiration also has advantage for treating or removing effusions, but generally the effusion (particularly traumatic effusion or haemarthrosis) will regather again (within 4-7 days).²⁶⁷

IMAGING – ULTRASOUND

Imaging methods have also been trialled to detect intra-articular effusion. Ultrasound methods to measure knee effusion have been developed, and is relatively convenient and inexpensive, it allows monitoring of intervention and real time scanning with moving tissues. It carries no ionisation radiation risk but accuracy can often depend on the experience of the operator. Ultrasound is more sensitive than examination alone for detecting knee effusion^{268,269}, however, even on ultrasound, smaller effusions may be missed as effusate may be distributed throughout the knee and connecting bursal compartments²⁷⁰. Factors that affect ultrasound detection include: - quadriceps contraction²⁷¹, depth of effusion, the experience of the examiner²⁷² and the type of fluid. Minimum levels for detection in the knees of embalmed cadavers were 10.1ml for saline, 9.7 ml for blood and 7.4 ml for synovial fluid²⁷³. In fresh cadavers threshold levels for detection of knee fluid range from 2ml to 7ml for saline²⁷⁴.

MAGNETIC RESONANCE IMAGING

MRI has been found to be sensitive in detecting the presence of effusion than ultrasound, and threshold levels for detection were 1ml in injected knees, with the suprapatella pouch as an area within the knee that was most sensitive for detection of effusion²⁷⁵. Other methods have been developed for quantifying effusion on MRI in knee arthritis.²⁷⁶

MRI has disadvantages of cost and time, and due to this, has been used more for diagnosis and detection of effusion and synovitis²⁷⁷ rather than quantification of joint effusion volume.

EXTRA ARTICULAR – VOLUMETRIC MEASURES

INTRODUCTION

Methods to investigate swelling from lymphoedema research have typically looked at whole limb volume and there are various methods described. These methods often do not discriminate between the compartments of the limb and it is difficult in a joint like the knee to evaluate the proportions of the volume measured which are attributed to intra or extra articular structures and the volumes attributable to different tissues, including synovium, fluid, bone and muscle. More recently there has been some investigation of techniques such as bioimpedance spectroscopy and dual-energy x-ray absorptiometry (DEXA) to allow more discrimination between the composition and volume of different tissue. The key volumetric methods used to measure oedema and swelling are described below.

LEG CIRCUMFERENCE MEASUREMENT

Leg circumference using a tape measure, has been the most widespread and currently used method for assessing oedema and swelling, and it is an inexpensive and convenient clinical measure. Measurement at the knee carries some difficulty due to the patella anteriorly and the extents of the knee capsule inferiorly to the tibial tubercle and superiorly to the suprapatella capsule. At this superior capsular level the vastus medialis portion of the quadriceps muscle also contributes volume to a girth measurement. A disadvantage of circumference measures is that they cannot distinguish between the girths of the various composite tissues. Knee ROM and muscle contraction both affect girth, and the position of the patella. The incident angle to read a tape measure can affect how accurately a tape measure is read. Many tape measures have some elasticity in their materials and some

investigators have commented that the tension at which tape measures are held is difficult to standardise between each measurement or tester²⁷⁸. Some studies have advocated a spring tape with a set tension.²⁷⁹ It is, therefore, advisable to have a standardised technique measurement protocol with the subject relaxed.

There has investigation of the most appropriate level to take a knee girth measurement. The circumference at 1cm proximal to the patella was found to correlate more closely with joint fluid volume from aspiration than the circumference at mid patella level. Kirwan et al²⁸⁰ found that in this section of the knee that the girth dropped 1cm for every 40ml of fluid aspirated from the joint. This means that in small effusions differences will be read in numbers of millimetres of measurement, and this requires great accuracy.

Tape measurements have an inherent risk of inaccuracy. One study, comparing a spring tape (equivalent tightening force) with a volumeter (Bozl Medizintechnik Aachen Germany), measured leg circumference and found a difference between the devices in mean circumference measurement of 67mm at the calf and 54mm at the ankle²⁷⁹. This level of difference in accuracy would seem unacceptable, and they recommend that the 2 methods should not be used interchangeably.

Many studies have attempted to use limb girth measurements by tape to calculate a measure of volume. Several of methods are described in a study by Kaulesar²⁸¹. The simplest method is the frustrum method, where the volume of an inverted cone is calculated with the lower (r) and the upper (R) circumferences of the frustrum formed by the proximal and distal limb circumference measures and (h) is the height (or length) of the segment. The volume is calculated according to the formula: -

$$V = \frac{\pi}{3} h(R^2 + Rr + r^2)$$

The second method for using circumferential methods is the disc method, where the limb circumference is measured every 3cm and successive disc volumes are added to make a full segment volume. The volume for the disc method can be calculated from the formula below:-

$$V = \sum_{i=1}^n \left(\frac{C_i^2}{4\pi} \times h \right)$$

Equation 2 Formula for disc method for calculating limb segmental volume

These measures have an inherent risk of inaccuracy as they are based on the assumption that the shape of the segments is a truncated cone (frustrum method), and the cross section of the segments is circular (disc and frustrum method), whereas in reality limb cross section more elliptical or not regular in shape at all. There are also surface irregularities not captured by spaced measurements. Furthermore, the thickness of the tape measure, although it is tiny, makes a measurement fractionally higher than the real circumference.²⁸² Kaulesar et al tested the lower limb (shank only) in health volunteers, and found that the disc model gave volume values closer to those obtained from water volumetry. They found that the frustrum model did not give adequate correlations or agreement. The disc model was closer to water volumetry measured volumes, but did tend to give a larger volume by 45ml than the water volumetry. This was also found by Tan et al comparing tape measurement (disc method) with perometry with a vertically orientated perometer²⁸³. They found that using tape measurements with the disc method gave a larger mean estimate of whole limb volume by 157ml (approximately 1.8%). Deltombe found this also²⁸⁴, however, Mayrovitz found that the tape measurement underestimated the volume in comparison to perometer measurement²⁸⁵. This may be due to their use of the Frustrum method. Sitzia, however, in a study investigating the calculation formulae, reported that both the disc and the frustrum

method consistently overestimated volume by approximately 1.5%²⁸⁶ and a modified frustrum formula has been advocated in some studies see below:-

$$V = (h)(R^2 + Rr + r^2)/12(\pi)$$

Equation 3 Formula for modified Frustrum method for calculating limb segmental volume.

In spite of this calculated volumes were still different from volumes measured by instrumented volumetry²⁸⁷. In light of this, while tape measurement is a widespread convenient clinical measure, most authors suggest that tape and instrumented methods of measurement of limb volume should not be used interchangeably.

WATER VOLUMETRY

Water displacement has been used as a measure of volume. It uses Archimedes principle of water displacement that the upward buoyant force that is exerted on a body immersed in a fluid is equal to the weight of the fluid that the body displaces. Water volumetry has been found to be valid and reliable as a measure for limb volume, with precision levels of 0.1-1.3% for retesting limbs (equating to between 2 to 30ml over a whole leg measurement).^{251,284,288,289}

It has the advantage of being more accurate than calculating volume from circumference measures^{282,284,290} but has disadvantage of being time consuming and complicated logistically, with subjects asked to stand or place their limb in a water filled Perspex container. Devices generally involve measurement in standing and subjects must remain completely still. Fluid dynamics can also alter very quickly in a limb on rising to stand and during a measurement session, meaning that the limb volume may not be static during a measurement. The hydrostatic pressure of the water also exerts some pressure on the limb, with different amounts exerted at different depths of water. Water volumetry has been found to be reliable in the measurement of knee volume²¹³. It has been found to be less accurate with a poor measurement technique²⁹¹, and Rabe et al mentions a plethora of potential sources of error that often result in under estimation of the true volume. They recommend that repeat

measures on the same patient at the same session should not be greater than 10-20ml. An inversion water volumetry system has been studied in upper limbs, with finding of good ICC²⁸⁸. The authors calculated that the reliability index of the measurements with the inverted apparatus was calculated as 0.14 kg. This means that only absolute changes in a patient's arm volume measurement of more than 0.14 kg would represent a true change in arm volume, which is about 6% of the mean arm volume of 2.3 kg. This may not allow enough sensitivity to determine volume changes in a limb or a smaller limb segment.

While water volumetry has advantages in non-surgical settings, it has disadvantages post-surgery due to immobility, pain and the risk of wound infection with water exposure. It could not be used after ACLR and was not deployed in these studies due to these reasons.

IMAGING – BIOIMPEDENCE SPECTROSCOPY

Bioimpedance spectroscopy which gives a measure of body composition, including segmental composition and has been used in more recent studies. This method measures impedance to small currents applied to the body and is easily performed and is more convenient, and less expensive than other instrumented procedures. Bioimpedance will also give a measure of volume of different tissues, allowing more discrimination between tissues than other volumetric methods. In upper limb lymphoedema, it has been found to have acceptable inter-rater reliability ($r=0.987$) and intra-rater reliability ($r=0.993$) and acceptable concurrent validity was reported in 2 studies as $r=-0.904$, and $r=0.926$ respectively, when compared perometry measures of limb volume.^{292,293} It has also been used by Pinchionnez et al in a knee post-surgical model in total knee arthroplasty.^{294,295} Bioimpedance will differ for metal implants or metal fixation components and these studies investigated this effect in a post-surgical model, and the utility or risk of error due to the arthroplasty. Other factors that may

cause error are skin sweating and temperature²⁹⁶. Bioimpedance measurement also uses a software algorithm to convert the electrical signals received to a volume estimate based on the impedance of different tissues. Unfortunately some of the companies that produce these devices do not publish their algorithms, preventing full analysis.

IMAGING – 3D SYSTEMS

There have been several volumetry studies using an adaption of the Microsoft Kinect device (Microsoft, Redmond, WA, USA), which is a commercially available device that uses the light patterns projected to give a 3 dimensional data capture. It can track body movement but also estimate the volume of whole and segmental body parts. Some researchers have used it to give a volumetric measure of the limb. It is cheaper than many of the other volumetric devices such as the perometer, and due to their compatibility with gaming consoles may be useable in a patient's home, allowing self-monitoring and feedback (telemedicine). One system linking with the Kinect showed good results with good ICC compared to water volumetry for measurement of limb volume²⁹⁷. Other studies, while finding good correlation with water volumetry, also found significant error ratings with the Kinect and the authors report ongoing work was required to address these.²⁹⁸

OPTOELECTRIC VOLUMETRY - THE PEROMETER

Knee volume in this work was measured using a Perometer® (Perometer 350S, Pero-System, Wuppertal, Germany). The Perometer is an optoelectronic imaging device, connected to computer software, which has been shown to be effective, valid and reliable for measuring upper and lower limb volume.^{282,284,290,299} It has particular application to measuring limb oedema²⁸⁵, and has also been utilised and validated for measuring knee volume.^{213,300} and the perometry measurement technique for this body of work followed these studies.



Figure 13 Perometer set up for measurement of limb and knee volume

There are several models including upright (400T) and horizontal models (350S), used in our work. Measurement of knee volume using a Perometer, involves the subject positioned on the test chair in long sitting, with one foot up with the leg horizontal, the heel resting on the foot plate, and the leg relaxed. The leg sits in the middle of a vertically orientated square frame (see figure 13), which slides along a track horizontally from the level of the subject's foot on the footplate, up toward the level of the subject's thigh. The square frame contains 378 infrared light switches and 2 rows of embedded infrared light emitting diodes which are spaced every 2.54mm, on two adjacent perpendicular inner sides of the square. On the opposing edges there are corresponding infrared light sensing diodes spaced every 1.27mm (Pero-System Mebgerate GmbH 2001). The frame is moved manually horizontally along the longitudinal axis of the leg from the original start point at the ankle toward the thigh and returned to the original start point. The rate of movement must be regular, and not too fast or too slow, and the software informs the operator to repeat the scan if the movement is not smooth, or too fast or too slow. It takes approximately 5 seconds to move the measurement frame along the length of the limb and back. As the square frame is moved along the length of the leg, the horizontal and vertical infrared light beams between the diodes are interrupted by the leg in the middle of the square. The limb, therefore, interrupts the light beams in two planes and the cross sectional area can be calculated in the software. The cross sectional slices

are then collated in the software and a limb volume is calculated and given in millilitres. With the software calculating from cross sectional slices 3.1mm apart.^{299,301} Volume subsections of the leg (including the knee) can be measured from the volume of the fully scanned leg, using the particular subsection distance from the footplate, giving the volume between two subsection distance points. This can be manipulated on the software screen of the computer, or the distance values entered manually (see figure 14)

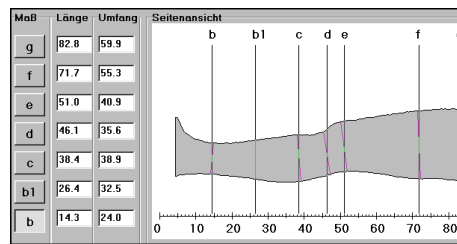


Figure 14 Perometer computer software screen

RELIABILITY AND VALIDITY

Four authors have given recommendations on optimising methods to ensure reliability of protocols when using a perometer. Man et al (2003), studying perometry in the knee, recommends ensuring knee angle consistency between measures. They showed that measured perometer knee volumes vary with different knee angles, and differences are particularly significant at angles beyond 20° flexion¹⁹⁹. Bulley et al have also given recommending ensuring the limb is in a neutral anatomical alignment to minimise rotation³⁰². Stanton et al²⁹⁹ found that volume readings for the perometer were less reliable if the measurement object was rotated in the frame (no longer perpendicular to the light beams). Engelberger et al found an effect of time of day and the speed of standing for measurement in the upright 400T perometer³⁰³.

Reliability of the perometer has been assessed by Man (2003) for measurement of knee volume, Stanton et al (1997) for volume measurement in the upper limb and by Bulley et al (2013) for the upright perometer for upper and lower limb.

Man (2003) found a 2.2% difference between perometer and actual volume using repeated measures on a known-dimension cylinder. The Coefficient of variation (Cv) was found to be 0.07% on 10 repeat measures. When using 40 uninjured knees on 2 occasions 24 hrs apart, response stability variables were found to be: - Measurement error (ME) =4.3% and CvME = 0.5% and for stability between test 1 and 2 ME=112% , CvME 1.2%.

The inter-rater reliability between 3 examiners, for single measures the ME and CVme were 3.1-0.4 and 7.7% to 0.8% respectively. The Intra Class Correlation coefficient (ICC) values ranged from 0.998-0.999 with CvME values 0.9-1.2%, and least significant difference (LSD) values 31 ± 3 , with range from 27-32ml.

Construct validity has been assessed by Stanton et al ²⁹⁹ using geometric shapes and using a mannequin arm, lymphedema and normal arms and by Man et al (2004) using an inanimate object (drainpipe). Criterion validity was measured using the, then, gold standard measure of limb water volumetry. This was done with both a section of a drainpipe and with 40 uninjured knees, and a good correlation was found between water volumetry and the perometer for both knee and object measurement. ($r=0.94$ $p<0.01$)

Perometer validity has been measured using cylindrical objects and test retest reliability studies. Levels of agreement were assessed in comparison with the, then, gold standard, water volumetry knee volume measures. Man et al found that the Perometer overestimated the true volume by only 2.2% (Coefficient of variance (Cv) – 0.1%) compared to 3.4% (Cv 0.2%) with water volumetry. Correlation between the 2 measurement methods was high ($r= 0.94$ – $p<0.01$) but there was a significant difference between the volumes obtained by the perometer and water volumetry ($t=24.256$, $P<0.001$). The perometer values were found to be closer to actual cylinder volumes, indicating that the perometer is a more accurate measurement method.

The LSD values for knee volume measurement were also calculated with same and later day repeat measures. These were lower than Water volumetry (LSD measure was 32 ml with the perometer vs 58 ml with water volume respectively). Method error (ME) and Coefficient of variation of method error (CVme) were 4.3 and 1.3 for same day measures and 11.2 and 1.2 for separate day measures. The Intra-class Correlation coefficient (ICC) for the perometer was 0.998 and showed good intra-rater reliability.

Bulley et al found high ICC values for intra-rater and inter-rater reliability in upper and lower limb measurement, ranging from 0.953 to 0.989. This is lower than Man et al and several other perometer studies.^{284,304,305} and they point out that this changed as they altered the technique to that of Man for retest sessions, which subsequently reduced the amount of skin marking.

Beyond the initial studies by Man et al investigating the knee, no study has further studied the knee. The perometer has also never been used in a postsurgery or post-injury context. This worked has undertaken the first studies using and examining the reliability the perometer for measuring knee volume in a knee surgery cohort of patients.

AIM

The aim in this study was to examine the reliability of using the perometer to measure knee volume pre and post ACLR. As a clinical utility test, the study also aimed to measure the brush test as a possible rapid easily performed clinical measure and to compare the brush test grading with perometer knee volume findings.

METHODS

SAMPLE

51 patients from a knee orthopaedic unit in an inner city teaching hospital, were approached, screened and recruited after giving written informed consent to take part in the study if they met the inclusion and exclusion criteria (given in chapter 3). They were all on the waiting list to have an ACLR surgery after a diagnosis of complete ACL rupture by a consultant orthopaedic surgeon. All recruited patients, had both knees measured pre operatively, and 11 days post ACLR. They attended the measurement visits for the larger study. In the preoperative and initial visit their knee volume in both legs was measured with the perometer, along with the other outcomes taken for the study. The term “patients” has been used in this thesis for chapters 2-4 as they relate to clinical studies on individuals undergoing a clinical, hospital treatment. It is acknowledged that they have made this research possible by their generous participation and are very much considered “participants” to this thesis.

MEASUREMENT METHOD – VOLUME

The perometer was used to measure knee volume and the methods followed those used by Man et al in their previous studies.^{213,300} Three consecutive measurements were performed on each knee, on each measurement visit occasion. The measurement visits were in the morning for all assessments to ensure a consistent period of day. Pre operatively, measures were performed within one week of surgery. Post operatively measures were taken 11 days after the surgery. The same investigator performed all measurements, with an experience of over 200 perometer knee volume tests. The measurements were performed after a period of quiet sitting of at least twenty minutes in a climate controlled waiting area, with consistent

temperature. Other factors that could affect swelling volumes were documented, including average daily amount of walking and standing in the prior week and the average daily medication use. An initial measurement was taken, with skin marks made 1cm above patella and the superior border of the tibial tuberosity. Measures and chair positions were subsequently entered into the perometer software, and these were documented for each subject, and the chair and equipment positions were reproduced for the subsequent test visits, to ensure their measurements were consistent. Skin distance markers were made 1cm above the patella and the superior border of the tibial tuberosity in order to approximate the knee joint capsule which extends from the superior tibial tuberosity to the proximal margin of the supra-patella pouch (SPP). The choice of this proximal segment boundary area aimed to limit volume measurement to the knee joint capsule, to attempt to obtain a measure of capsular effusion within the volume measure but without encompassing too much of the quadriceps muscle component, which could waste significantly post-surgery. Circumference and volume measurements too far above the patella will include some muscle volume from the vastus medialis of the quadriceps. This volume can change before and after surgery as muscle atrophies and hypertrophies. In a study assessing intra-articular fluid volume aspirated from effused knees, Kirwan et al demonstrated that tape measurements of circumference 1cm above patella correlated better with fluid volume aspirated than tape circumference measured at the mid patella level²⁸⁰. In an MRI study investigating the distribution of intra-articular knee effusions post trauma, it was found that 79% of subjects had effusions in the supra-patella pouch³⁰⁶. For these reasons and to be consistent with previous studies, the proximal skin marker was made 1cm above the patella.

The horizontal distance from these skin markers to the perometer footplate was measured in millimetres (mm) with a tape measure (initial measurement visit) and three perometer knee volume measures were made for each leg, in a consistent order. The perometer footplate measurement was noted for each patient, and reproduced for each measurement session.

The initial knee tape measurements/ computer distance markers of bony landmarks were used in follow up visits to obtain volume measurements from the computer software.

Several metrics were trialled for specifically defining /measuring the knee segment. These included: defining the segment with skin markers, or cursor manipulation of segment limits on the scanned image on the computer. The final technique, however, used skin markers, and measurement of the horizontal distance from the footplate. This method was chosen based on personal communication with Man, and we used the same equipment protocol as their 2003 studies. It was found by Man that ME and CVme were 34.8 and 4.7% for computer distance measurement, versus 9.8 and 1.1% with skin markers and distance measurement to footplate, indicating that the footplate method was the most accurate. A further pilot measurement trial for this study with a round cylindrical object also found this to be the most accurate measurement method.

A consistent angle of 15° knee flexion was used as the knee angle has been found to affect accuracy.^{279,281,284,285,290,300} Full extension was not chosen as the participants did not have consistent hyperextension, range of movement (ranging between -25° and zero degrees). Some subjects did not have equal extension ROM between their unaffected and affected knee and, postoperatively and many of the subjects could not achieve full extension due to pain or stiffness. 15° flexion was therefore chosen as a consistent ROM that every participant could achieve bilaterally, both pre and postoperatively. This angle was measured with a goniometer³⁰⁷. The same goniometer was used throughout the study. The perometer footplate was adjusted and fixed in position to hold the subject's foot and to maintain this knee angle with complete relaxation of the leg. This allowed the leg to maintain relaxation in a neutral alignment position, without rotation. This was to ensure no muscle activity during the test, so that muscle activity would not change the external measured volume of the knee.

Both tape and knee angle (goniometer) measurements were also repeated each time the leg was moved (3 times for each leg).

Subjects were asked to sit on one side of the perometer seat, with the tested leg longitudinally aligned parallel to the perometer track below. This was repeated with each measure, which ensured that the leg position was reproduced in horizontal, vertical and longitudinal planes for each measurement. This is important, as it has been found that small alterations in limb alignment in all 3 planes can affect measurement accuracy²⁹⁹.

After measurements were completed, the knee volume measurements were obtained from the Perometer software by correlating the marker to foot plate tape measurements, and measurement values for this same distance on the computer software. Computer distances were in 4 mm intervals, and the closest 4mm interval to the tape measurements was chosen. Tape measurements were averaged for each leg over the 3 measurements, and the 4mm interval from the computer that came closest to this average was used. This computer value for the distance of knee markers (Tibial Tubercle and 1cm superior to patella) was then applied to all the measures pre-operatively, and on all subsequent post-operative measures. A knee volume in millilitres (ml) was obtained for each of the 3 measurements on each leg, and these were averaged. Post-operative measures were compared with pre-operative measurements, and the differences with pre-operative and contra-lateral side volumes were calculated.

The measurement method aimed to minimise sources of error and also followed the work of Bulley et al³⁰² who gave recommendation on optimum technique after performing a series of validity and reliability studies on a Perometer 400T. While their recommendations relate to a vertically orientated machine (400T), for whole limb measurement, many of the recommendations were applicable to the 350S measurement that we used. They recommended having a period before the test where the lower limb was relaxed for at least

10 minutes. They recommend allowing the frame to move sufficiently proximally to give sufficient proximal segment measurement (although this is easier in sitting on the 350S than in standing on the 400T). They reported that, unlike Man et al, comparison of measurements taken with the limb at different angles to the vertical with normal postural variations were not found to influence limb volume significantly, however, positioning in the long axis may reduce variability. They found that consistent positioning in the anatomically neutral position without rotation gave the most reliable results, and recommend using bony and marker reference points when obtaining segment volumes. They did not find that the speed of the movement of the frame caused the measured volumes to vary but suggested maintaining a consistent speed. They recorded little diurnal variation in volume measures but recommended measures at the same time of day where possible as diurnal differences have been found, when investigating on the upright perometer (400T)³⁰³. Another study has found that the upright perometer may not have as much concurrent validity as the horizontally orientated one that was used in our studies²⁸³. This may be because of the body sway and movement required to maintain the upright position during the testing and this may explain the slightly lower ICCs found in this group's work³⁰². No study has measured minor subject movement or sway during testing.

BRUSH TEST

To further quantify knee swelling, a quick clinical test was performed, using a peripatella fluctuation test (minor effusion or brush/stroke test/ sweep test) and a ballottement test.^{261,262,264} Brush tests were performed with the subject resting, with the knee in Extension. The same experienced examiner performed all the tests and each subject had a period of at least 20 minutes resting prior to the test.

The inter-rater reliability of the stroke test ²⁵⁹ has been investigated in a recent article by Sturgill et al ²⁶³. They graded a 5 point scale from 0-3 plus a “trace” level, and found inter-rater reliability good, with an overall Kappa value of 0.61. They also report difficulty discriminating between “trace” and “grade 1”. The grading system used in this study followed that of Sturgill et al ²⁵⁹, but with a modification, to account for this difficulty discriminating between these levels. The aim was to minimise subjective judgement, in this study we, therefore, chose to use four points of grading from 0-3, (leaving out the “trace” grade) with; grade 0 if there was no swelling; 1 weakly positive minor effusion/ brush test; 2 strongly positive minor effusion test/ brush, but negative ballottement test, and grade 3; large effusion with positive patella ballottement test (see table 1).

Table 1 Brush Test Classification (adapted from Magee and Sturgill et al)

Brush Test Grading (0-3)			
		Brush test	Patella Tap
Brush test Grade	0	no observed wave on down stroke	Negative
	1	small observed wave on down stroke	Negative
	2	effusion spontaneously returns to medial side after upstroke	large effusion but negative patella tap or ballottement test
	3	so much fluid that it is not possible to move the fluid from medial aspect	a positive patella tap or ballottement test

The measurements were performed with consistent time of day, order, and rater. Subjects rested for 20 minutes prior to each test with their shoes and socks off, and avoided prolonged periods standing or walking.

ANALYSIS

The statistical tests performed for reliability were the Intra class correlation ICC(3, 3), as only one rater was evaluated and the test was performed three times on each occasion. Inter-rater reliability was not assessed. Response stability was measured using Standard Error of the Measurement, and coefficient of variation. Paired T tests were used to compare the pre and postoperative volume measures.

ETHICAL APPROVAL

Ethical approval for the study was obtained as part of the approval for a larger clinical study through the National Health Service (NHS) Committee of Research Ethics Committees (COREC) and the joint UCL/UCLH ethics committee A, with approval number 05/Q0505/120 (See Appendix 3). Written informed consent was obtained from all subjects before testing with the participant information leaflets and consent forms given and written informed consent taken prior to taking part (Appendices 4 and 5).

RESULTS

SAMPLE

124 patients attended the knee unit at our institution during the study period from September 2008 to June 2010, and were assessed for eligibility for the overall large clinical study. Figure 15 summarises the exclusion and group randomisation for the study. In total, complete data sets were available for 43 participants.

For the reliability study, 8 Subjects were lost to follow up due to non-attendance at the 2 week clinic appointment. Preoperatively, no subjects reported past pathology or symptoms in the unaffected knee, however, there were 2 subjects with incidental findings of positive brush tests in their unaffected knees. There were 51 subjects available for preoperative measurements and 43 complete data sets for postoperative measures.

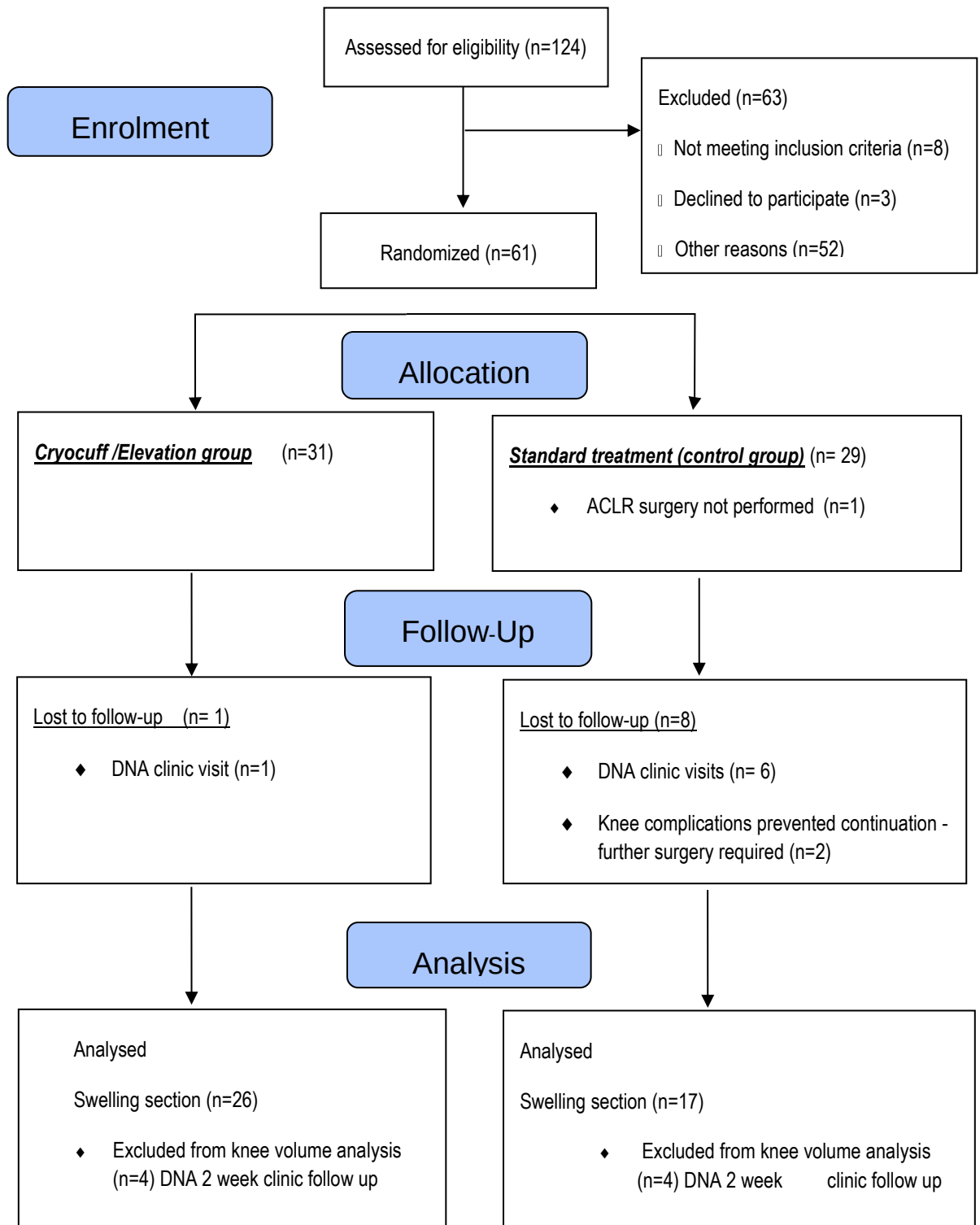


Figure 15 Recruitment and retention flow diagram Summarising recruitment patients lost to follow up and DNA (did not attend) clinic appointments for the large ACLR clinical study.

KNEE VOLUME

The knee volumes are listed in table 2.

Table 4 summarises the knee volume measures for each of the 3 consecutive measurements performed using the perometer on each knee.

Table 2 Perometer measured knee volume (ml) with 3 measures on each knee and means

Knee Volume (ml) (mean (SD)) (95%CI)	Unaffected knee (n=51)	Affected knee (n=51)
Pre-operative	1222 (234) (1156, 1287)	1227 (225) (1163,1290)
2weeks post-operative (n=43)	1199 (249) (1123, 1274)	1265 (224) (1196, 1334)
Pre to 2 Weeks post Differences (ml) (n=43)	1.2 (45.5) (-12.6, 15.1)	67.4 (56.1) (50.2, 84.7)

The unaffected knee average volumes were not significantly different pre op vs 2w post op ($p=0.866$) with a correlation between scores of 0.984.

The affected knee average volumes were significantly different pre op vs. 2w post op ($p<0.001$) with correlation of 0.968.

Table 3 summarises the reliability and validity statistics calculated from the repeated measures on both the affected and unaffected knees.

Table 3 reliability and validity statistics for the Perometer measure of knee volume in both the affected and unaffected knees

Statistical measures		Unaffected knee	Affected knee	Total
Pre-operative (n=51)	ICC (3,3)	0.998	0.997	0.984
	SEM	10.12	11.20	10.66
	CV	0.842%	1.04%	
10-17D post-operative (n=43)	ICC (3,3)	0.998	0.999	0.983
	SEM	10.06	8.86	9.46
	CV	1.19%	0.79%	
TOTAL SAMPLE	ICC (3,3)	0.998	0.996	0.991

BRUSH TEST RESULTS

The results of the brush tests are reported below. The numbers of knees with positive brush tests is shown. The examiner used the grading system in table 1, and the numbers of patients having grade 0 -3 respectively are tabulated. The results are shown for both affected and unaffected knees and before and two weeks after ACLR surgery (see Tables 4 and 5).

Table 4 Brush / Ballottement test results number of subjects in each grade of effusion on brush (Grade 0-3)

Number of Subjects with Brush test grade		Affected knee	Unaffected knee
Brush test pre operatively (n=51)	Grade 0	34 (66.7%)	49(96.0%)
	Grade 1	10 (19.6%)	1(2%)
	Grade 2	6 (11.8%)	1 (2%)
	Grade 3	1(2.0%)	0 (0%)
Brush / ballottement test 2 Week post op ACLR (n=45)	Grade 0	8(17.8%)	44(100%)
	Grade 1	9(20.0%)	0(0%)
	Grade 2	11(24.4%)	0(0%)
	Grade 3	17(37.8%)	0(0%)

Table 5 Pre to post-operative knee volume differences (ml) measured with the perometer versus the brush test grades at 2 weeks post op ACLR and the change, pre operatively to postoperatively, in brush test grade (-2-3)

Affected knee	grades on Brush test	Number of subjects	Affected knee volume Difference pre to 2weeks post-operatively (ml)		
			mean	SD	95% CI
Brush / Ballottement test 2W post operatively (n=45)	Grade 0	8(17.8%)	43.6	57.0	(15.0 , 142.3)
	Grade 1	9(20.0%)	66.9	46.3	(7.7 , 161.7)
	Grade 2	11(24.4%)	72.1	57.4	(-5.7 , 197.7)
	Grade 3	17(37.8%)	76.2	60.7	(-56.7 , 172.7)
Change in grade on Brush test pre to 2 weeks post-operatively (n=45)	-2	1 (2.2%)	21.7		
	-1	1 (2.2%)	-15.0		
	0	6 (13.3%)	57.0	59.5	(-3.7 , 142.3)
	1	16 (35.6%)	51.1	52.9	(-56.7, 161.7)
	2	13 (28.9%)	74.5	53.8	(-5.7 , 197.7)
	3	8 (17.8%)	108.4	48.0	(47.0 , 172.7)

Preoperatively, no subjects reported past pathology or symptoms in the unaffected knee, however, there were 2 subjects with positive brush tests in unaffected knees.

The knee volume difference preoperatively to 2 weeks postoperatively, measured by the perometer, was not significantly different between the swelling grades, ANOVA test ($p=0.711$). There is also not a consistent change in volume when compared against the change in brush test grade pre to post op. (ANOVA ($p=0.162$), or with percentage volume change to control for knee size ANOVA ($p=0.121$).

A trend emerged following further evaluation of the brush test between the change in brush test grade with the perometer measured change in knee volume (see figure 15). This trend got stronger when the perometer measured change in knee volume in ml was normalised to total knee volume (ml) (see figure 16), however neither of these trends reached statistical significance.

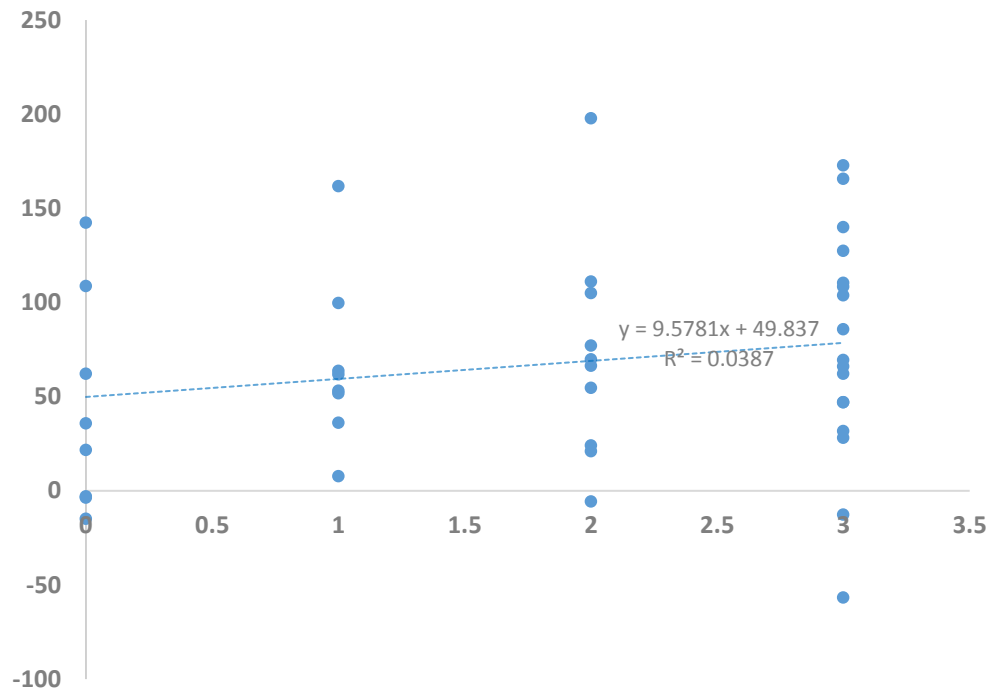


Figure 16 Brush test grade (0-3) affected knee brush test examination from preoperative to 2 weeks versus the change in knee volume (ml) measured with the Perometer from preoperative to 2 weeks post ACLR (linear correlation trend line)

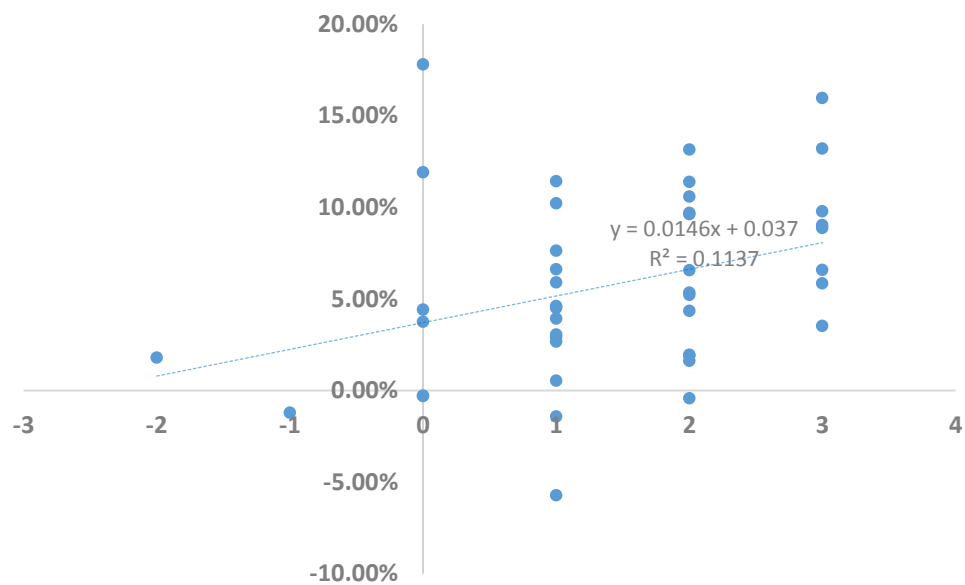


Figure 17 change of Brush test grade (-2 - 3) affected knee brush test examination from preoperative to 2 weeks versus the change in knee volume (ml) measured with the Perometer from preoperative to 2 weeks post ACLR (linear correlation trend line)

DISCUSSION

PEROMETER

The ICC(3,3) in this study for the perometer measures of knee volume was 0.998 and 0.999 for unaffected knee volumes, which is equivalent to the levels found by Man et al (2003) (ICC(3,k) =0.998) and affected knee ICC(3,3) was found to be lower 0.997 preoperatively but 0.999 post operatively with a finding of 0.996 for this cohort of patients as a whole. Average knee volumes were higher as body size in this sample was larger. This indicates that the perometer gives a reliable measure of knee volume after ACLR. The response stability, measured by coefficient of variance between our 3 measures for each session was good, with unaffected knee at 0.84% and 1.19% pre and post op and affected knee at 1.04% and 0.79% pre to post op, however, small knee effusions may be below this level and difficult to detect with the perometer measure. This was confirmed by The Standard Error of the Measurement which was 10.12 and 10.06 for unaffected and 11.20 and 8.86 for affected knee, pre and post operatively respectively. This was higher for the differences with 11.93 and 14.46 for unaffected and affected leg respectively.

BRUSH TEST

The brush test was found to be a rapid clinical test that was easy to perform and clinically useful. When comparing the brush test grades with the perometer measured whole knee volumes, the changes in brush test grades did not show significant differences in changes in

whole volume measured by the perometer, indicating that it is not possible, with this sample, to ascertain the approximate volume change of one grade change on the brush test. The change in volume showed difference (non-significant) between the 0 and 3 levels, but even less difference between the 1 and 2 levels. This may indicate that the brush test shows less discrimination in the intermediate grades. This agrees with the findings of Sturgill et al.

There was a 50ml average volume difference in those who had 0 on the change in brush test scores. This may relate to a component of perometer error. This may, however, indicate that the 50ml change in volume was not within the joint capsule and may have been extra-capsular or subcutaneous. It could also indicate that the brush test is not sensitive to detect effusion until it gets beyond 50ml, or that whole knee volume measures will not alter in the knee at 15° flexion until the intra-articular volume gets to at least beyond 50ml. This may be helpful clinically as there is evidence that an experimentally induced effusion of 60ml can cause inhibition to VL in quadriceps, however parts of quadriceps or soleus already show motor neuron inhibition even with 30ml^{101,102}, and a 50ml detection threshold may not be sufficiently precise.

Further, this may indicate that the brush test and perometer are testing different types of oedema. I.e the brush test tests intra-capsular effusion and the perometer tests extra-capsular oedema. It would be useful to have measurement methods that could encompass both. Much of the oedema and swelling from an ACLR is within the joint capsule, however there is a large volume of oedema around the portal sites and the graft harvest sites (pes anserine-hamstrings, and patella tendon – patella tendon graft). Measurement, therefore, should encompass both intra and extra-capsular aspects of knee swelling.

LIMITATIONS

The perometer measures whole limb volume and does not discriminate between intra versus extra-capsular volume and it is not possible to determine if the volume changes seen after ACLR related to intra-capsular or extra-capsular swelling. It is also not possible to determine which tissues comprise the total knee volume.

We had seven subjects lost to follow up after their initial measurement visit. They may have affected the results of this study, however, this is less likely as, for the reliability study the subjects' knees were only compared within measurement visits and for the same knee, comparisons were not made between knees or between measurement visits for this study.

CONCLUSIONS

The perometer is a reliable method for measuring knee volume after ACLR. The reliability and validity findings in this study were similar to the levels found in other studies that investigate knee and lower limb volume with the horizontally orientated perometer. This shows that the perometer is a useful tool to measure knee volume in a knee surgical cohort before and after ACLR surgery.

The brush test is a rapid easy complimentary clinical test to register the presence of an Intra-articular effusion but cannot be used to discriminate grades beyond grades of small or large.

CHAPTER 3-INTERVENTION FOR CONTROL OF SWELLING IN ACLR

BACKGROUND / INTERVENTIONS FOR SWELLING

Having established the perometer as a reliable and repeatable method to evaluate alterations in knee volume, we designed and executed a randomised controlled clinical trial investigating the effects of methods to control swelling in a postoperative ACLR model.

It is very difficult to find a consistent model of injury or joint damage and, although ACLR is not a perfect model, it represents a reasonably consistent operation with similar level of surgical trauma applied to the knee. Because the swelling and bruising and initial inflammation last longer than just 24 or 48 hours and because the patients require consistent follow up it allows an opportunity to study knee swelling and effusion over a period of time. This also allows the application and evaluation of interventions to prevent, limit or “treat” swelling and to assess their effects. The perometer provided an ideal, easy to use, tool to assess patients in this situation and to evaluate changes in knee volume following interventions.

This study evaluated one device that is commonly employed clinically with the stated aim to reduce inflammation after knee surgery, the Cryocuff. These devices are one of the main tools globally that orthopaedic knee units use to control or treat knee swelling and pain in the postinjury, postoperative and rehabilitation periods. This chapter reports a randomised controlled trial investigating the Cryocuff versus a traditional method of swelling control – Robert Jones Bandage.

THE CRYOCUFF

The Cryocuff is a commercially available, dry cooling device which has been widely used globally to cool and compress the knee after ACLR and other forms of surgery (Don Joy Orthopaedic DJO Global, Aircast, Summit, NJ, USA). It comprises an ice and water filled bucket and a tube leading to a plastic cuff placed around the knee. It uses gravity with a cylindrical container held above the knee, allowing a flow of ice cooled water through the tube into the cuff, and in the opposite direction, allowing the water in the cuff to flow back to the bucket for re-cooling before returning to the knee.



Figure 18 Cryocuff applied to the knee with container and connection hose

It is advantageous post-surgery, as it provides a dry mode type of cooling- without wetting dressings and introducing infection risk. It has been shown to cool to intra-articular (suprapatella pouch) temperatures ranging from 28°C (normal temp 33.7°C) and to skin temperatures of 25.1°C¹²³. While not cooling to temperatures as low as ice applied directly to the knee, the Cryocuff cools gently, decreasing the risk of adverse effects of cooling such as frostbite²⁵⁶ or transient nerve palsy¹⁸³. Warren et al also found that the cooling effect

lasted after the cooling was removed¹²³. The manufacturers recommend lowering the container every 30 mins for one minute to allow cuff drainage of warmed water and replenishment with cooled water from the bucket (see Appendix 1).

It provides some compression which varies with the height of the water bucket above the cuff around the knee. The cooling bag/compartment portion of the cuff is anterior and is attached by proximal and distal straps which wrap around the supra-patella and infra-patella sections of the limb. This is supposed to avoid circumferential compression in the popliteal space posteriorly, which avoids compression popliteal nerves and vasculature, however there are no studies that offer a definitive answer to the distribution of compression around any joint including the knee. It would appear that the cooling effect is not uniform and the anterior to medial and lateral aspects are cooled more than the posterior portion of the knee. It appears that the proximal and distal circumferential straps may also give a tourniquet effect to the limb.

This type of device has been studied since 1994.^{117,123,254,308,309} Whilst not cooling intra-articular temperature as low as ice bags, it has been found to cool intra-articular knee temperature to 25°C (corresponding skin temp 15°C)¹²³. Some studies, however, have not shown any extra benefit to patients who use the Cryocuff after ACLR.^{252,254-256,310,311}

There are a relatively small number of clinical studies reviewing the effects of the Cryocuff after ACLR surgery. Two studies have investigated the effectiveness of the Cryocuff after anterior cruciate ligament reconstruction.

Barber et al²⁵² studied 100 patients for the first week post patella tendon ACLR, using a continuous flow cold device connected to a bladder, incorporated into the compressive dressings. A control group had dressing only, as empty bladder (or room temperature water filled bladder) were thought to be provocative of pain. Their outcomes were pain, measured with a vas and likert scale, medication use, and range of movement. A measure of swelling

was taken but the method was not specified. The post-operative regimen involved daily exercises and CPM (6-8hrs /d). Pain measured by likert scale, and VAS was found to be significantly less in the cold group for the initial post op day then moved toward equivalent levels by 6 days. Significance of pain levels after day 1 were not quoted, nor were standard deviations given. Medication use was not different for Percocet but was greater in the non-cold group for Vicodin up to day 2 – differences were then not significant. Interestingly while the non-cold group consumed more medication in the first days their pain levels were still higher. This raises the possibility of a placebo effect. As it is difficult to blind subjects to group in this sort of study, being randomized to non-intervention group may set up the possibility of a nocebo.³¹² At one week, swelling was not different between groups, however, flexion range of movement was better in the cold group. This may have been due to a significantly longer CPM usage in the cold group. In spite of significantly longer prone hang exercises in this group, the extension range of movement was not significantly different between groups. This study seems to suggest that the continuous flow cold therapy benefits pain in the early period (48hrs) but not in the later period (1-8 d post op) and does not benefit swelling.

In a study measuring pain in the first 48 hours post ACLR, Brandsson et al used the Cryocuff in combination with an injection of either intra-articular morphine and bupivacaine or normal saline⁹². A control group received intra-articular saline injection only. There was a significant difference in pain levels between the control and the Cryocuff group by approximately 1-2 VAS points at each time measurement point. The combined Cryocuff and morphine / bupivacaine group showed a significantly greater pain reduction (approximately 0.5-1 Visual Analogue Score points) than the Cryocuff group alone. There was also a significant difference between the treatment and control groups in analgesic use, but no difference between the Cryocuff and morphine only group. This suggests that, in the first 48hrs at least, the Cryocuff has a significant effect on pain reduction and analgesic use. Unfortunately Swelling was not measured.

A further study has investigated using the Cryocuff for the initial 3 days after ACLR, using the Cryocuff ²⁵⁴ with 3 groups including 2 control groups – having no Cryocuff, and room temperature Cryocuff. This potentially allowed for control of any placebo effect associated with using the Cryocuff. There were no significant differences between the groups in any variable measured, including blood loss, analgesic use, VAS pain scores and range of movement. These results may be complicated somewhat by the patients' use of patient controlled morphine and continuous passive movement machine. This suggests that the Cryocuff has no effect on pain or medication use in the initial 3 days post-surgery. Again swelling was not measured.

Cohn ²⁵⁶ investigated hot / cold thermal pads connected to a water pump for the initial 4 days post ACLR. The pad temperature was set at 50°F with pads on continuously, apart from physiotherapy or bathroom sessions. The amount of elevation was not stated. They found a significant difference between the thermal pad group for use of 2 medications, but not Vicodin and no difference in hospital stay. Pain and swelling were not measured. Other difficulties with this study involved a transient peroneal nerve palsy in one patient in the control group and several machine malfunctions. Although subjects were randomized, blinding was not reported.

Konrath et al used cold pads during a hospital 1day stay after ACLR, then for 3-5 days post discharge from hospital. They had a control and 3 treatment groups consisting of an ice pack group and 2 cooling pad (connected to pump and cooling device) groups (70-80°F and 40-50°F groups)²⁵⁵. Outcomes included: - drain output, length of hospital stay, use of pain medication and range of motion. There was no significant difference in any of the variables between the groups and no differences found between the cooling systems. No specific measures of pain or swelling were taken. They also mention the possible complicating effects of compression.

Most of these studies have investigated effects on pain (Table 7), rather than swelling (Table 6), and have used limb girth measurement, by tape measure, to assess swelling only as a secondary variable²⁵⁷. Single circumferential tape measurements, however, have been found to be inaccurate²⁸⁰, and cannot be extrapolated to give the measurement of volume^{251,313}. A recent review of the literature has found evidence for benefit of cryotherapy on pain after ACLR, but states that the evidence for reduction in edema is insufficient to draw definitive conclusions. Measurements of oedema were found to be somewhat subjective and imprecise²³⁰. No study to our knowledge has used a sensitive measurement device to evaluate knee swelling after ACLR.

Two further studies investigating cryotherapy after arthroscopic knee surgery. Lessard et al used gel packs post day surgery arthroscopy with patient use for 20minutes prior to exercises with 4 sessions per day¹⁴⁰. The control group performed exercises only, and both groups were measured pre and seven days post-surgery. There were no significant differences found between groups for pain scores (measured with the McGill pain questionnaire), knee ROM, knee girth, and quadriceps isometric strength, however there was a difference in compliance noted, with the treatment group more compliant. They measured knee girth for swelling, but acknowledge that the effects of cryotherapy on knee girth, and the reliability and validity of knee girth measures remain unclear.

Daniel et al investigated cold therapy for the initial week post knee arthroscopy using cold pads with a control, and four different temperature treatment groups. There was a difference in skin temperature between the 5 groups. Other variables measured included knee girth, range of movement, pain scale scores and length of hospital stay. There was no significant difference in these variables between the groups, suggesting cryotherapy made no difference to these variables, including swelling measure – knee girth³¹¹.

The combined weight of these studies would seem to suggest that cold therapy with Cryocuff, pads or ice bags post ACLR provides no, or only very limited gains in patient outcome in the variables measured. Swelling was not measured in these studies, and knee girth was the only swelling measure, which is acknowledged to have questionable reliability and validity³¹⁴.

The use of the Cryocuff, and cryotherapy in general, while widespread post ACLR, has been based on the results from a very small number of studies. Whilst there is evidence of an effect of cryotherapy on temperature (skin and intra-articular temperature), there does not seem to be translation to strong positive effects on pain post ACLR, and no study has effectively measured the cryotherapy effect on swelling.

Despite the limited evaluation of the Cryocuff's effect on joint swelling after injury and surgery, and even less available information on the effects of limb elevation, these treatments continue to be commonly used in clinical practice.

Table 6 Summary of studies that have evaluated the effects of knee cooling on SWELLING after anterior cruciate ligament reconstruction

Author	Treatments evaluated	Graft type	Overall treatment duration	Daily treatment duration	Test points	Swelling measure(s)	Findings
Present	Cryocuff/elevation	HS - STG	2 weeks	Continuous 8.5hr/d wk1 7.1hr/d wk2 Elevation 8.8hr/d wk1 6.6hr/d wk 2	Pre-surgery; recovery room; 2, 6 & 12 weeks	Infrared volumetric Perometer	No difference in knee volume change between groups
Dervin et al. (1998)	Cryocuff cooled vs. uncooled	PTG	Hospital stay (55-60 hrs)	Constant	24 hrs post-surgery	Intra-articular drainage	No significant differences between groups
Edwards et al. (1996)	Cryocuff cooled water vs. uncooled water vs. neither	PTG	36 hours	Constant	Total drainage time (not stated)	Intra-articular drainage	No difference in blood loss between groups
Ohkoshi et al. (1999)	flow device w pads 3 groups: 5°C/ 10°C & control groups	HS - STG	48 hours	Constant	first 48 hrs after surgery	Intra-articular drainage	No difference in blood loss between the 10°C and control group but significantly lower in the 5°C group
Konrath et al. (1996)	flow device w pads 4 groups: 40°F / 70°F/ crushed ice & control	PTG	Hospital stay (48 hours)	Constant	Hospital stay (48hr)	Intra-articular drainage	No difference in blood loss between groups
Cohn et al. (1989)	flow device w pads 50°F group vs. control	PTG	Hospital stay (4 days)	Constant	Hospital stay 4 days 1d drainage	Intra-articular drainage	No difference between groups. Swelling resolved between 3 and 6 weeks regardless of group.
Schröder & Pässler (1994)	Cryocuff vs. ice	PTG	14 days	Cryocuff constant, ice 3 times/day	1,2,3,6,14 & 28 days after surgery	Intra-articular drainage and knee + calf girth – tape measure	Calf girth less in Cryocuff group knee girth only less day 3 + 6 (superior patella) Mid patella girth No difference
Daniel et al. (1994)	flow device w pads 5 groups :40°F/45°F/ 55°F/ 70°F	PTG	Hospital stay (3-5 days)	Intermittent between CPM	3d, 10-14d post op	Knee girth – tape measure	No difference in knee girth between groups
Barber et al. (1998)	Continuous flow cold	PTG	1 week	Constant first 4 days then prn	1 week	Knee examination only	No difference in swelling

hr = hour / prn = pro re nata /HS-STG = Hamstring – semitendinosus graft /PTG= Patella tendon Graft / CPM= continuous passive motion

Table 7 Summary of studies that have evaluated the effects of knee cooling on PAIN after anterior cruciate ligament reconstruction

Author	Treatments evaluated	Overall treatment duration	Daily treatment duration	Test points	Pain measure(s)	Findings
Present	Cryocuff/elevation	2 weeks	Continuous 8.5hr/d wk1 7.1hr/d wk2 Elevation 8.8hr/d wk1 6.6hr/d wk 2	Pre-surgery; recovery room; 2, 6 & 12 weeks	VAS for all but recovery room (Likert)	Recovery Room -pain higher in standard group but not significantly Post-day surgery stay – no significant differences in pain at any time point tested
Barber et al. (1998)	Continuous flow cold	1 week	Constant first 4 days then prn	1, 2, 8 hrs post-surgery then daily for 1 week	VAS & Likert	Pain higher in non-treatment group but only significant difference at day 1 post-surgery.
Dervin et al. (1998)	Cryocuff cooled vs. uncooled	55-60 hours	Constant	24 hrs post-surgery	VAS	No significant difference between groups
Edwards et al. (1996)	Cryocuff cooled vs. uncooled vs. neither	36 hours	Constant	Evening of surgery; 24 & 48 hrs	VAS	No significant difference between groups
Ohkoshi et al. (2000)	Icing System 2000 at 5°C, 10°C & none	48 hours	Constant	Worst pain in first 48 hrs after surgery	VAS	10°C group pain significantly less than other 2 groups
Schröder & Pässler (1994)	Cryocuff vs. ice	14 days	Cryocuff constant, ice 3 times/day	1,2,3,6,14 & 28 days after surgery	VAS	Cryocuff only significantly less on day 6.

hr = hour / prn = pro re nata / VAS = visual analog scale

AIMS

This clinical study had several aims. Firstly, to compare two treatments which aim to prevent or limit knee swelling after surgery - the normal postoperative treatment (a Robert Jones bandage) with a regimen of cooling and elevation applied by a Cryocuff and a wedge pillow. Secondly, to measure and compare knee volume using a perometer before and after ACLR surgery.

HYPOTHESES

The following hypotheses were formed: -

1. Mean knee volume in our sample would increase after the ACLR from preoperative levels.
2. The pre to postoperative change in knee volume after ACLR will differ between patients who receive a regimen of Cryocuff cooling in elevation (cooling , elevation and compression) in the early post-operative period versus patients who receive a regimen of compression alone (Standard RJB bandage treatment)
3. The perometer would reliably measure knee volume after ACLR

METHODS

PATIENTS

A total of fifty one Anterior Cruciate Ligament deficient (ACLD) patients were recruited between September 2008 and October 2010 from orthopaedic clinics of two Orthopaedic knee surgeons (FSH/JVP) at University College London (UCLH) NHS foundation trust. All patients had a diagnosis of ACL tear after clinical examination of the Consultant Orthopaedic surgeon, and were on the waiting list for ACL reconstruction (ACLR) surgery. Patients were recruited by the researcher (BP) several weeks after study information was given in the orthopaedic or preadmission clinic, allowing time to consider taking part. Patients were included if they had primary ACLR with a semitendinosus and gracilis graft. Note of concurrent procedures was made for data analysis. Patients were excluded if they had systemic rheumatological conditions or conditions causing lower limb oedema, such as vascular insufficiency or diabetes. Patients with contra-lateral knee pathology were also excluded. If the patient had a concurrent ligament reconstructions with the ACLR (e.g. Posterior cruciate ligament reconstruction), they were also excluded, as rehabilitation landmark times differ significantly in these groups.

ETHICAL APPROVAL

Ethical approval for the study was obtained through the National Health Service (NHS) Committee of Research Ethics Committees (COREC) and the joint UCL/UCLH ethics committee A, with approval number 05/Q0505/120 (See Appendix 3). Written informed consent was obtained from all subjects before testing with the participant information leaflets and consent forms given and written informed consent taken prior to taking part (Appendices 4 and 5). Ten Cryocuffs were donated for the research study by Don Joy Orthopaedic.

The larger trial, of which this study formed part, was also registered for an International Standard Randomised Controlled Trial Number (ISRCTN) - 30554985 (DOI 10.1186/ISRCTN30554985) and a Protocol/serial number N0209181918.

Information can be found at the below web site –

<http://www.isrctn.com/ISRCTN30554985?q=cruciateligamentreconstruction&filters=&sort=&offset=8&totalResults=17&page=1&pageSize=10&searchType=basic-search>

STUDY DESIGN AND RANDOMISATION

Study design followed an experimental randomised single (experimenter) blind controlled clinical trial. Recruitment into the study was made after approaching and screening appropriate patients from the knee unit they were identified by the clinical team and given written and verbal information about the study, and were contacted by the author prior to their ACLR surgery and given any further information they required and were given one week “cooling off” period to consider participation. Written informed consent was taken from each participant at the start of this session, prior to taking measurements. Following consent and the initial measurements, patients were randomised into 2 groups: the Normal Treatment Group; and the Swelling Control Group. Block randomisation to the 2 groups was made in blocks of 4, by a research colleague, external to the acute knee team using a statistics software package – GraphPad InStat version 3.00 for Windows (GraphPad Software, San Diego California USA, Copyright 1992-1998 GraphPad Software Inc.). This was then communicated to the surgical recovery room staff, who applied the intervention based on this randomisation (normal treatment, or Cryocuff and leg elevation wedge immediately post-surgery, as soon as the surgery was completed, and the knee incisions were closed). Due to the nature of the study (as for other Cryocuff studies) it was not possible to completely blind patients to their group, however, they were blinded for the first 2 hours of the intervention, until they awoke sufficiently to know their group. They were instructed not to communicate this to their

treating therapists or the author (BP) in order to ensure both remained blinded. The researcher (BP) performing the measurements remained blinded to group throughout the data collection period, as did all of the treating physiotherapists.

PREOPERATIVE MEASUREMENTS

PREOPERATIVE ASSESSMENT

Baseline data were recorded to ensure our sample groups were equivalent in body height, sex, body mass and body mass index (BMI). Injury data were also recorded: method of injury, time from injury to surgery.

Measures were taken of the knee during a preoperative visit within one week of the surgery, and for the majority of the patients, in the two days before the surgery. Measures taken included measurements of knee volume, questionnaires to measure knee function, a brief knee examination, and tests of knee laxity. Measurements were made at the same time of day in similar order with an initial period of sitting to complete questionnaires to allow a “quiet” knee for testing.

KNEE SWELLING

The primary variable measured in this study was knee volume. It was measured using a Perometer (Perometer 350S, Pero-System, Wuppertal, Germany) using the method described in the previous chapter. Perometer measures were taken of both knees preoperatively and at day 12 postoperatively before the follow up visits to the morning orthopaedic knee clinic appointment, although several patients did not attend this appointment and they were tested 2 days later the same week, and just prior to their physiotherapy appointment (morning times only – to ensure consistent testing procedures). Perometer testing was also performed at week 6, again after the morning orthopaedic clinic visit, again, several patients were unable to attend this and were tested several days later in the same week.

SUBJECTIVE KNEE FUNCTION QUESTIONNAIRES

The questionnaires were chosen based on validity, reliability, sensitivity to change, and utility, and included the below questionnaires. The subjective questionnaires were administered both preoperatively and postoperatively at the clinic visits at 2 weeks, 6 weeks, 12 weeks, 6 months, and the order of the questionnaires was varied between visits and patients to minimise order effect.

THE INTERNATIONAL KNEE DOCUMENTATION COMMITTEE KNEE FORM (IKDC), (SUBJECTIVE SECTION)

The IKDC is a standard tool for the assessment of knee outcome and function after ligamentous injury in the knee. The IKDC consists of a comprehensive form, and contains six subsections: a demographic section, current health assessment, subjective knee evaluation, knee history, surgical documentation^{315 316}. This score was developed by an international collaboration group, which has developed a consensus score which has become a gold standard tool for the subjective assessment of function after ACLR. The questionnaire was refined using two initial versions with 48 and 41 questions, respectively. These 2 versions were pilot tested for reliability and validity in several orthopaedic centres in North America and Europe. It is a widely used questionnaire for knee ligament reconstruction outcomes. Only the subjective part of the questionnaire was used in this study.³¹⁷ Scores are calculated to a score out of 87, anchored by zero, which represents very poor function and 87 represents normal or highest level function (see Appendix 6).

THE LYSHOLM KNEE SCORING SCALE

The Lysholm score also measures knee function³¹⁸. Patients are asked to grade their responses to questions such as “How much pain do you have?” and “How much do you notice your knee swelling?” It is one of the oldest subjective outcome questionnaires used in ACLR. A modification was made in 1985 with a question added on locking and a question related to

thigh atrophy excluded. A total of 8 questions are answered, with a score being calculated out of a maximum of 150.

THE TEGNER ACTIVITY SCALE

The Tegner Activity Scale ³¹⁹ is used to measure current activity level with a scale from 0-10, with lower impact, speed and pivoting activities scoring lower on the scale and high impact, twisting, pivoting sport activities such as “international football”, scoring higher. Tegner activity score was recorded preoperatively and for pre-injury level in this study. The Tegner and Lysholm scores (see Appendix 7) were initially developed together, then separated, because running, walking, and participation in recreational sports formed different levels on the International Classification of Impairments, Disabilities and Handicaps (ICIDH). ³²⁰ Test – retest reliability and criterion validity have been tested, as has responsiveness. ^{318,319} A more recent review also suggests good performance of both Tegner and Lysholm score in areas including: Test-retest reliability, internal consistency, Content, criterion and Construct, Validity and responsiveness. ³²¹

THE LOWER EXTREMITY FUNCTIONAL SCALE (LEFS)

The lower extremity functional score (LEFS) was used to measure functional lower limb ability as a functional scale with score from 0-80, with 0 representing very low level of function and 80 representing high functional level ³²². Twenty questions are asked, covering daily activities such as getting up from a chair as well as higher impact activities, such as making sharp turns while running fast. Patients rate their level of difficulty with Likert type scale (0-4) for each question (see Appendix 8). The LEFS is easy to administer and relevant for a variety of lower limb orthopaedic conditions. Reliability, validity and sensitivity to change have been assessed in comparison with SF36 ³²².

PAIN

Pain was measured using the 0-10 subjective rating scales on the IKDC subjective form (see Appendix 6). Question 2 and 3 on the form respectively deal with frequency and Intensity of pain. Measures of pain, therefore, were taken with each administration of the IKDC form.

Initial postoperative pain was measured in the recovery room with a likert pain scale (0-4) used by Barber et al (1998) in their study using continuous cooling after ACLR.²⁵² 0-4, which is used in an anaesthetic recovery situation when a patient is recovering from an anaesthetic and is unconscious or only partially conscious. While VAS scores would be more ideal, VAS scores are difficult for patients in the initial minutes waking from anaesthetic. Score was recorded by recovery room nurses every 10 minutes during the recovery room stay (40-50 minutes).

KNEE JOINT LAXITY

Knee joint laxity was measured using a KT-1000 Arthrometer (MEDmetric Corporation, San Diego, California, USA). It is the most commonly used, and most frequently tested knee ligament testing device for measuring Anterior Posterior plane laxity in the knee³²³, with use starting in 1985³²⁴. It has been tested for accuracy and reliability³²⁵, in measuring the amount of anterior tibial translation produced by a controlled force in normal knees³²⁴, ACL deficient knees^{326,327}, and ACLR knees³²⁸. The measurement technique applied in this study, followed that of Daniel et al (1985) and MEDmetric Corporation's Reference, Maintenance & User's Guide for the Knee Ligament Arthrometer³²⁹, with positions and zeroing of baseline following this reference guide. The measurement positions can be seen in Figures 18-20.

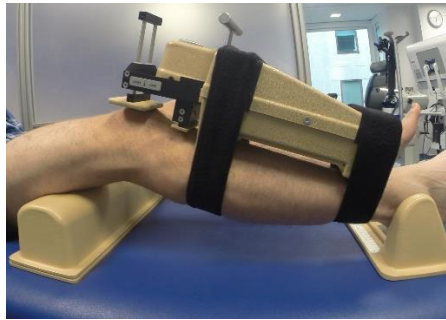


Figure 19 KT1000 dynamometer start position



Figure 20 KT1000 measurement dial zeroed prior to initial measurements

Audio tone signals occurred when the force through the handle reached 15 (67N 6.8kg), 20 (89N 9.1kg), and 30lb (13.6kg N) of force. Note was made of the value in millimetres on the AP tibial displacement measurement dial. This testing was repeated 3 times, and then a further Manual Maximum test was performed by drawing the tibia forward, applying force by hand to the posterior aspect of the calf for each leg with the unaffected leg tested first (see figure 20).



Figure 21 KT1000 Manual maximum test

The manual maximum test was added, as this has been found to be the most sensitive test, with sensitivity and specificity found to be 92% and 95%, respectively³²⁷. The manual maximum test was also repeated 3 times and the displacement value recorded for each test. When the unaffected leg completed testing, the tests were repeated on the affected leg, and the differences in displacement between the unaffected and affected leg were noted.

The Intra tester reliability of the KT1000 is measured with intra class correlation coefficients (ICC) between 0.9 and 0.99, with the Standard Error of the measurement (SEM) at 0.3-0.6mm³³⁰. In a further study, the Standard Error of the difference (SED) was found to be to be 2-3 mm, with 2 SED at 4-6 mm, to be 95% confident of difference in two measurement³³¹. Experience is one factor that has been found to affect accuracy³³⁰. To improve accuracy, all tests were taken by the same experienced examiner who had previously performed more than 300 KT1000 tests.

OPERATIVE PROCEDURE

Patients underwent early morning ACLR surgery with 4 strand single bundle semitendinosus and gracilis grafts. All operations were performed by the same orthopaedic consultant Team (FSH/ RVP), using the same technique. The sequences of the surgery involve application and inflation of a tourniquet (figure 21) after the initial skin preparation and draping. This was inflated to 300mmHg and left on throughout the procedure. It was released after wound closure dressings and the application of the Coban and Crepe bandages.



Figure 22 Tourniquet applied prior to the surgery

The initial graft harvest with a pes anserine anteromedial proximal tibia region vertical incision. The semitendinosus and gracilis tendons were harvested from here under the skin, and the graft was prepared with these tendons combined and sutured to form a four strand graft (figure 22). During the graft preparation the orthopaedic consultant performed an arthroscopy on the knee joint and documented any concurrent pathologies and concurrent procedures performed within the joint. The Outerbridge classification system was used to grade cartilage change, with a grading of 1-4 for thickness change.^{332,333} Tears of menisci were repaired, partially excised or left alone. Chondral lesions were drilled or left alone (there were no lesions in our cohort that required repair).

The surgeon then prepared the joint to receive the ACL graft, by drilling the tibial and femoral tunnels and inserting the graft. A small endo-button (see figure 23 and 24) and suture system was used for the fixation point for the femoral side of the graft. On the tibial side of the graft

a headless interference screw (figure 23 and 25) was inserted to fix the tibial end of the graft. Finally a small metal staple was inserted over the graft remnant at the end of the tibial tunnel (figure 26) to hold this graft remnant down. Note was made of the size of the fixation components and the size of the femoral and tibial tunnels, which corresponded respectively to the diameters of the femoral and tibial ends of the graft.

All patients received intra-articular infiltration of bupivacaine (10ml, 0.5%) and morphine sulphate (10 milligrams (mg)) and subcutaneous infiltration of bupivacaine (10ml, 0.5%) to the arthroscopic portals at the end of the procedure³³⁴.



Figure 23 Preparing the ACLR graft after the hamstring and gracilis harvest



Figure 24 Lateral radiograph of the knee after ACLR with fixation shown – the interference screw and the staple in the tibia and the endobutton sitting on the surface of the cortex of the femur in the lateral suprapatella area



Figure 25 Endobutton



Figure 26 Interference Screw



Figure 27 Metal staple onto tibia to hold final graft remnant down flush onto the tibia

CRYOCUFF INTERVENTION

In the immediate postoperative period, as soon as possible after wound closure, dressing, and tourniquet release, a sterile compression bandage was applied to the operated knee for all patients. This is the normal infection control practice of the UCLH Knee unit. The compression bandage comprised 1 layer of Coban (3M, St Pauls, MN, USA) type wrap, and 1 crepe bandage²⁴⁹. The bandage was removed at 48 hours by the patients at home. Dressings covered the extent of the wounds only. The swelling-control group received additional treatment, with application of a Cryocuff (Don Joy Orthopaedic DJO Global, Aircast, Summit, NJ, USA) bandage and a foam leg wedge pillow (Richardson Products IL USA) to elevate the operated leg as high as possible (typically around 40 degrees, and above heart. The bed was inclined up at the foot end to aid this. This was, however, within safety boundaries of maintaining a safe airway in the anaesthetised patients. Recovery room nursing staff applied the Cryocuff and elevation wedge pillow, after 2 training / education sessions explaining the study and the correct use of the Cryocuff. The method of application followed that of the Cryocuff instruction leaflet (see appendix 1). The cuff was placed on the knee, with the posterior straps attached as the manufacturer's instructions recommend, gently without strap tension. As per the instructions, an initial 5 minutes was allowed for the cooler to sit after the ice and water were added. The water and ice was then mixed to allow the cold water to mix before connection to the cuff via the connecting tube, and the water then flowed from the container into the cuff. The recovery room staff used an adjustable drip stand to hold the filled Cryocuff cooler container above the knee. They were encouraged to maintain a height of approximately 20cm of the cooler above the knee. The Cryocuff operating instructions recommend not going beyond 38cm to avoid excessive pressure. Instruction recommend a 6-8 hr treatment period, with reconnection of the connecting tube from the cuff to the cooler, and lowering of the cooler to remix the water. Initial lowering and remixing was performed

after 15 minutes, then every 30 minutes thereafter. Training for the recovery room staff was repeated at several intervals through the year, and several site visits were completed by DJO/Aircast representatives, independently of the researcher, to review the recovery room staff application of the device, and to ensure correct application of the Cryocuff, in line with the manufacturer's specifications.

Post-operatively, both groups received standard rehabilitation (see the enclosed ACLR protocol Appendix 2). In the initial 2 week post-operative period regular gentle range of movement and muscle activation exercises were performed each day (every hour) in both groups. The Cryocuff group were additionally required to maintain their legs in elevation, with the Cryocuff on and filled, between hourly exercises. Both groups were allowed to fully weight bear and be as active as they wished within pain limits per the normal practice in the UCLH knee unit. Group 1 (Cryocuff) patients, however, were asked to attend to regular use of the Cryocuff through the day, with the cooler filled with ice and cold water several times per day for the first 2 weeks. The normal treatment group was given no instructions to maintain elevation or icing. Both groups were permitted to fully weight bear with crutches and to start exercises from the day surgery ward after their surgery. Both groups received instructions to remove bandages and Coban padding after 48 hours, and to increase work on range of movement exercises. Wounds were still covered by small adhesive dressings which conformed closely to the skin around each wound. These were left on until the first postoperative clinic visit, when stitches were removed and a further small skin conforming dressing was applied. Wound care instructions and infection warnings were given to all patients, as were circulation exercises and DVT warnings, as is the normal practice at UCLH.

The swelling-control group were provided with their own Cryocuff for use within the first two weeks, together with instructions on its use, given both verbally, prior to participant consent, and written with the Cryocuff instructions. A further set of instructions for use were printed

on the side of each Cryocuff ice container (see Appendix 1). This group were asked to rate their average daily use of the Cryocuff. Outpatient appointments were made for knee clinic review at 12 days post-operatively. Physiotherapy rehabilitation commenced after the initial post-operative clinic visit (between 10 – 21 days post operatively) and followed the attached protocol (Appendix 2) for all patients. Outpatient physiotherapists who provided the rehabilitation were unaware of the patient grouping and remained blinded throughout the study period.

POSTOPERATIVE MEASURES

Perometer measures of knee swelling were repeated at the patients' clinic visits at 2 weeks (12 days postoperatively) and 6 week clinic or physiotherapy visits. Three Measurements were taken of each knee, at each Perometer measurement session. Functional Questionnaires, and KT1000 laxity tests were repeated at each post-operative clinic visit or at post-operative physiotherapy visits at 2 weeks, 6 weeks, 3 months, and 6 months. All perometer measures were taken in the morning, and where possible, measures were taken at the same time of morning, before the clinic or physiotherapy appointment. The order of testing was consistent, with questionnaires completed initially, then KT1000 laxity measures, followed by Perometer measurement. This aimed to minimise activity or temperature effects on connective tissues and swelling.^{335,336}

Immediate post-operative measurements included analgesic medication use and time given post-surgery was recorded from the drug charts. Finally, the time to reach the day surgery discharge criteria (ie subject was ready for discharge) was recorded from the day surgery discharge summary. A further pain measure was taken from the IKDC forms questions 2 and

3, recording 0-10 values for pain intensity and frequency at each questionnaire completion pre and post operatively (see Appendix 6).

Some early post-operative factors were also recorded from patient diaries (see Appendix 9) of the initial 2 weeks post-operatively, including: average daily: medication use (Anti-Inflammatory, codeine based and Paracetamol), elevation time, standing and walking time and home exercise frequency. These were taken in order to check compliance with the Cryocuff regimen. Finally, a knee physical examination was also performed at each measurement session with (ROM), laxity and swelling examination tests performed, as described in Chapter 2 and documented at 2 weeks, 6 weeks, 3 months and 6 months. Any complications were also documented including harvest site morbidity.

DATA ANALYSIS

Data were analysed using the Statistical Program for Social Sciences (SPSS 21.0, Chicago, Illinois) software package. T Tests were used for Comparison of group means with data for swelling measures and score values for questionnaires following a normal distribution. For the main outcome of knee volume a two way repeated measures ANOVA was used with between group effects considering time. Analysis of the interaction effect between group and time was carried out. An analysis of covariance (ANCOVA) was also used on the post-operative affected knee volume measurements, using the pre-operative affected knee volume measure as covariate. A 95% confidence interval was adopted with P values set at 0.05 for significance. Perometer measurement of knee volume (in ml) was the main outcome. Only one experimenter measured patients. Sample size was calculated, considering a statistical significance level of 0.05 with an 80% power and a clinically important treatment effect between groups, of 45 ml, with a standard deviation of 50ml. This volume was chosen based on the study by Palmieri-Smith et al where knee function was significantly altered with

experimental introduced knee effusions of 60ml. There were some effects found with effusions of 30ml but not the significant effects that an effusion of 60ml had on quadriceps muscle Arthrogenic inhibition, where functional tasks were affected detrimentally³³⁷. An effusion of 45 ml was chosen for this sample size as it was considered that this volume of effusion could be argued to show clinically significant effects in the knee. An additional 10% for drop out gave a sample size of 22 patients per group.

Data were analysed with an on-treatment, and a treatment received analysis.³³⁸ An intention to treat analysis was also included for missing measurement data, with those patients included who were randomised. A conservative approach was taken with a “last measurement brought forward” approach. I.e their preoperative volume measure was brought forward as their two week postoperative measure. The analyses were repeated with this data modification also. A less conservative approach was also taken with average percentage change in volume from the rest of the sample applied to the missing patients’ preoperative volume to obtain an estimate of their postoperative knee volume.

RESULTS

124 patients attended the knee unit at our institution during the study period from September 2008 to June 2010, and were assessed for eligibility. Figure 27 summarises the exclusion and group randomisation for the study. In total, 51 patients had preoperative measurements performed, however, complete data sets were available for 43 patients. The flow diagram for the recruitment and retention of patients is below.

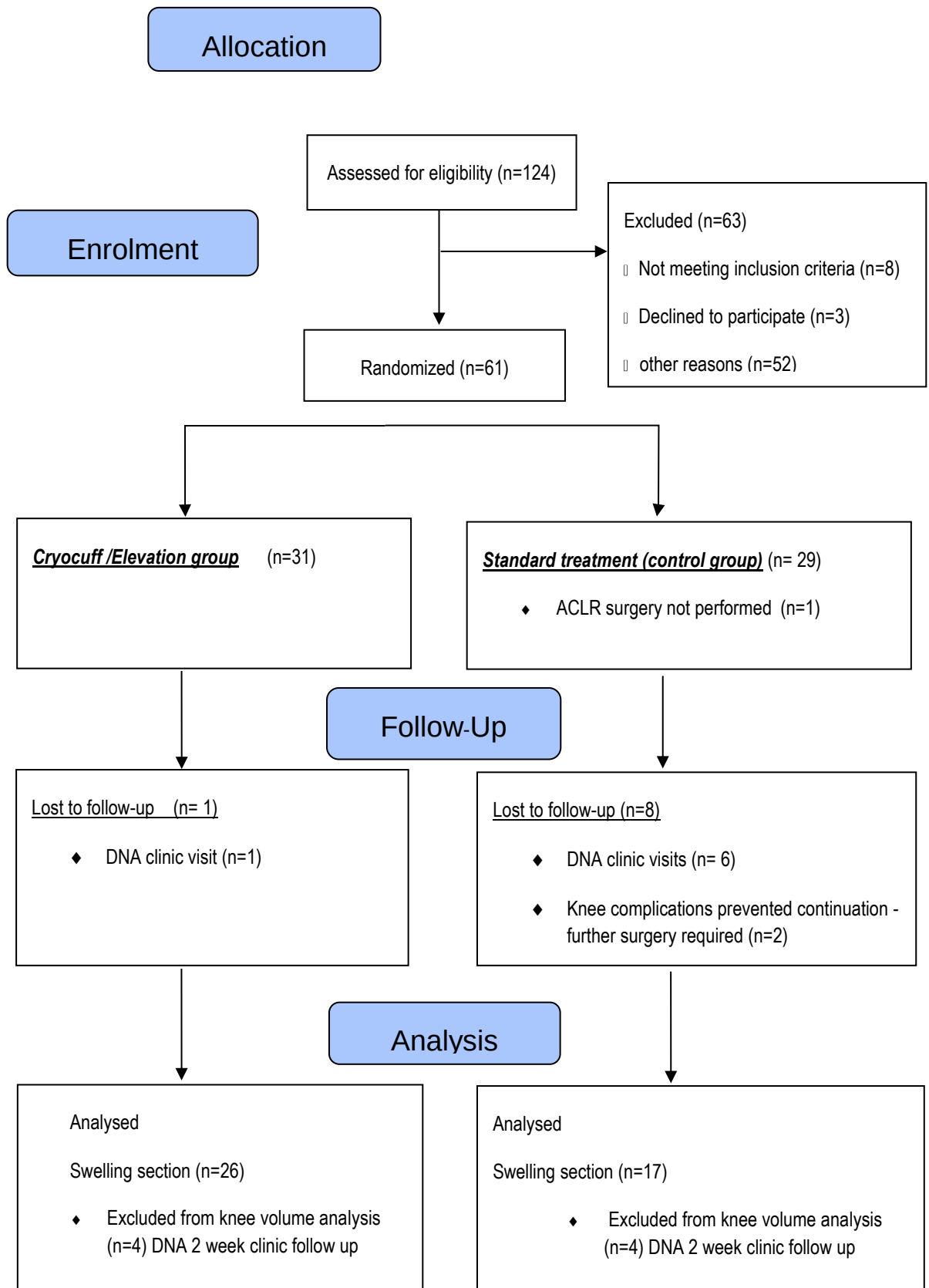


Figure 28 Recruitment and retention flow diagram Summarising recruitment patients lost to follow up and DNA (did not attend) clinic appointments

Baseline data showed equivalence between groups in Knee volume, demographic (Table 8).

Note that all P values relate to group comparison between the Cryocuff and the standard treatment group.

Table 8 Demographic and time to surgery data

Mean (SD, 95%CI)	Cryocuff group	Standard group	P-values
Number	26	17	
Male	14 (54%)	9 (53%)	
Female	12 (46%)	8 (47%)	
Mean Age (years)	32.3 (7.1, 29.5-35.2)	32.3 (9.0, 27.7 -36.9)	0.983
Body Height (centimetres)	173 (8, 170-176)	170 (9, 166-174)	0.284
Body Mass (Kilograms)	70.2 (11.0, 65.8-74.6)	76.2 (19.3, 66.2-86.1)	0.206
Body Mass Index (Kilograms per metre squared)	23.6 (3.0, 22.4-24.9)	26.3 (6.0, 23.2-29.4)	0.102
Time - injury to surgery (months)	39.5 (53.6, 17.9-61.1)	31.6 (35.3, 13.5-49.8)	0.597

The groups showed no significant difference at baseline for demographic variables. Mean mass was greater in the standard group by 6kg and the BMI was greater, however these differences were not statistically significant.

Surgical and pathology data (Table 9), are shown below, and significant differences were shown between the fixation sizes of the endobutton, with the mean larger in the standard group by 4mm. There were, however only 5 sizes of endobutton used – 15,20,25,30 and 40mm used. Only one 40mm button was used, and this was in the standard treatment group, this outlier skewed the results.

Table 9 Knee pathology and surgical data with tunnel size (millimetres) and tourniquet time (minutes)

Surgery Data		Cryocuff group (n=26)	Standard group (n=17)	P-value
Concurrent finding Meniscal tear	No meniscal pathology	8	6	0.757*
	Medial meniscus tear	3	5	0.272**
	Lateral meniscus tear	7	3	0.481*
	Medial and lateral meniscus tear	8	3	0.335*
Concurrent finding Chondral lesion	Medial compartment	5	4	0.735*
	Lateral compartment	3	2	1.000**
	PFJ compartment	4	4	0.692**
Concurrent medial collateral ligament injury		0	2	0.151**
Prior knee surgical procedure		5	4	0.735*
Tunnel size (millimetres) Mean (SD, 95%CI)		7.7 (0.5, 7.5-7.9) (n=21)	7.6 (0.8, 7.1-8.0) (n=14)	0.664*
Tourniquet time (minutes)		53 (13, 48-58)	52 (8, 48-57)	0.820**
Surgeon	FSH (n=32, 74.4%)	(n=19, 65.4%)	(n=14, 91.6%)	
	RVP (n=11, 25.6%)	(n=9, 34.6%)	(n=3, 8.3%)	
Fixation mean(SD, 95%CI)	Interference screw Diameter (mm)	8.72 (0.6, 8.5 -8.9)	8.63 (0.6, 8.3 -8.9)	P= 0.634
	Interference screw Length (mm)	27.1(5.5),25.029.2)	27.4(4.2,25.3-9.4)	P=0.851
	Endobutton (mm)	21.36 (3.8, 20.1,22.8)	25.0 (6.0,22.0-27.5)	P=0.012*

*Pearson's Chi-square test/ ** Fishers exact test (2 sided) / PFJ= patellofemoral joint

Knee volume and 2 week post-operative knee volume change (i.e. 2 week minus pre-operative knee volume) showed no significant differences between the groups when analysed using unpaired T tests (Table 10) (Figure 29 and 30).

Knee volume is recorded as 2 weeks post operatively. Patients attended measurement with their initial postoperative clinic visit at 12 days postoperatively. Several of the patients had this clinic appointment delayed and were measured 2days later. The results are therefore reported as 2 weeks postoperatively.

Table 10 Knee volume (millilitres) measured with the Perometer

Knee volume (ml) Mean (SD, 95%CI)	Knee	Cryocuff group (n=26)	Standard group (n=17)	P-values for group comparison
Pre-operatively	Unaffected	1202 (209, 1118-1286)	1198 (291, 1049-1348)	0.964
	Affected	1199 (169, 1131-1267)	1196 (271, 1057-1336)	0.969
2 weeks post-operatively	Unaffected	1196 (222, 1107-1286)	1211 (298, 1058-1364)	0.855
	Affected	1267 (170, 1198 -1335)	1263 (295, 1112-1415)	0.966
Pre surgery to 2 weeks post-operatively	Unaffected	-5 (39, -21- +10)	13 (54 , -15 - +41)	0.207
	Affected	68 (52, 47-89)	67 (64 , 34-100)	0.977
6 weeks post-operatively	Affected	1204 (148, 1080-1328) (n=8)	1368 (333, 1089-1646) (n=8)	0.234
Pre surgery to 6 weeks post-operatively	Affected	25 (41, -9-59) (n=8)	65 (68, 8-122) (n=8)	0.173

Mean affected knee volumes were equivalent between the groups preoperatively with mean of 1199 ± 169 ml for the Cryocuff group and 1196 ± 271 ml for the normal treatment group.

Mean change in affected knee volumes pre to 2 weeks postoperatively were 68 ± 52 ml for the Cryocuff group and 67 ± 64 ml for the normal treatment group. When this was converted to a percentage, this represents a mean knee volume change pre to 2 weeks postoperatively of 5.67 ± 4.34 % for the Cryocuff group and 5.60 ± 5.35 % for the normal treatment group.

The mean change in knee volume for the sample as a whole was 5.77 ± 5.01 %.

The repeated measures ANOVA did show significant within group and subject effects with respect to time with significant difference pre to 2 weeks and 6 weeks postoperatively ($p=0.12$ and $p=0.19$ respectively).

The between groups however showed not significant difference with ($p=0.986$ for both 2 and 6 week comparisons). The interaction effect group by time did not show significant effect ($p=0.298$).

Post hoc T tests revealed no significant differences between the groups for the affected or unaffected knee, with affected knee P values > 0.95 , strongly non-significant. This indicates that the Cryocuff did not show an advantage over the standard treatment of a RJB for reducing knee swelling in the first 2 weeks after ACLR. A further analysis of results used an ANCOVA test with 2week affected knee volume scores analysed via group, and corrected for preoperative affected knee volume, which was used as a covariate. This analysis was performed to reduce the within group error variance.

The results again did not show statistical significance $F<0.001$ and $P=0.991$.

Six week postoperative volume data were analysed using independent unpaired T tests for the two groups based on absolute Knee volume and also based on volume differences (ie 6 Week minus preoperative knee volume). There appeared to be a trend toward a lower volume difference at 6 weeks in the Cryocuff group, however, while the p values were less, there were still no significant differences between the groups. Caution is noted on viewing these results however as the number of 6 week scores was low (reducing the statistical power) as many subjects did not attend their 6 week clinic appointment, attending only at 3 months.

The 6 week affected knee volume difference pre to postoperatively was not significantly different from the 2 week affected knee volume difference pre to post op using paired T test. ($t=0.998$, $p=0.334$).

A further analysis of results used an ANCOVA test with 6week affected knee volume scores analysed via group, and corrected for preoperative affected knee volume, which was used

as a covariate. This analysis was performed to reduce the within group error variance. The results are displayed below, again with non-significance levels $F=0.851$ and $P=0.372$.

INTENTION TO TREAT

An intention to treat analysis was also performed to account for the 8 patients who did not attend their 2 week measurement. There were 51 patients who had preoperative measures taken. The initial analysis was performed with the initial knee volume measure for the affected knee brought forward for the 2 week knee volume. After this the scores are displayed in table

Table 11 Intention to treat analysis 1 – preoperative knee volume brought forward for missing data

Knee volume (ml) Mean (SD, 95%CI)	Knee	Cryocuff group (n=31)	Standard group (n=20)	P-values for group comparison
Preoperatively	Affected	1224 (188, 1155 -1293)	1231 (279, 100 -1361)	0.921
2weeks Postoperatively	Affected	1281 (183, 1214-1347)	1288 (292, 1151 -1424)	0.918
Pre to 2 weeks post-operatively	Affected	57 (54 , 37.1 – 76.4)	57 (64, 27.3 -86.8)	0.985

The mean postoperative volume for the sample with the missing values was found to be 1283.65 ± 233.47 ml. The change in knee volume pre to 2 weeks postoperatively for the sample as a whole was 56.86 ± 59.24 ml. The volume differences for the groups are shown in table – this represented a $4.79 \pm 5.73\%$ mean volume difference for the normal treatment group and a $4.91 \pm 4.67\%$ mean volume difference for the Cryocuff group. On testing the samples the T test showed no significant difference.

The second analysis used the mean percentage increase in affected knee volume (pre to 2 weeks postoperatively) for the sample as a whole. This was $5.77 \pm 5.01\%$. This was used to bring the volume forward for the patients with missing postoperative measures. See table 12 below

Table 12 Intention to treat analysis 2 – postoperative knee volume estimated from the percentage change in the sample as a whole

Knee volume (ml) Mean (SD, 95%CI)	Knee	Cryocuff group (n=31)	Standard group (n=20)	P-values for group comparison
Preoperatively	Affected	1224 (188,1155 - 1293)	1231 (279, 1100 - 1361)	0.921
2weeks Postoperatively	Affected	1294 (193, 1223 -1364)	1300 (301, 1159 - 1441)	0.924
Pre to 2 weeks post-operatively	Affected	69 (48, 51.8 – 86.9)	69 (59 , 41.7 – 97.1)	0.997

The mean postoperative volume for the sample with the missing values was found to be 1296.15 ± 234.11 ml. The change in knee volume pre to 2 weeks postoperatively for the sample as a whole was 69.36 ± 55.40 ml. The volume differences for the groups are shown in table – this represented a $5.65 \pm 5.35\%$ mean volume difference for the normal treatment group and a $4.91 \pm 4.67\%$ mean volume difference for the Cryocuff group. On testing the samples the T test showed no significant difference

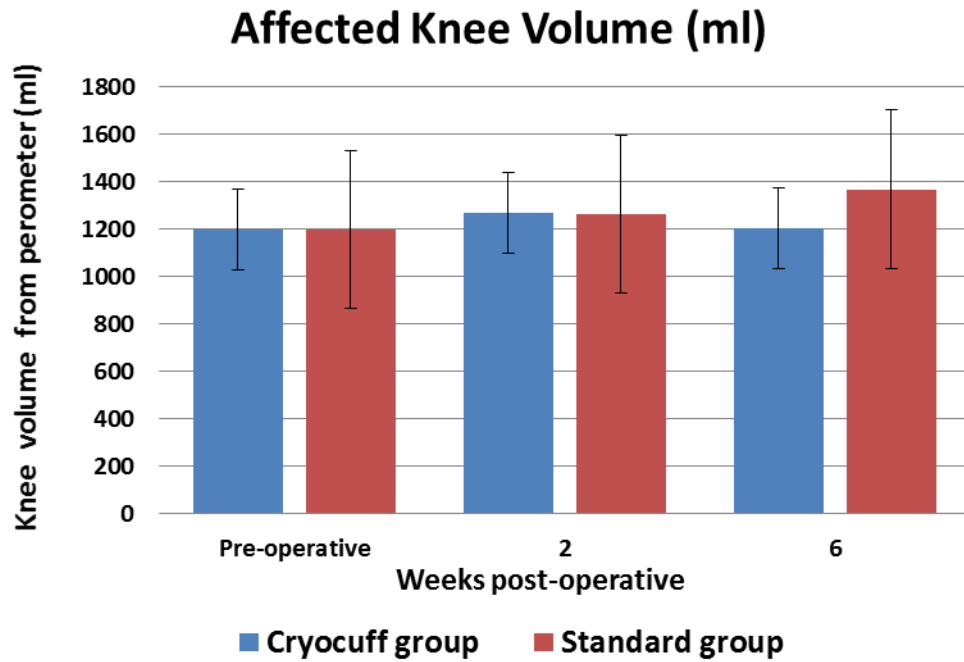


Figure 29 Affected knee volume (ml) means Pre-operative time point and at 2 and 6 weeks post-operatively in the two groups. Measured with the Perometer (V) (Note that in all figures – error bars represent one standard deviation above and below the mean).

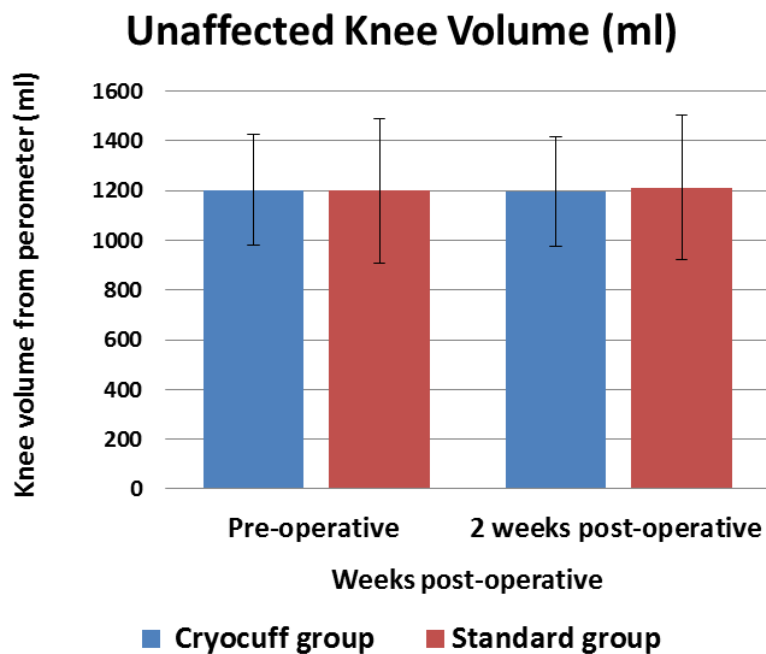


Figure 30 Unaffected knee volume (ml) means Pre-operative time point and at 2 and 6 weeks post-operatively in the two groups. Measured with the perometer

Knee pain did not differ significantly between groups at any time point (Figures 31-33), although the Cryocuff group showed a small trend toward lower recovery room pain scores (Figure 33).

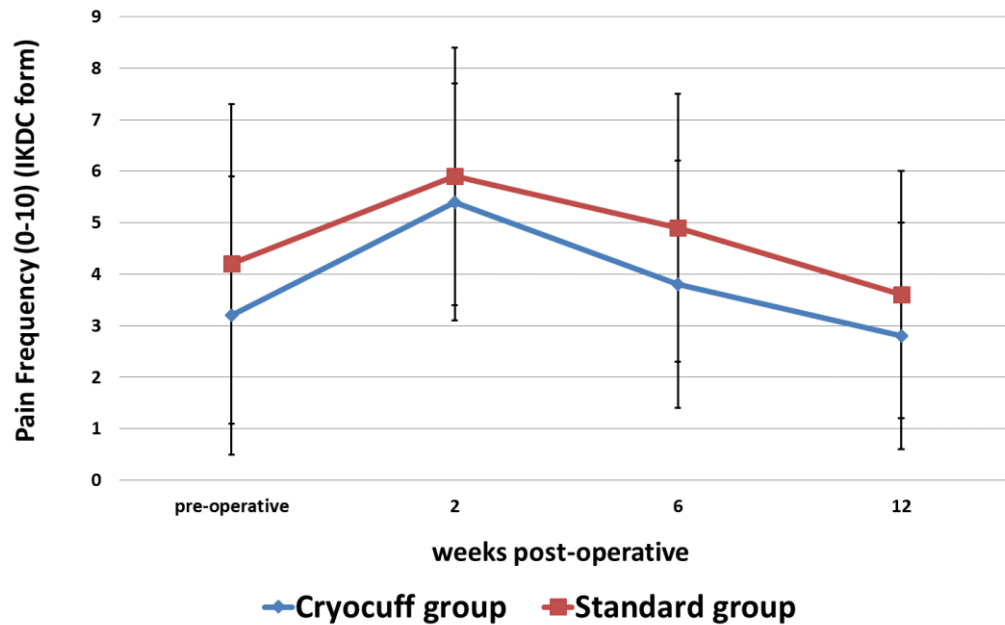


Figure 31 Mean knee pain before and after ACLR (Pain Frequency 0-10) from question 2 on IKDC subjective form (appendix 4)

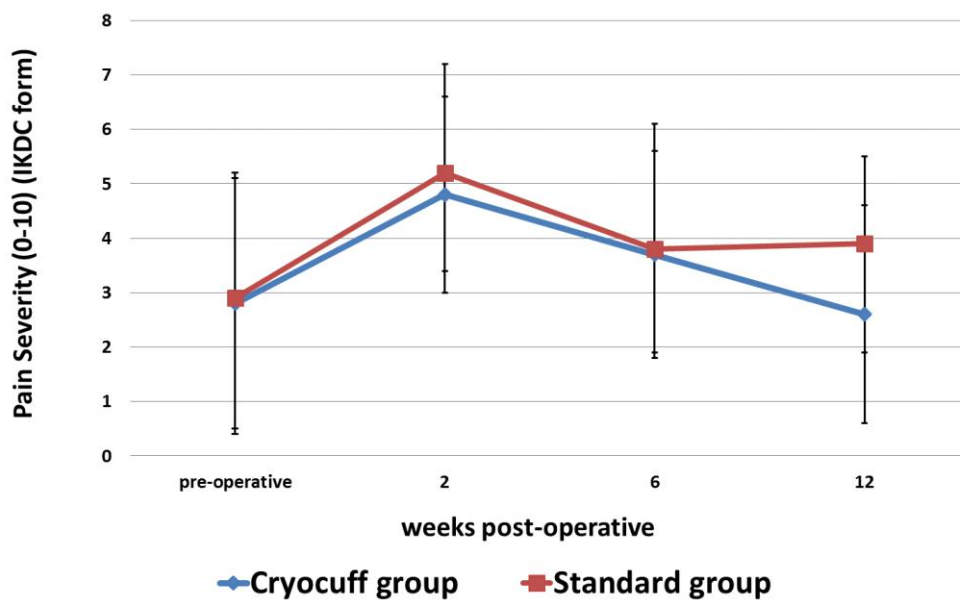


Figure 32 Mean knee pain before and after ACLR (Pain Severity 0-10) from question 3 on IKDC subjective form (Appendix 4)

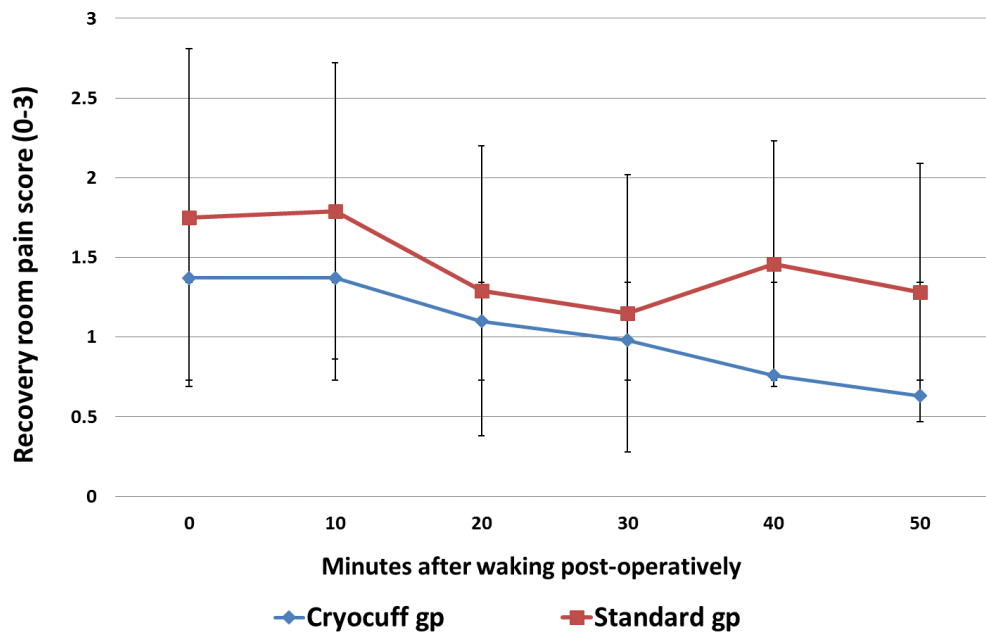


Figure 33 Mean knee pain (0-3 likert score) from waking to 50 minutes post-operatively Recorded in recovery room.

There was no significant difference in post-operative analgesia consumption between groups, except for Diclofenac, given in the recovery room, with a significantly higher amount in the Cryocuff group ($p=0.034$) (Table 13).

Table 13 Post-surgery to hospital discharge medication use

Drug (no of patients requiring)	Number of doses taken	Cryocuff group (n=26)	Standard group (n=16)	P-values for group comparison
Diclofenac	1	8	1	0.034 *
Ibuprofen	1	18	13	0.402
Paracetamol (1g- 6hrly)	1	24	15	
	2	0	1	
	overall	24	16	0.104
Dihydrocodiene (30mg 6 hourly)	1	24	12	
	2	2	4	
	overall	26	16	0.176
Tramadol (50mg 6 hourly)	1	13	12	
	2	0	0	
	3	1	0	
	overall	14	12	0.495

Significant to $p<0.05$ */ g= gram

There was no significant difference in post-operative analgesia consumption between groups, except for Diclofenac, given in the recovery room, with a significantly higher amount in the Cryocuff group ($p=0.034$) (Table 11). 1 patient had data missing from the recovery room notes and medication use was not obtainable. In the remainder of the sample, the medications used most were paracetamol/ Di hydrocodiene (DHC), with almost blanket use. Lower amounts of diclofenac / tramadol and ibuprofen were given. Only nine patients were given diclofenac (1 dose only) in the recovery room, with eight out of 9 in the cryocuff group, therefore the Cryocuff group had a significantly greater mean use of Diclofenac than the normal treatment group. Paracetamol use was significantly less in the Cryocuff group, and, while the use of ibuprofen was less in the Cryocuff group, the amounts were not found to be significant. Tramadol was used as a heavier analgesic and was not routinely given unless a patient's pain was more severe. It was also used less in the Cryocuff group, but without statistical significance. A second dose of DHC was given in the day surgery unit in six of the forty two DHC users, with the majority in the normal treatment group.

Knee function questionnaires (Figures 34-37), range of motion (Figure 38), and knee laxity (Figure 39) did not significantly differ between groups at any test point except for the 6 months Tegner score, which was significantly higher in the Cryocuff group.

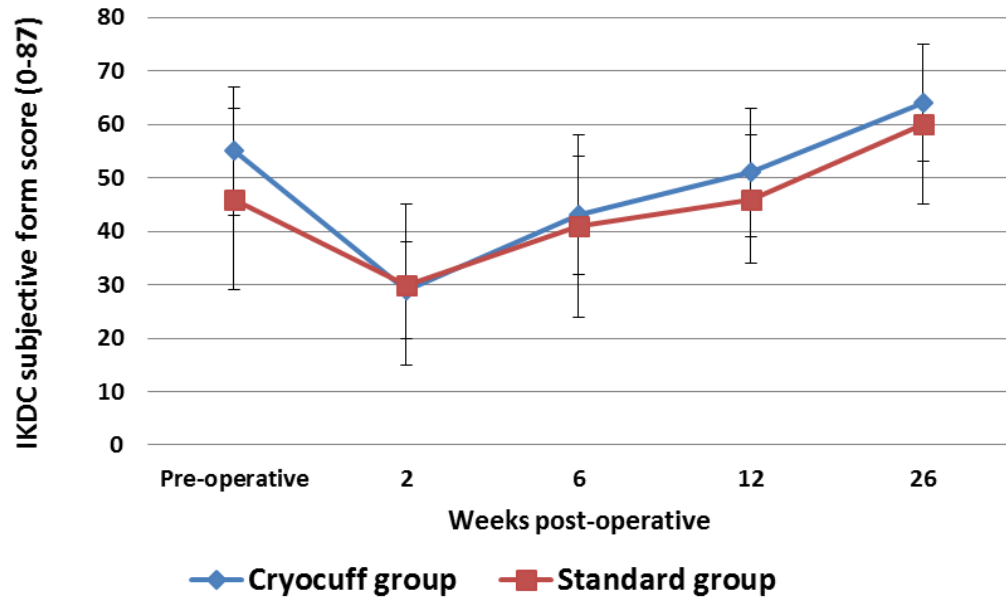


Figure 34 International knee documentation committee subjective form (out of 87) (appendix 4) Mean score and post-operative week

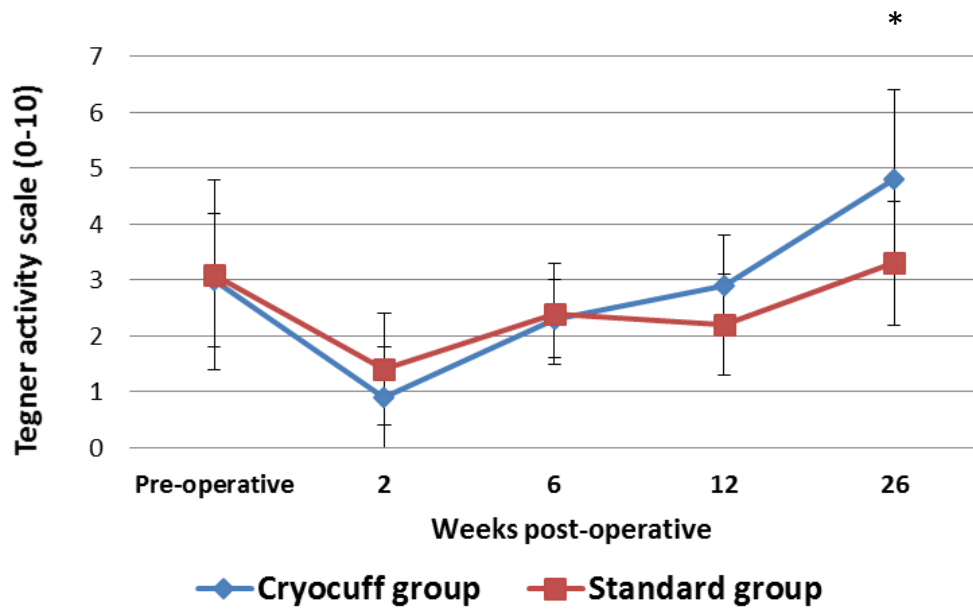


Figure 35 Tegner activity scale (0-10) pre and post-operatively (appendix 5) (*= significant difference between groups $P < 0.05$)

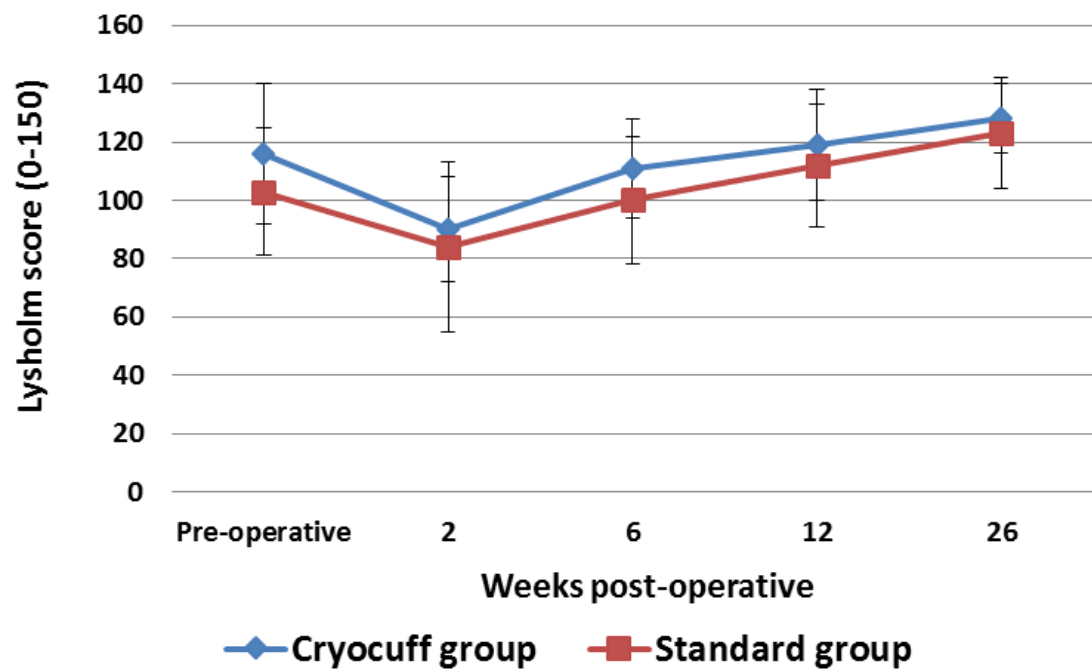


Figure 36 Lysholm score (0-150) pre and post-operatively (appendix 5)

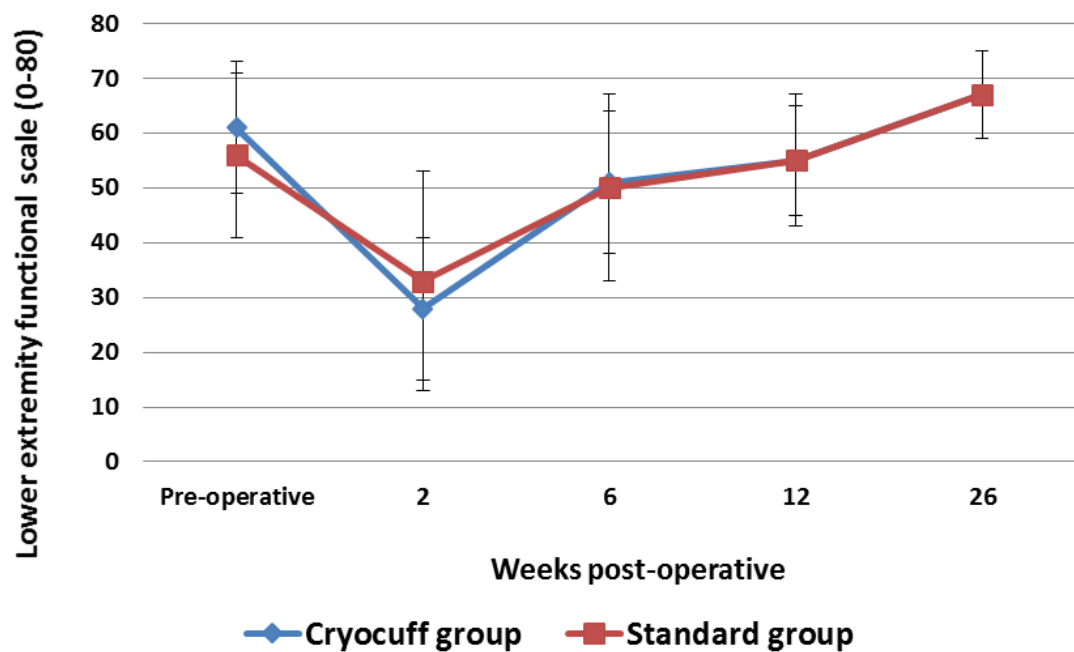


Figure 37 Lower extremity functional scale (0-80) measured pre and post-operatively (appendix 6)

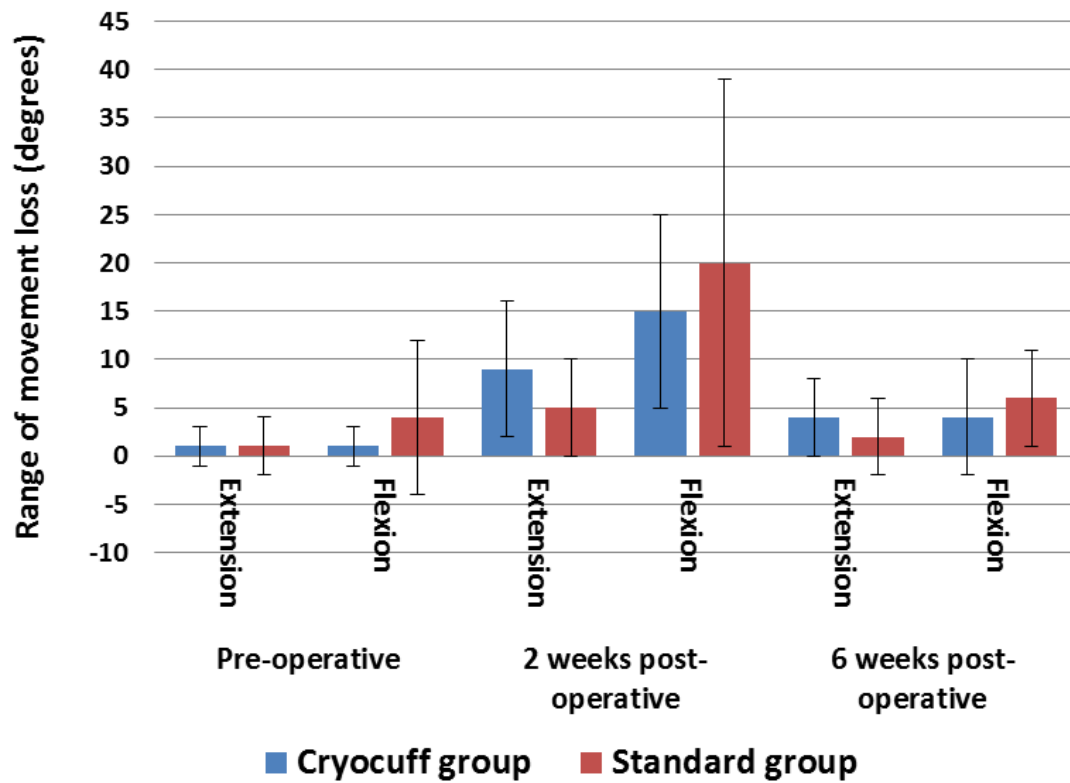


Figure 38 Range of motion loss (degrees) pre to post-ACLR (Note - Negative values indicate increased range compared to contralateral knee)

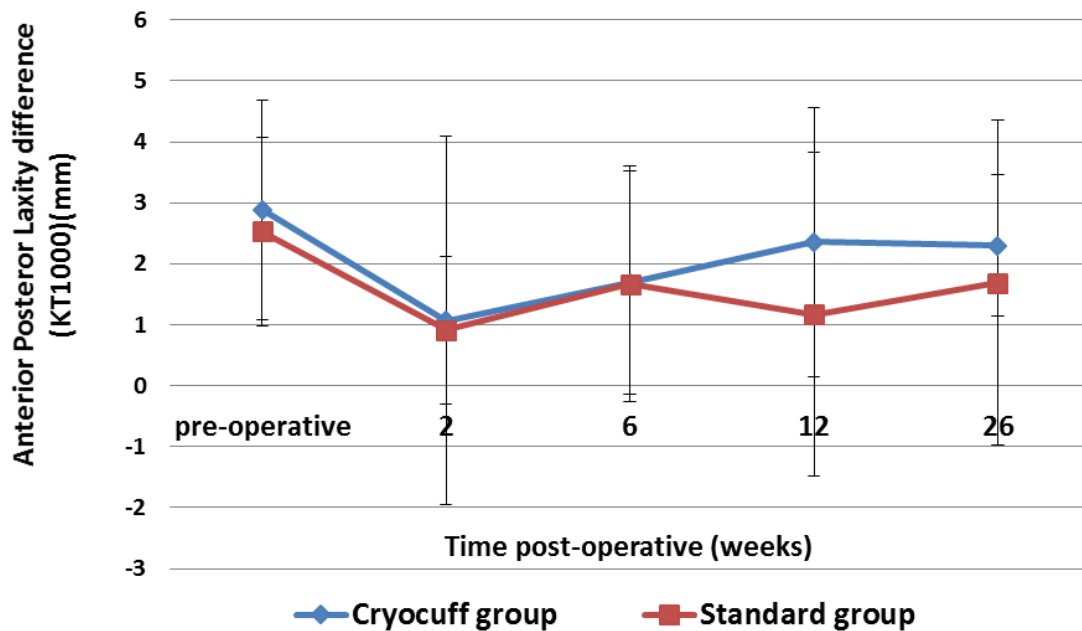


Figure 39 Anterior posterior knee laxity difference (millimetres) between affected and unaffected knee at 30 Pounds (lb) force measured by the KT1000 arthrometer

Evaluating subject adherence to treatment, some patients in the standard group spent some time using ice and elevation, but the daily cryotherapy use was significantly longer in the Cryocuff group (Table 14), indicating adherence to the regimen.

Table 14 Average daily time (hours) using cryotherapy on injured knee after surgery

Daily average hrs using Cryotherapy Mean (SD,95%CI)	Cryocuff group (n=25)	Standard group (n=13)	P-value for group comparison
Post-operative Week 1	8.5 (4.7, 6.3-10.6)	3.7 (2.4, 2.1-5.3)	0.004
Post-operative Week 2	7.1 (3.9, 5.4-8.9)	2.8 (2.1, 1.3-4.2)	<0.001

There were no significant differences in mean times for average daily leg elevation (Table 15).

Table 15 Average daily time (hours) in standing/walking and time with injured leg in elevation after knee surgery

Week number after knee surgery	Daily hours standing or walking Mean (SD,95%CI)	Cryocuff group (n=26)	Standard group (n=15)	P-values for group comparison
Post-operative Week 1	Leg in elevation	8.8 (3.3, 7.5-10.1)	9.2 (4.9, 6.5-11.9)	0.738
	Standing/walking	2.7 (4.9, 0.70-4.6)	2.5 (2.6,1.0-3.9)	0.897
Post-operative Week 2	Leg in elevation	6.6 (3.5, 5.2-8.0)	6.7 (4.7,4.1-9.4)	0.919
	Standing/walking	4.1 (4.0, 2.5-5.8)	3.5 (3.8, 1.4-5.6)	0.629

This indicates that the standard group spent equivalent time with the leg elevated or dependant. The number of home physiotherapy exercise sessions did not show significant difference between groups (Table 16).

Table 16 Number of post-operative home physiotherapy exercise sessions per day

Daily average number of home physiotherapy sessions Mean (SD, 95%CI)	Cryocuff group (n=26)	Standard group (n=15)	P-values for group comparison
Post-operative Week 1	3.8 (1.7, 3.1-4.5)	3.8 (2.1, 2.6-4.9)	0.943
Post-operative Week 2	4.1 (2.8, 3.0- 5.2)	3.5 (1.8, 2.5-4.5)	0.451

This indicates that both groups complied with the initial home physiotherapy exercises.

DISCUSSION

KNEE VOLUME

The main finding of this study is that the use of the Cryocuff and knee elevation in the immediate postoperative period does not decrease knee swelling in the early period after ACLR, when compared to compression with the RJB alone. We therefore cannot accept the hypothesis that the Cryocuff regimen would result in less knee swelling post ACLR.

Comparison with other Cryocuff ACLR studies is difficult, as many do not have an equivalent measure of swelling. Blood volume loss from intra-articular drainage ²⁵⁴⁻²⁵⁶, knee girth measurement ^{140,252,253}, or both ²⁵⁷ have been used to assess swelling, but blood loss was not normalised to body size in any study. Intra-articular drainage was not used in this study sample, as the insertion of a drain increases infection risk, and may change the Intra-articular pressure gradients, and hence the fluid exchange, across synovium ⁷⁸.

The average change in knee volume of the whole sample was 69ml which represents approximately 5-6% of the whole knee volume. Clinically this magnitude of change could account for significant functional effects on Quadriceps Arthrogenic muscle inhibition and on knee function, particularly if this related to a change in intraarticular effusion, as in introduced effusion of 60ml has been found to give significant Arthrogenic inhibitory effects in the knee³³⁷. The magnitude of difference between the 2 groups was less than 0.5% of the whole knee volume.

Cryocuff studies also differ in graft type, anaesthetic method, tourniquet times, length of hospital stay, dose of cooling, and measurement interval postoperatively (Table 15). It is

therefore difficult to recommend an optimum dose of cooling. Okhoshi et al ¹²⁴ found that a low temperature (5°C) group had a lower drainage than a 10°C and a control group, and it may be possible that this depth of temperature is required to decrease swelling. Cryocuff temperatures in this study may not reach the temperatures required. There have, however, been reports of complications such as nerve palsy with cooling dressings of very low temperature. ^{255,256,339}

BASELINE DATA BETWEEN GROUPS

The baseline sample showed equivalence between groups on demographic variables of sex, age, height and body mass. There was some difference between groups for body mass index (BMI), with a lower value in the Cryocuff group but this was not significant on testing. Group numbers were different, with a greater number of patients lost to follow up in the standard treatment group, making the groups uneven. The number of data points analyzed was also different between groups with some lost follow up measurements, related to clinic non attendances and re-bookings.

Knee concurrent pathology did not show statistically significant difference between groups for meniscal or chondral pathology or concurrent surgery. Injury to surgery time, and other pathology data was not statistically different. Functional outcomes showed good group equivalence, however they differed in preoperative flexion ROM but non-significantly. Laxity and functional questionnaire scores were also equivalent, although scores trended to being slightly higher for LEFS/Lysholm and IKDC in the cryocuff group. This difference was not statistically significant. Surgical data showed some differences as a slightly higher percentage of the standard patients had had prior affected knee surgery .Graft and tunnel and interference screw diameters trended to being slightly higher in the Cryocuff group but not significantly, although the endobutton size was greater in the standard treatment group. The average tourniquet or operation time did not differ between groups, however, the percentage of surgeon A (FSH) to Surgeon B (RVP) was higher in the normal treatment group.

In summary the main differences between the samples included: - number, BMI , functional variables of preoperative Flexion ROM plus LEFS / Lysholm and IKDC forms slightly and finally, the surgical variables of prior affected knee surgery, endobutton size, the proportion of surgeon A to surgeon B, and the concurrent surgery performed including chondroplasty and meniscal repairs. None of these differences, however were significant on testing.

PAIN

Several studies, have used the Cryocuff/elevation combination to lessen pain.^{252,254,255,257,310,340}

(Table 16). This study shows a possible small non-significant effect from Cryocuff in the recovery room. This study found no significant difference between the treatment and control group at any time point on our other pain measures, suggesting that Cryocuff is not effective for pain relief beyond the initial recovery room period.

MEDICATION USE

In the hospital recovery stay, a dose of Diclofenac (given as required) was used by significantly more patients in the Cryocuff group, whereas Ibuprofen use was not significantly different between groups. Greater Diclofenac use was anticipated to give a reduction in pain and swelling for the Cryocuff group, but this was not our finding. This may indicate that Diclofenac is ineffective at reducing swelling, or, if effective, the Cryocuff group had more swelling. The home medication use in the present study did not differ significantly between groups. In the initial 2 weeks, some studies have found a reduction in medication use for Cryocuff and cooling groups. Barber et al²⁵² found Percocet and Vicodin use was significantly less in their cold group up to day 6. The control group consumed more analgesic medication, however their VAS pain levels remained higher. They suggest a possible placebo effect for the control group. This effect may play a role in any Cryocuff study, including this study and many patients, even in the control group, expressed a preference for the Cryocuff regimen. This has been found in other studies with users of these devices subjectively reporting positive effects, with a strong belief in the efficacy of the device³⁴¹. Edwards et al showed that the room temperature Cryocuff group actually required less injectable analgesia than the cooled Cryocuff group²⁵⁴. No other medications showed between-group differences in consumption. Konrath et al²⁵⁵ also showed no significant differences in analgesia use between four groups. Brandsson et al³⁴² did show a reduction in both the intramuscular and oral supplementary

analgesic medication required in the Cryocuff group versus a control, as did Schröder and Pässler ²⁵⁷, who used 2 hourly 15ml doses of epidural bupivacaine, with Tramadol infusion. They found intake lower in the Cryocuff group for all medications, but only significantly so for Tilidine and Piritramide.

SECONDARY VARIABLES

This study also failed to show significant differences between groups for secondary outcome variables of discharge time from hospital, function, ROM and laxity. The Cryocuff does not seem to have a longer term significant impact on these variables above standard treatment.

DISCHARGE TIME

Many cryotherapy studies in ACLR have inpatient periods post operatively. Many of these studies do not report ACLR as a day surgery procedure. The mechanics of performing cryotherapy type studies on a Day surgery group becomes harder as there is less control of the postoperative environment of the initial days when anti-inflammatory treatments are arguably the most important. The time from end of surgery to discharge criteria met was equivalent between groups, with no significant differences found. It was therefore not possible to say one regimen sped the subject's discharge from hospital.

FUNCTION

QUESTIONNAIRES

The groups had some baseline differences (non-significant) in questionnaire scores with the Cryocuff group having higher IKDC/ Lysholm and LEFS scores. At 2 weeks post operatively the scores were closer between groups, indicating a greater score drop in the Cryocuff group. The scores were still reasonably equivalent at 6 weeks, but by 3 months the slight difference in

score had returned, with the C group slightly higher on IKDC and Lysholm, but less with LEFS. Again, however, none of these differences was significant.

Changes in scores (IKDC/Lysholm/ LEFS) between time periods showed a significantly greater drop from pre-op to 2 weeks post op for the Cryocuff group compared to the standard group. The improvement score values showed only an equivalent change between the groups (IKDC/Lysholm/ LEFS), indicating that the improvement in score levels did not happen faster in either group. I.e. the Cryocuff group (higher at baseline) dropped more initially and did not regain this against the N group for the rest of the rehabilitation. Warning must be made re the reduction in numbers of questionnaire scores in both groups with time from surgery.

RANGE OF MOVEMENT

The Cryocuff group showed a reduced ROM in Extension at 2 weeks postoperative compared to the standard group after starting from equivalent baseline, indicating a greater Extension loss in the C group. This, however, again was not statistically significant on testing.

The Flexion started significantly higher in the Cryocuff group and reached an equivalent level at 2 weeks, indicating a greater Flexion loss in the Cryocuff group. Both Extension and Flexion loss, however, were not significant. At 6 weeks both groups were equivalent.

LAXITY

Anterior Posterior Laxity differences between affected and unaffected knee were different at baseline, greater in the Cryocuff group but minimally and not significantly. The laxity measure differences affected to unaffected knee were equivalent at the 2 week and 6 week mark, showing little difference between the groups. The Cryocuff regimen did not appear to have any effect on laxity in the early period. The 3 month and 6 month laxity measures did show some difference between the groups with the Cryocuff group having a greater AP difference (ie more laxity) however the sample numbers were lower due to drop outs. The differences

were small for KT1000 difference measures (1.3 mm at 3 months and 0.6mm at 6 months). The inflammatory process forms part of a healing cascade. It may be that, reducing inflammation compromises the ACLR graft's ability to fibrose and strengthen, thereby increasing laxity. Anti-inflammatory medication has been shown to compromise healing in both Rat MCL and patella tendon 14 days after transection and repair.^{98,343} In our sample medication may be a factor as the NSAID consumption differed between groups. Other factors that decrease inflammation may also effect healing. While a possible trend may exist, the group differences were not significant on testing. There may be a need for greater subject numbers to show any possible trend.

The elevation Cryocuff regimen followed the manufacturer's instructions on ice filling, and regular lowering and raising to drain / remix and refill the cuff around the knee. The recovery room and day surgery staff were trained to follow this procedure accurately. While it was not possible to blind surgery and recovery room staff, the treating outpatient physiotherapists were blinded.

The patients were trained and given instructions on the use of the Cryocuff. Diary sheets were used to test compliance and adherence to the regimen but some patients did not complete the sheets. The patients with missed diary sheets were contacted and retrospectively questioned on compliance verbally, possibly allowing a recall bias.

Patients in our normal treatment group used ice as we could not ethically prevent them at home, however, we included questioning to ascertain the length of use / day to quantify this and factor into analysis.

STUDY LIMITATIONS

This sample contains a number of patients lost to follow up (greater in the standard treatment, than the Cryocuff group). The number of patients who dropped out of the study or did not attend their appointments for follow up data collection mean that the study is underpowered, considering our initial sample size calculation.

With respect to duration and intensity (dose) of cooling, studies with longer inpatient admission allow closer monitoring of patient adherence, with more intense and prolonged joint cooling. ACLR, in this study, was performed as a day surgery procedure, with patients returning home after average 6 hour stay. Home diary sheets showed reasonable adherence, with the average daily time using the Cryocuff in week 1 (8.9 hours/ day), and week 2 (6.8 hours/ day), with the leg in elevation for 9 hours and 7 hours in week 1 and 2 respectively. Inpatient programmes, also allow more frequent testing in the days post-surgery.^{252,257} More test iterations may show effects of Cryocuff, particularly over the initial days/hours.

Preoperative knee volume was used as the baseline volume measure, however, an immediate postsurgery/ pre intervention measure was desirable. This was not possible for several reasons including the difficulty of measuring an anaesthetised subject, infection and safety issues, and transporting the perometer. This measurement, while desirable, could also compromise the intervention, by delaying the time (minutes) postsurgery that the Cryocuff and elevation are applied. The aim of the regimen to decrease haemarthrosis necessitates applying the cuff before the haemarthrosis gathers –in the first minutes/ seconds postsurgery.

The lack of testing until 2 weeks after surgery in the present study makes it possible that any positive, earlier effects of the Cryocuff and elevation regime were missed. This is supported by Schröder and Pässler ²⁵⁷, who found that knee girth (swelling) was only better in the

Cryocuff group at days 3 and 6 post-operatively. This lack of difference at 2 weeks suggests that any early advantages of the Cryocuff are short-lasting.

In some trials, the Cryocuff was applied directly to the skin²⁵⁷, however in the majority of postsurgical trails with ACLR the devices are applied over dressings^{117,230}. This aims to reduce risk of infection, as infection has been reported as one postoperative complication of cryotherapy.^{187,229} In this study, the Cryocuff was applied after the application of dressings and bandages. Bandages were equivalent between groups and were removed after 48 hours, allowing the Cryocuff group to apply the device directly to the skin until the 2 week measurement point. Knee joint cooling has been found to be successful with cryotherapy applied after bandaging of the ACLR knee.^{124,255,340} It is likely, however, that the cooling is greater, when applied directly to skin, with a possible increase in treatment effectiveness.

The level and effect of compression is unknown, as it was not measured in this study (or in any other Cryocuff study). While effort was made to apply the Cryocuff per the manufacturer's instructions (Appendix 1) and the cuff was put on without strap tension, it was observed that tension in the superior and inferior straps posteriorly increased as the cuff filled. The straps therefore delivered a great deal of circumferential pressure to the knee. The amount of this compression is not known but could also have been a reason for our negative findings. These observations formed the basis for the study conducted in chapter 5.

Some of the patients in the standard treatment group used ice and elevated the leg at home, even though they were discouraged from doing this. Ethically, it was not possible to prevent this, but diary sheets allowed monitoring of use and compliance and indicated that the standard group used ice for significantly less time. Daily amounts of home knee elevation, however, were equivalent between the groups. This may have reduced any potential post discharge difference in effect between the groups. The patients were trained and given instructions on the use of the Cryocuff. Diary sheets were used to test compliance and

adherence to the regimen but several patients did not complete the sheets. The patients with missed diary sheets were contacted and retrospectively questioned on compliance verbally, possibly allowing a recall bias.

The dose of cooling and elevation, importantly, was different between groups during the hospital stay (initial post-operative 6 hours) the period when bleeding into the knee joint (haemarthrosis) could be expected to be maximal. The use of ice by the standard group demonstrates a subjectively strong belief in the effectiveness of the RICE regimen, indicating how widespread and disseminated the public education on the RICE regimen is.

CONCLUSIONS

The Cryocuff is a device widely used after ACLR to reduce pain, swelling and inflammation. This study failed to find a significant difference in knee volume change, measured using a Perometer, when comparing a Cryocuff and elevation regimen with standard treatment in the early post-operative period after ACLR. This questions the effectiveness of the Cryocuff and elevation regimen to reduce swelling in the first 2 weeks after ACLR in comparison with treatment with a compression bandage alone for the first 48 hours. In line with other studies, a small effect on pain was found in the recovery room, but this was not significant. Diclofenac use by the Cryocuff group was significantly greater, but no other secondary variable was found to show significant difference between groups. Cryocuff may not provide any longer term significant advantage beyond the very early period post-operatively in ACLR.

CHAPTER 4 CORRELATES OF SWELLING IN ACLR

BACKGROUND

Attempts to control swelling may be more successful if the variables can be identified, that influence it. There is little literature on the pre or postoperative correlates of swelling in ACLR. It is currently unclear how swelling relates to outcomes post-ACLR. A reliable method for measuring knee swelling may permit an investigation of the correlated variables in ACLR.

The previous chapter reported a randomised controlled trial of the Cryocuff device in ACLR. We used data from the same cohort of patients to investigate the potential correlated variables relating to the patients' knee swelling after ACLR. This chapter reports the observational arm of the experiment reported in the previous chapter.

The perometer allowed the possibility to assess for variables that correlate with swelling and knee volume changes after surgery. Variables were chosen pragmatically for their potential to have a relationship with the level of inflammation post ACLR: - such as the length of the surgery and the amount of concurrent arthroscopic surgery performed. Other variables that may relate to fluid exchange were also chosen, including the amount of intravenous (IV) fluid given to the patient perioperatively, and their perioperative blood pressure values during the ACLR. None of these variables have to the best of our knowledge, been investigated for possible association with swelling. Given the Starling equation (Figure 6), however, it would seem logical that these variables could affect microcirculation, including that of the synovium in the knee. The perometer also allowed for the assessment of the relationship between knee volume, and the final outcomes after ACLR, providing valuable insights into the importance of swelling to effect the final outcome in ACLR.

FACTORS THAT MAY RELATE TO SWELLING IN ACLR

The Influences on fluid dynamics are multiple, and inflammation postsurgery further complicates fluid dynamics in an operated joint. There are multiple variables that will relate to inflammation and fluid dynamics. The following variables were chosen pragmatically to investigate in the ACLR cohort of patients studied. They are recorded in Figure 40. They relate to preoperative, perioperative, postoperative factors that have influence on inflammation and fluid exchange as well as the most frequently reported outcomes for ACLR surgery.

CORRELATE VARIABLES SUMMARY

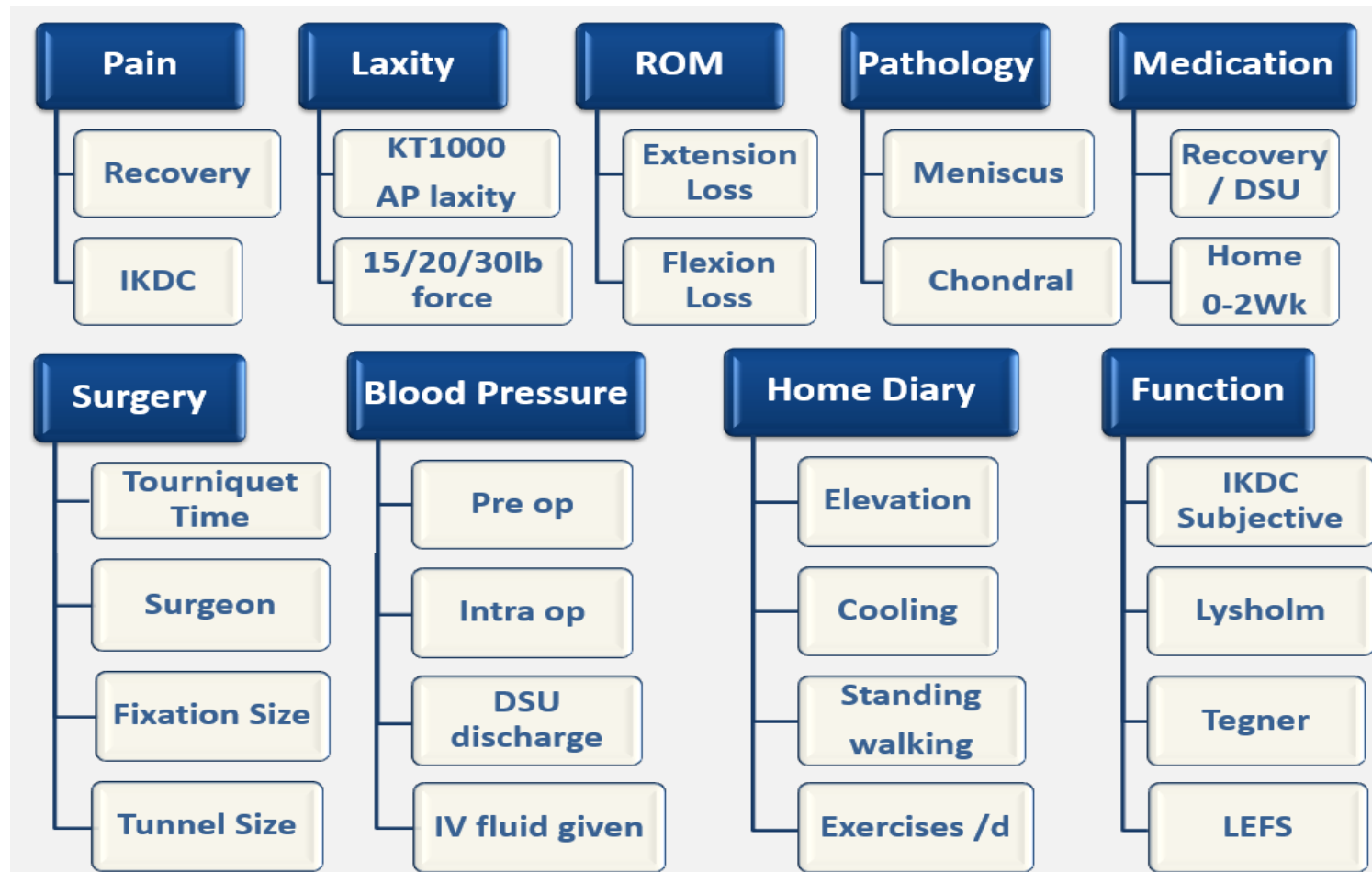


Figure 40 Summary of correlate variable data collection with possible relation to knee volume

AIM

This study aimed to assess pre or intraoperative variables that could relate to swelling and to determine the correlates of swelling in ACLR. This included those pre or perioperative and early factors that associate with early knee swelling postoperatively.

This was also undertaken to determine if early postoperative swelling is associated with poorer long term outcomes in ACLR.

HYPOTHESIS

1. Significant correlate variables would be found, that would associate with changes in knee volume pre to postoperatively: -
 - a. Pre, intraoperative , perioperative and early postoperative factors that relate to early knee swelling
2. Early knee swelling would associate with poorer long term outcome after ACLR.

METHODS

SAMPLE / PATIENTS

This study used data obtained from the same cohort of patients reported in the previous chapter. This study has been separated from the previous for convenience of both the reader and the author.

STUDY DESIGN AND RANDOMISATION

This arm of the study followed an observational design with factor correlation analysis, followed by a multiple linear regression model using the strongest correlates.

MEASURED VARIABLES

The variables were measured using the methodologies described in chapter 2 and 3. Knee volumes were measured using the perometer, with the measurement method, and timings previously outlined. Other outcome variables measured in chapter 3 were also included in this arm of the study. The following variables were measured and recorded: surgery variables: the length of surgery or tourniquet time, the amount of IV fluid given during the surgery, fixation and tunnel sizes.

Knee pathology variables: - the presence of meniscal or chondral pathology
 subject variables:
 - blood pressure (BP) and medication use

Home diary variables: - average daily cooling, elevation and walking times and other

Outcome variables: - function, pain, ROM and AP laxity (measured with KT1000 arthrometer).

Correlate analysis was performed using the pre- to 2 week post-operative change knee volume change measured by the perometer in millilitres.

PREOPERATIVE ASSESSMENT

Factors that could affect postoperative swelling were recorded, including demographic data: body height, sex, body mass and body mass index (BMI). The time from injury to surgery also recorded. The other measurements were taken in the preoperative visit as already described in chapter 3 (measures of knee volume, function, laxity, range of movement and pain).

OPERATIVE VARIABLES

It is not known if the amount of bleeding or swelling are affected by intraoperative variables, and detailed notes was made of the most pertinent variables in the surgery that could influence bleeding and swelling. The arthroscopic examination findings were documented and any concurrent procedures that were performed. It was thought that these factors may have a relationship to the amount of joint swelling. Note was made of the concurrent pathologies found, including: - medial and or lateral meniscal pathology, chondral pathology and the. Note was also made of the size of these fixation components (the endobutton, the interference screw and the staple) and the size of the femoral and tibial tunnels, which corresponded respectively to the diameters of the femoral and tibial ends of the graft. Several further operative factors were recorded from the operation and anaesthetic reports, including: Blood pressure, tourniquet time (as a measure of operation time), concurrent meniscal or chondral surgery, plus graft, tunnel and fixation screw sizes. The amount of intravenous (IV) fluid (in ml) given to the patient during the operation and in the recovery room was noted. These factors have not to our knowledge been assessed before in relation to postoperative knee swelling.

POSTOPERATIVE VARIABLES

Some early post-operative factors were also recorded from patient diaries (see appendix 9) of the initial 2 weeks postoperatively. Patients were asked to document the average daily amount or time that they: took medication, stood, walked, elevated the affected leg and performed their physiotherapy exercises. Pain was measured from the recovery room scores and IKDC forms (appendix 6) as previously described.

SUBJECTIVE QUESTIONNAIRES

The patient reported function questionnaire (IKDC subjective form, Lysholm, Tegner scale, and the LEFS) results were recorded from the pre and postoperative measurement visits

DATA ANALYSIS

Secondary data analyses were performed to ascertain which variables among those which were investigated (see figure 38) which correlate with the change in postoperative knee swelling after the ACLR surgery. Correlation statistics were used and Pearson's "r" product-moment correlation coefficient was used to investigate linear correlation / or association of the above variables, with our main outcome variable being the change in affected knee volume (measured by the perometer in ml) from preoperatively to 2 weeks postoperatively.

A multiple linear regression model was used with the significant correlates to determine the proportion of variance (R^2) explained by each relevant independent variable.

RESULTS

SUBJECT DATA

Fifty one patients were measured for the initial knee volume measurement and the preoperative measurement session but full follow up knee volume measures were available from 43 patients – see figure 10 for flow diagram.

Mean preoperative and two week post-operative affected and unaffected knee volume measures (SD) were found to be respectively 1226.8(216) and 1265.4(242) ml. The affected knee Volume difference pre to 2 weeks post op was 67.4 (58.6) ml.

The correlate analysis results are shown in Tables 17-19 with correlation coefficients and p values for each variable measured. The correlation graphs for the different variables are below. Only those variables with significant correlations are shown. The graphs are documented for several other variables with non-significant findings but considered important to discuss. The main outcome variable for the study was the change in knee volume from preoperatively to postoperatively at 2 weeks. This was measured with the perometer and is in millilitres. This variable was correlated with the below variables. The correlation coefficient was the Pearson correlation product moment unless stated otherwise. P values of < 0.05 were significant

CORRELATES

Table 17 Demographic Variables Correlation analysis with correlation coefficient and P values for correlation with pre to 2 week post-operative change in knee volume (ml) measured by perometer

Variable	Measure	Mean (SD)	(95%CI)	Correlation Coefficient	P Value
Demographics	Age (years)	32.8 (7.7)	(30.3, 35.3)	-0.160	0.306
	Height (cm)	171.5 (8.2)	(168.8, 174.2)	0.092	0.558
	Weight (Kg)	71.7 (15.5)	(66.6, 76.8)	0.170	0.276
	BMI (kg/m ²)	24.4 (4.8)	(22.9, 26)	0.194	0.212
Knee Volume (ml)	Initial Affected knee volume	1191.4 (218.8)	(1119.5, 1263.4)	0.091	0.561
	Initial Unaffected knee volume	1196.0 (247.2)	(1114.7, 1277.3)	0.133	0.390

for all tables below *Significant variables to $p < 0.05$ shaded dark grey / Correlation coefficient is Pearson correlation coefficient r value unless stated. Note – means and SD for variables are given by groups in chapter 3.

Table 18 Perioperative Variables Correlation analysis with correlation coefficient and P values for correlation with pre to 2 week post-operative change in knee volume (ml) measured by perometer

Variable	Measure		Mean (SD, 95%CI)	Correlation Coefficient	P Value
Surgery	Tourniquet time (mins)		52.3 (11.7) (48.5, 56.2)	0.041	0.792
	Fixation sizes (ml) (endobutton)		22.4 (3.9) (20.5, 24.2)	0.164	0.301
	Graft size (mm)		7.7 (0.7) (7.3, 8.0)	0.110	0.527
	IV Fluid given (mls)		1539.5 (537.5) (1362.8, 1716.2)	0.144	0.387
Blood Pressure (millimetres mercury – mm Hg)	Preoperative	Diastolic	75.3 (8.4) (72.8, 77.8)	0.108	0.550
		Systolic	123.3 (14.9) (118.9, 127.8)	0.204	0.256
	Intraoperative	Diastolic	60.8 (10.8) (57.6, 64)	0.137	0.455
		Systolic	106.5 (15.3) (102.0, 111.0)	0.236	0.193
	Recovery room discharge	Diastolic	70.9 (9.9) (67.9, 73.8)	0.350	0.029*
		Systolic	126.5 (14.6) (122.1, 130.8)	0.276	0.088
Medication use (Diclofenac)	Home diary average daily doses	Week 1	2.9 (1.5) (2.4, 3.5)	-0.238	0.134

Table 19 Postoperative Variables Correlation analysis with correlation coefficient and P values for correlation with pre to 2 week post-operative change in knee volume (ml) measured by perometer

Variable	Measure	Week	Mean (SD, 95%CI)	Correlation Coefficient	P Value
Home diary (average/day)	Daily elevation time (average hours)	Week 1	9.0 (4.8) (7.3, 10.7)	0.301	0.056
		Week 2	7.2 (4.7) (5.6, 8.9)	0.307	0.051
	Daily cooling time (average hours)	Week 1	7.1 (4.6) (5.5, 8.7)	-0.216	0.236
		Week 2	6.0 (4.1) (4.6, 7.4)	-0.062	0.735
	Daily standing time (average hours)	Week 1	1.8 (1.9) (1.2, 2.5)	-0.138	0.390
		Week 2	3.3 (2.3) (2.5, 4.1)	0.130	0.450
	Daily exercises (average sessions)	Week 1	3.6 (1.7) (3.0, 4.2)	-0.138	0.390
		Week 2	3.8 (2.5) (3.0, 4.7)	0.178	0.264
Knee Function (6m)	IKDC score (/87)		63.2 (10.9) (57.9, 68.4)	-0.265	0.150
	Lysholm (/150)		128.0 (14.3) (121.1, 134.9)	0.105	0.520
	Tegner activity score (/10)		4.5 (1.6) (3.7, 5.3)	-0.203	0.209
	LEFS (/80)		67.9 (7.4) (64.3, 71.5)	-0.262	0.107
Pain	Recovery room (20min) (0-3)		1.857 (0.90) (1.03, 2.69)	Chi Sq = 3.292	0.349
	IKDC Que 2 Pain frequency(0-10) (2w)		7.29 (2.75) (4.74, 9.83)	0.227	0.144
	IKDC Que 3 Pain severity (0-10) (2w)		6.00 (2.00) (4.15, 7.85)	0.154	0.354
Range of Movement (degrees) (preoperative)	Extension loss		1.3 (2.9) (0.4, 2.1)	0.326	0.033*
	Flexion loss		1.8 (5.2) (0.4, 3.3)	-0.220	0.157
Knee AP Laxity (mm) (KT1000 arthrometer) (Lbs - pounds of force) (preoperative)	Affected knee	15lb force	3.7 (1.8) (3.2, 4.2)	0.317	0.038*
		20lb force	5.5 (2.1) (4.9, 6.1)	0.306	0.046*
		30lb force	10.1 (2.7) (9.3, 10.8)	0.227	0.144
	Unaffected knee	15lb force	3.2 (1.5) (2.8, 3.6)	0.380	0.012*
		20lb force	4.5 (1.8) (4.0, 5.0)	0.368	0.015*
		30lb force	7.3 (2.6) (6.6, 8.1)	0.255	0.099

*Significant variables to $p < 0.05$ shaded dark grey / Correlation coefficient is Pearson correlation coefficient r value unless stated / Que= question/ lb= pounds. Note – means and SD for variables are given by groups in chapter 3.

The significant correlates change in the affected knee volume pre to 2 weeks post operatively were: to $p < 0.05$: - Diastolic BP at recovery room discharge; knee joint AP laxity (both knees) from early levels of force on KT1000 measurement and extension loss. Several variables came close to significance: - diastolic BP at DSU discharge, and daily home elevation time (week 2) from the home diary. No other variables measured correlated significantly with change in knee volume.

The multiple regression model is table is given below with the main independent variables used which showed significant correlation with the change in affected knee volume from pre to 2 weeks postoperatively.

Table 20 Independent variables with significant correlation to knee volume change pre to two weeks post ACLR for multiple regression model

Variable	Measure	Unstandardised Coefficient B	T value	P Value
Blood Pressure (mm Hg)	Recovery room Diastolic Blood Pressure at discharge	1.689	1.877	0.070
Range of Movement (degrees) (preoperative)	Extension loss	6.287	1.548	0.131
Preoperative Knee AP Laxity (mm)	Unaffected 15Lb force KT1000	10.523	0.569	0.573
	Unaffected 20Lb force KT1000	-0.767	-0.057	0.955
	Affected 15Lb force KT1000	3.393	0.218	0.829
	Affected 20Lb force KT1000	-0.933	-0.073	0.942

When the above 6 variables were put into a linear regression model the $F(6,32) = 1.18$, $R^2 = 0.263$ ($p = 0.112$) indicating that these variables combined in this model did not significantly predict the increase in knee volume pre to 2 weeks post operatively after ACLR .

Due to the lower N values and to avoid violating a model assumption, only one KT1000 laxity variable was used. The 15Lb force KT 1000 value (in mm) for the unaffected knee was chosen, to give three independent variables only in the model. The $F(3,35) = 4.093$, $R^2 = 0.260$

($p=0.014$), with DBP in recovery room and KT1000 AP laxity of unaffected knee as the most significant predictors of variance in the model. See table 21 below

Table 21 the Three Independent variables with significant correlation to knee volume change pre to two weeks post ACLR for the final multiple regression model

Variable	Measure	Unstandardised Coefficient B	T value	P Value
Blood Pressure (mm Hg)	Recovery room Diastolic Blood Pressure at discharge	1.698	2.009	0.052
Range of Movement (degrees) (preoperative)	Extension loss	6.224	1.610	0.116
Knee AP Laxity (mm)	Unaffected 20Lb force KT1000	12.204	2.019	0.051

The statistically significant correlates and some of the most relevant data and graphs are presented below. The knee volume correlates are outlined first together with the body size versus knee volume correlates then the variables that showed a statistically significant correlation with the change in knee volume pre to two weeks postoperatively. The variables that showed no significant correlations are presented for completeness.

BASELINE KNEE VOLUME

The knee baseline volume was correlated against the postoperative knee volume with a finding of very strong correlation, as expected (see Figure 41).

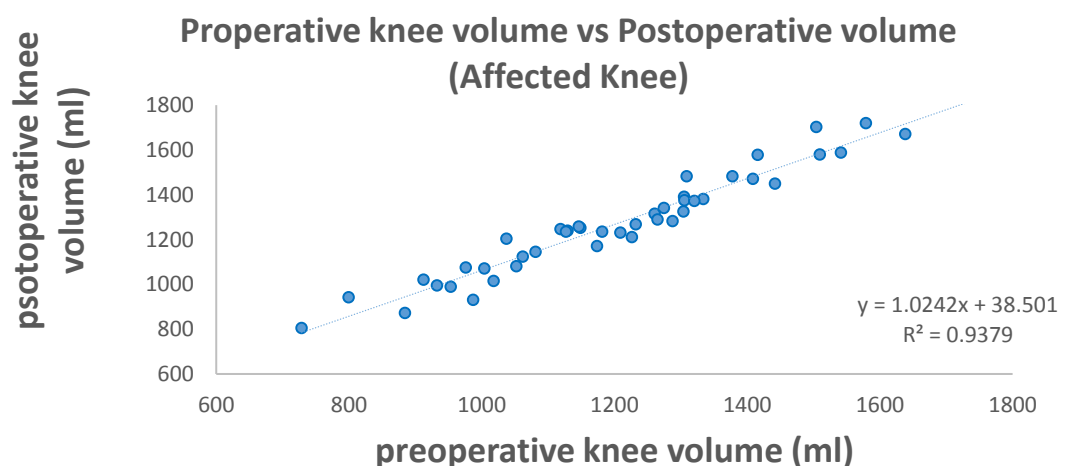


Figure 41 Preoperative volume (ml) vs postoperative knee volume (ml) for the affected knee measured with the perometer

The scatter plot of preoperative knee volume versus the change in knee volume from preoperatively to 2 weeks postoperatively is presented below in Figure 42.

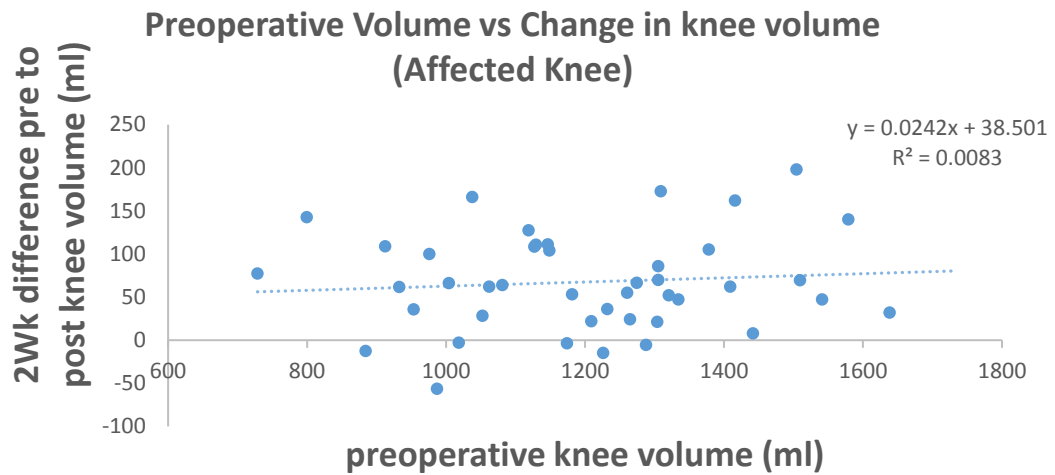


Figure 42 Preoperative volume (ml) vs change in knee volume pre to 2w postoperatively (ml) for the Affected knee measured with the perometer

Pre to post op knee volume scores correlated strongly in the affected knee ($r = 0.968$, $p < 0.01$) (Figure 40) and the unaffected knee ($r = 0.984$, $p < 0.01$), however, there was weak correlation found between volume difference and preoperative volume for the affected knee ($r = 0.091$, $p = 0.561$) (Figure 41) and the unaffected knee ($r = 0.133$, $p = 0.390$). This indicates a weak relationship between the starting volume and the amount of fluid added post knee surgery.

BODY SIZE VARIABLES AND KNEE VOLUME

The perometer measure of knee volume may encompass a measure of knee size. This may not always associate with body size, but in the initial correlate analysis it was desirable to see if there was an association with the perometer measure and body size. The initial analysis investigated the association with body size variables (height and weight) and the raw volume measure preoperatively (Figures 43 and 44). Then any association between body size

variables (height and weight) and the change and the change in knee volume pre to 2 weeks post operatively (Figures 45 and 46).

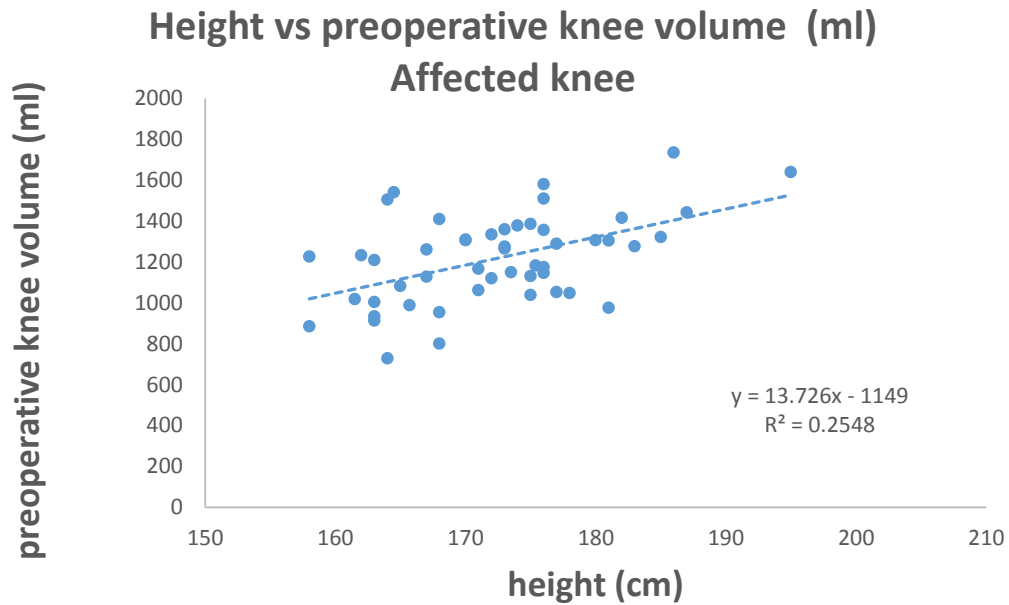


Figure 43 Preoperative Affected knee volume (ml) vs height (cm)

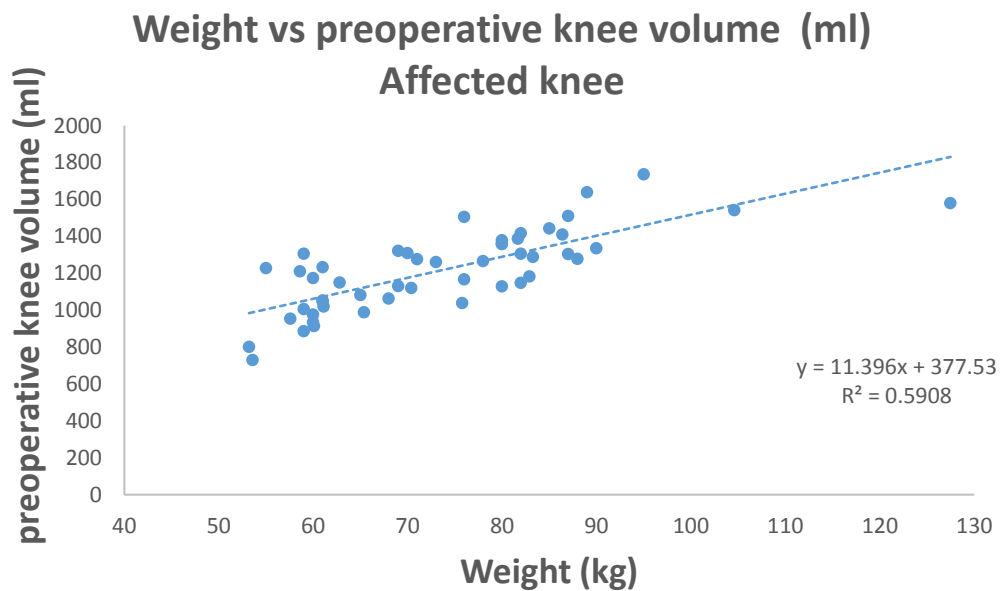


Figure 44 Preoperative Affected knee volume (ml) vs weight (kg)

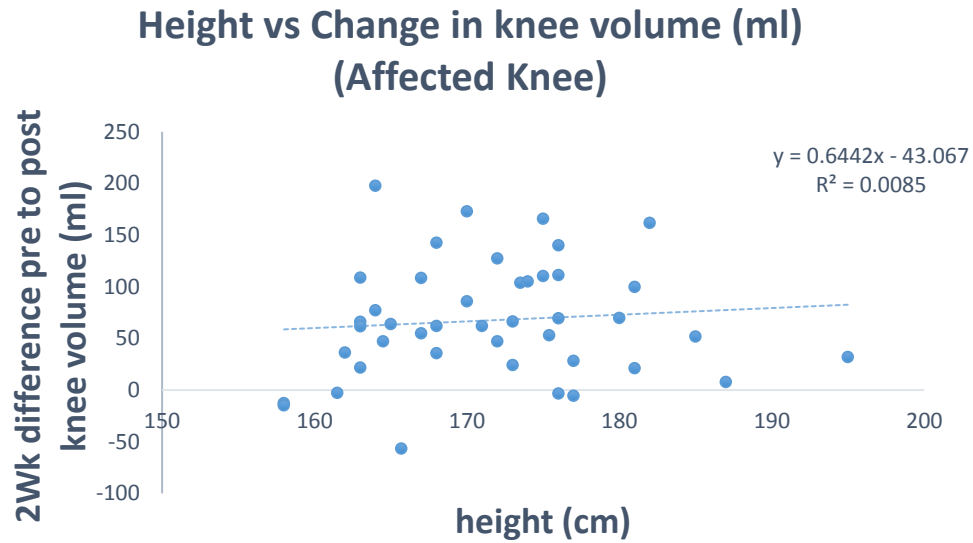


Figure 45 change in affected knee volume pre to 2w postoperatively (ml) vs Height (cm)

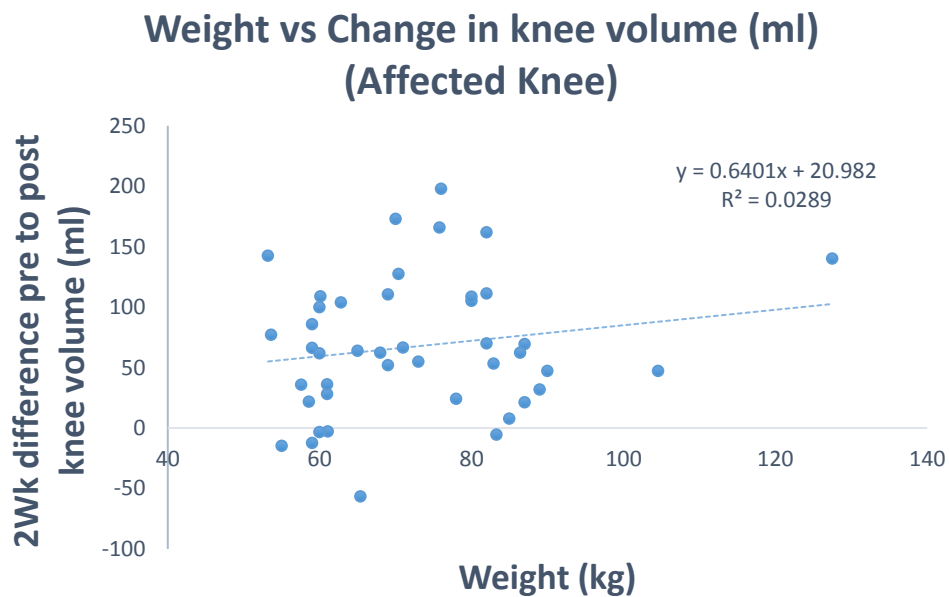


Figure 46 change in affected knee volume pre to 2w postoperatively (ml) vs weight (kg)

Height and weight showed a correlation with the preoperative knee volume (Figures 43 and 44). Whilst this may indicate that the knee volume does correlate with body size. There was significant association with the change in knee volume (Figures 45 and 46), indicating that the change in knee volume was not related to body size. I.e the amount of knee swelling does not correlate with body size

VARIABLES THAT ACHIEVED STATISTICAL SIGNIFICANCE

The following correlate variables achieved statistical significance in correlation with the change in knee volume pre to 2 weeks postoperatively and are graphed and described below.

BLOOD PRESSURE

The blood pressure at final discharge from recovery room is displayed plotted against change in knee volume in figure 47.

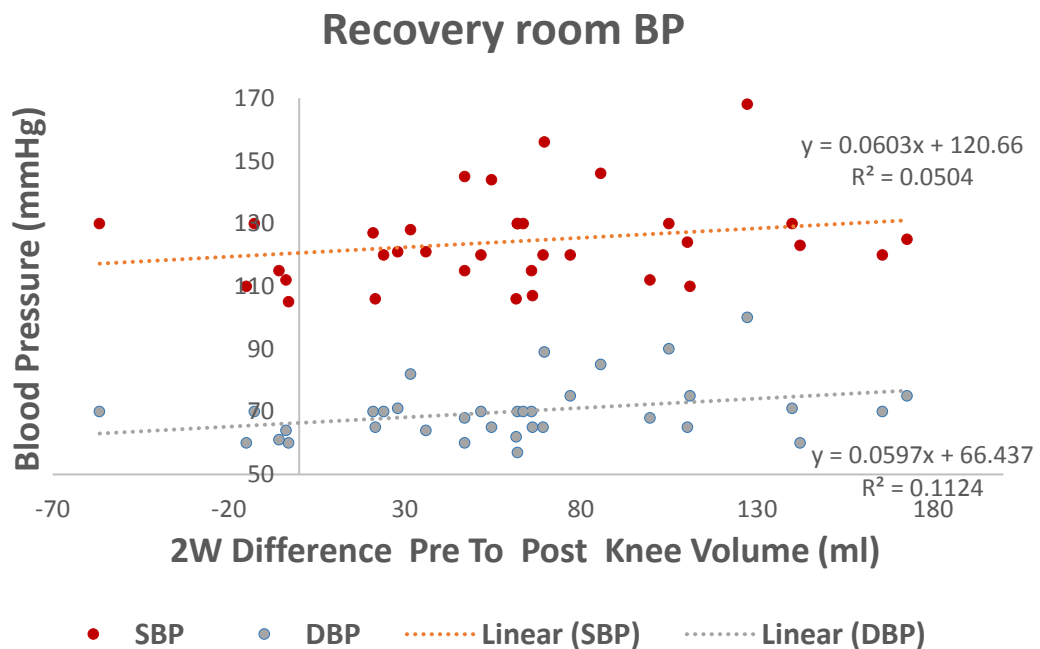


Figure 47 end recovery room blood pressure (mmHg) diastolic and systolic vs change in knee volume preoperatively to 2weeks postoperatively

Blood pressure showed a significant correlation for the final recovery room diastolic blood pressure taken but not for the systolic blood pressure, however, the systolic blood pressure showed correlation that was close to statistical significance.

The laxity correlates are presented in Figures 48 and 49 for the affected and unaffected knee respectively.

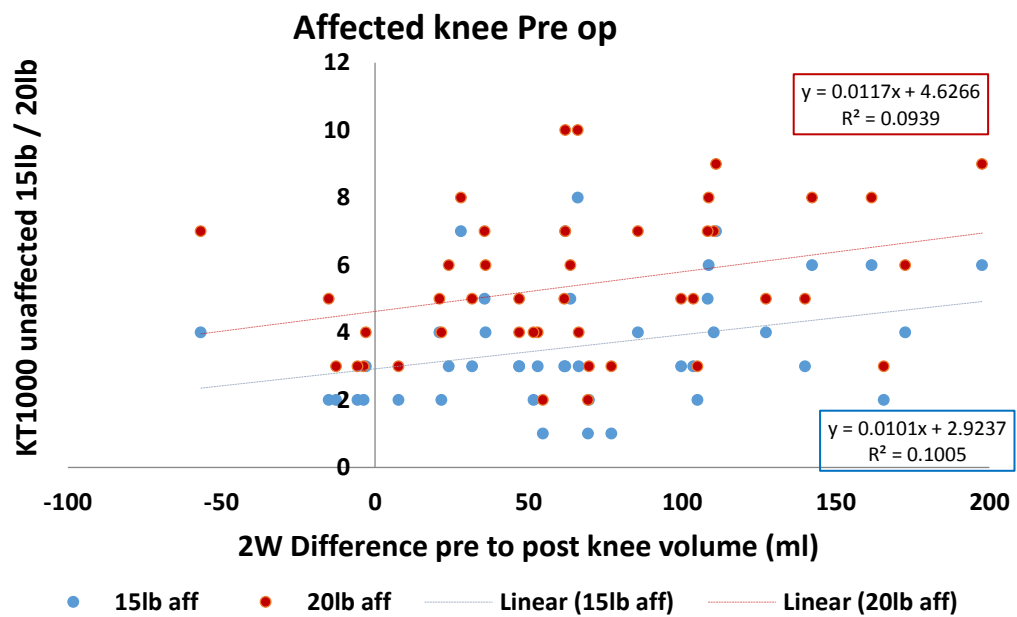


Figure 48 AP Laxity KT1000 (mm) vs Volume difference pre to post op 2w (ml) Affected knee

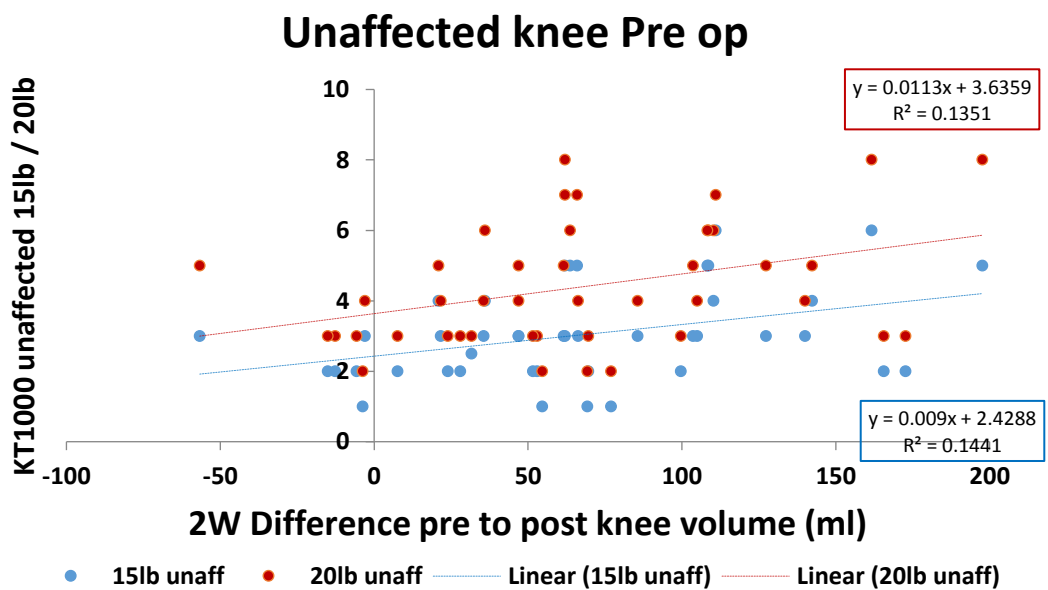


Figure 49 AP Laxity KT1000 (mm) vs Volume difference pre to post op 2w (ml) Unaffected Knee

The Anterior posterior laxity tested with the KT1000 dynamometer and measured in mm, correlated with the change in knee volume pre to 2weeks postoperatively. The correlation was with the low levels of force only – the 15 and 20Lb of force levels. There was not significant correlation with the high force levels of 30lb or the manual maximum test.

RANGE OF MOVEMENT

The loss of knee range of movement compared to the unaffected knee for both flexion and extension is shown in Figure 50.

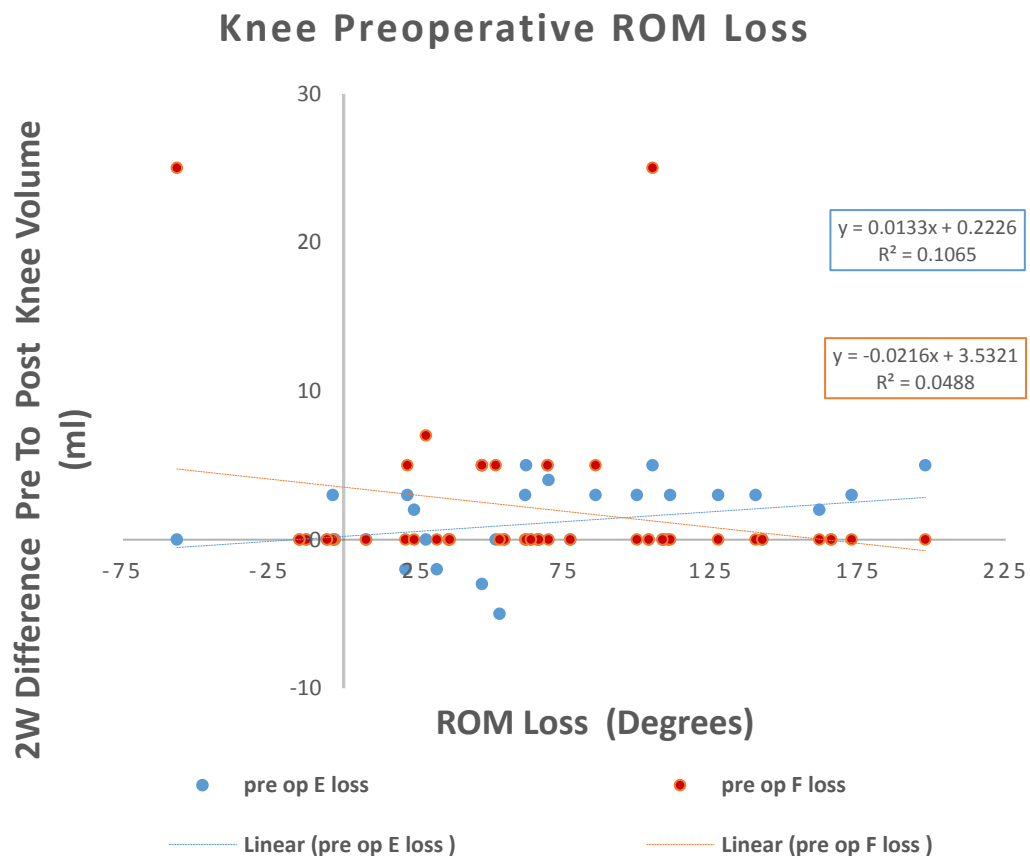


Figure 50 Preoperative Range of movement loss in degrees for both Extension and flexion vs the change in knee volume pre to 2 weeks postoperatively

Loss of knee extension preoperatively did significantly correlate with change in knee volume pre to 2 weeks postoperatively.

VARIABLES SHOWING NO SIGNIFICANCE

The following variables have come close to significance in correlation with change in knee volume pre to 2 weeks postoperatively and are graphed and described below.

IV FLUID GIVEN

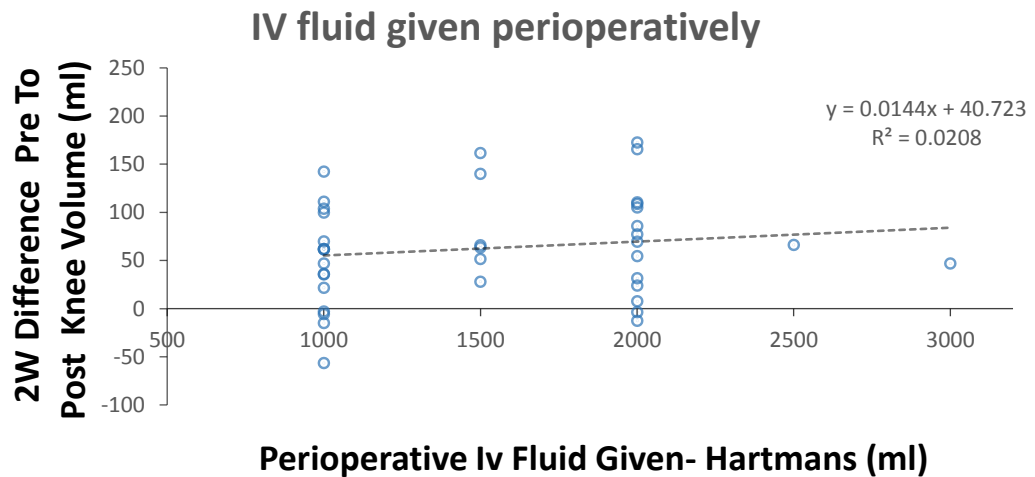


Figure 51 Volume of IV fluid given intraoperatively vs Volume difference pre to post op 2w (ml)

The amount of IV fluid given in the operating theatre and recovery room did not show correlation with the change in knee volume see Figure 51), however, graphing each fluid level separately, there may be a trend toward larger volumes with more fluid given (Figure 52).

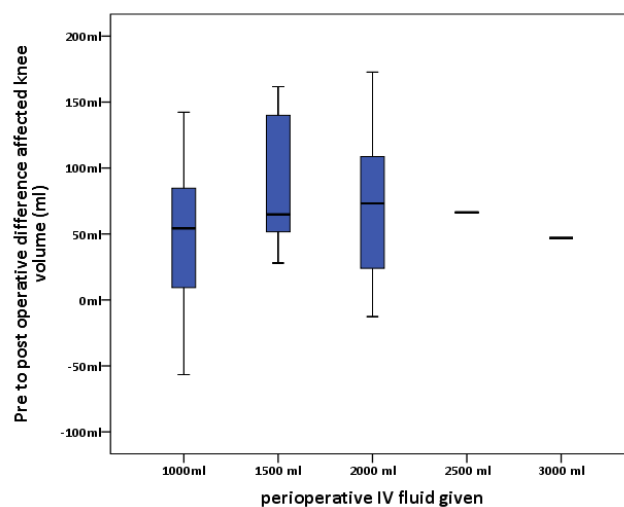


Figure 52 Graph of IV fluid levels given perioperatively and change in knee volume pre to 2 weeks post operatively

AVERAGE ELEVATION TIME IN THE INITIAL 2 WEEKS – REPORTED FROM HOME DIARIES

The scatter graphs of average time elevating per day versus change in knee volume pre to 2 weeks postoperatively is shown in Figure 53.

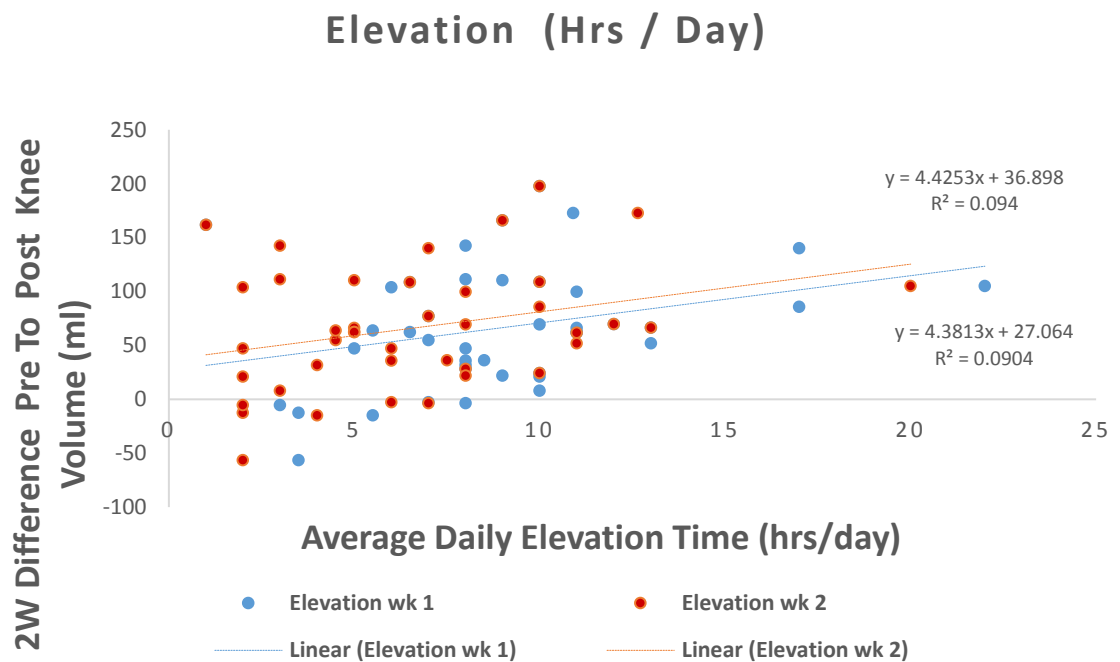


Figure 53 Average daily elevation time in week 1 and 2 postoperatively graphed against the change in knee volume pre to postoperatively at 2weeks.

There was a close to significant positive correlation with the elevation time and the change in knee volume. Those who elevated longer had greater increase in volume.

Many of the variables assessed did not significantly correlate with the change in knee volume pre to 2 weeks postoperatively. They have been reported in Tables 17 to 19. All the graphs are not displayed here but the most notable variable non-significant correlates are shown graphically below.

TOURNIQUET TIME

The Tourniquet times in minutes are graphed in figure 55

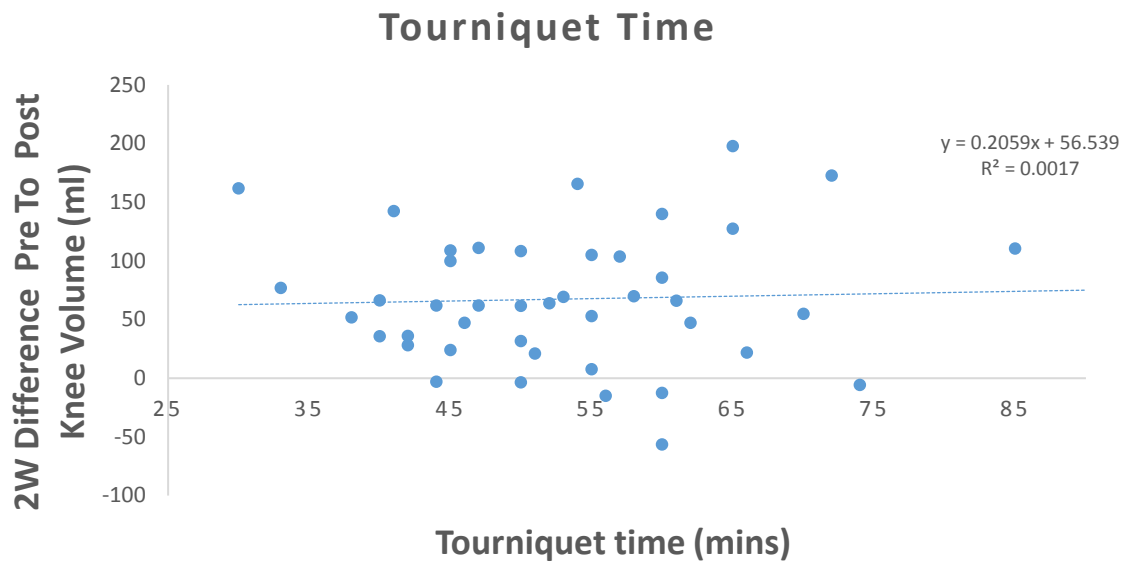


Figure 55 Tourniquet time (minutes) vs the change in affected knee volume preoperatively to 2 weeks postoperatively

The tourniquet time (operation time) did not correlate with the change in knee volume preoperatively to 2 weeks postoperatively

AVERAGE DAILY USE OF CRYOTHERAPY - POSTOPERATIVE 2 WEEK DIARY

The average time of using cryotherapy per day is given in Figure 56. This showed no significant correlation with postoperative change in knee volume from pre to 2 weeks postoperatively

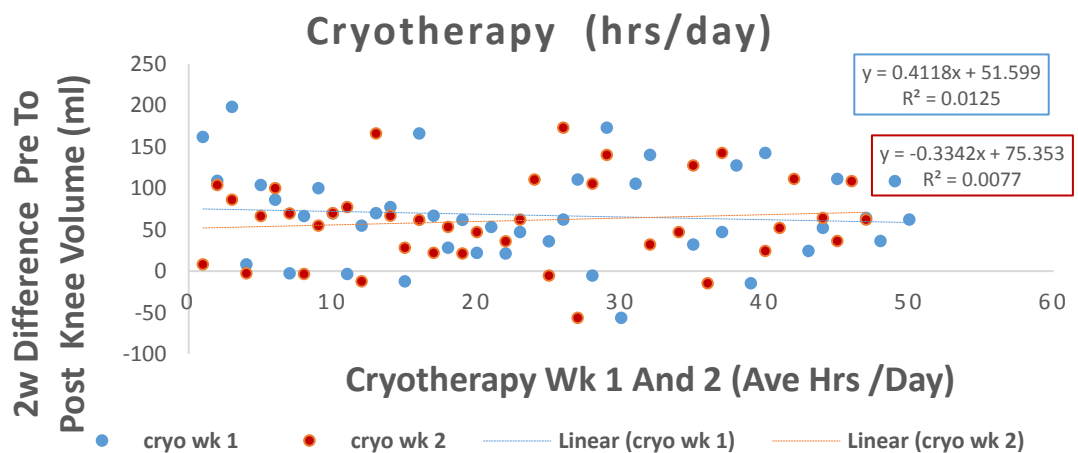


Figure 56 Average daily cryotherapy (hrs/d) week 1-2 vs change in knee volume pre to 2 weeks postoperatively (ml)

AVERAGE DAILY STANDING AND WALKING IN INITIAL 2 WEEKS (DIARY)

The average daily amount walking and standing (hrs/day) is given for week 1 and 2 in figure 57.

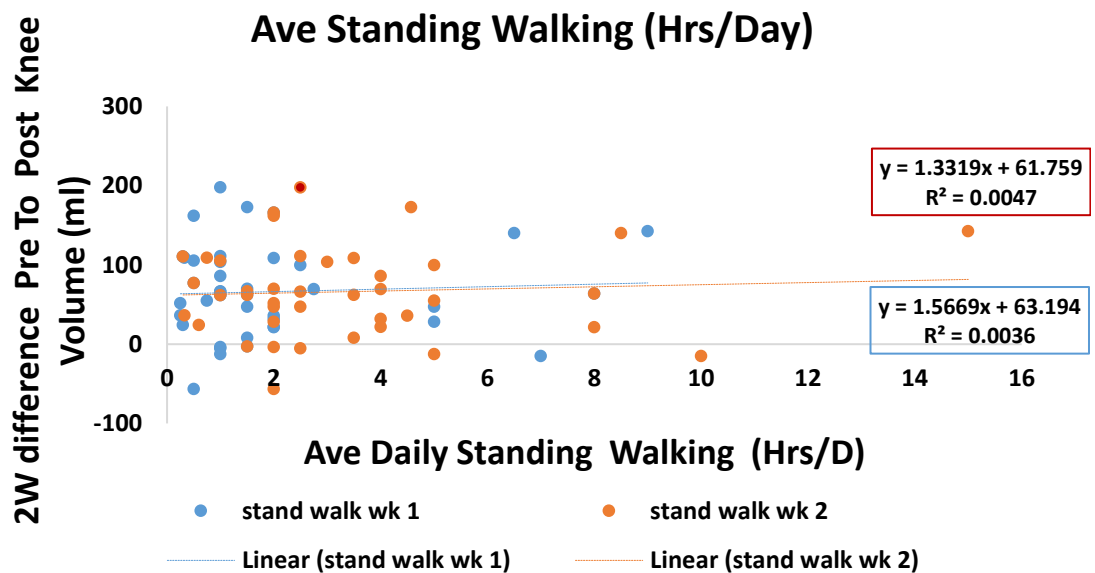


Figure 57 Average daily standing or walking (hrs) for week 1 and 2 graphed against the change in knee volume from pre to 2 weeks postoperatively (ml)

The amount of daily walking and standing did not significantly correlate with the change in volume. Indicating that the amount of standing and walking did not seem to link with the knee swelling.

DISCUSSION

KNEE VOLUME

The two week post-operative knee volume measure on the perometer correlated strongly with the preoperative affected knee volume, as was expected. The affected knee volume difference pre to 2 weeks postoperatively, however, did not correlate strongly, indicating a varied response to surgery with swelling. The Perometer gives a measure of total knee volume, and the most significant swelling after ACLR probably relates to the intra-articular effusion, although due to graft harvest surgery Extra articular effusion is also relevant. It is difficult to ascertain the proportion of the change in perometer measure that relates to intra-articular effusion, although the knee segment length on the perometer aims to pick this up. The lack of correlation of the volume difference scores with preoperative affected knee volume suggests this measure is picking up more than just the size of the knee and may capture at least some component of the intra-articular volume.

The 6 week volume perometer data were also collected, however these were not used in the correlation analysis as there were only a small number of 6 week scores and this was judged insufficient for statistical analysis.

DEMOGRAPHIC CORRELATES

Age, sex and body size measures showed no correlation with affected knee volume difference pre to post op 2 weeks, but body size measures showed strong correlations with the raw 2week knee volume measures (not differences). This indicates, as expected, that the raw knee volume measure contains some size component, i.e. larger patients have larger knees. The correlation analysis has therefore concentrated on the difference in affected knee volume pre to post op 2W, to attempt to control for the body size component to our perometer volume measure.

To further account for the possibility of size effects with the analysis the change in knee volume change pre to 2 weeks post operatively was converted to a percentage change in volume pre to 2 weeks post operatively. When the correlations were performed with this measure, the same variables showed significant correlation. The results were therefore presented using the raw change in volume pre to 2weeks postoperatively in milliliters.

PATHOLOGY DATA

Injury to surgery time showed no significant linear correlation with affected knee volume difference pre to 2 weeks post, however, it may be possible that there is a non-linear relationship, whereby postoperative swelling changes with duration of time from the injury. It is not always certain when the optimal surgery time is after injury. Some authors advocate early surgery in the initial weeks, although this has been associated with arthrofibrosis and possibly more inflammatory reaction in some cohorts.

Meniscal pathology groupings were also equivalent in the differences in affected knee volume pre op to 2 weeks post, and not statistically different, however, the medial meniscus group showed a reduced volume. Interestingly the group with both menisci affected did not show greater swelling volumes post operatively. This seems to indicate that the amount of swelling is unrelated to the concurrent meniscal pathology. Medial, lateral and PFJ compartment chondral pathology, similarly, showed no significant swelling difference in those subjects affected, indicating that swelling may not be affected by the presence of chondral pathology.

There were only 2 subjects with concurrent ligament pathology (MCL) but they did not show greater affected knee volume difference values at 2 weeks post operatively. This again contradicts expectation that concurrent pathology in the knee would adversely affect postoperative swelling. The inflammation post ACLR may come mainly from the ACLR surgery, and not be worsened or affected by the other pathology within the joint.

Another explanation for the lack of association between pathology and swelling, may be that the joint capsule will have a finite capacity to swell no matter what the surgery, and volume will not increase once this is reached. This may also hold true for the fixation and surgical tunnel sizes also (see below).

SURGERY DATA

The operation / tourniquet time did not show correlations with swelling, and there were no differences between surgeons in the affected knee volume difference pre to 2 weeks post op. The length of surgery, therefore, may not predict the level of knee swelling. The capsule of the knee has a fixed volume, and the capsular volume may decide the level of effusion rather than the length of the surgery. Some authors have found that knee surgery (TKA) with a more limited tourniquet time was associated with less postoperative complication or swelling^{344,345},

although other studies have found no effect³⁴⁶, or even advantage in extending the tourniquet time until after wound closure and application of the compressive dressing³⁴⁷. A recent meta-analysis suggests that releasing the tourniquet before wound closure is associated with an increase in blood loss (and swelling) but lower incidence of postoperative complications³⁴⁸. The level of tourniquet compression has also been investigated, and while not associating with reduction in blood loss, lower pressure levels have been found to be associated with less thrombotic complications.^{349,332}

The concurrent pathology that requires surgical intervention at the same time as ACLR is also not significantly correlated with swelling in either meniscal surgery (repair or excision) or chondroplasty. There were no differences in affected knee volume difference pre op to 2 weeks with or without these concurrent surgeries. This may indicate that the swelling after an ACLR comes mainly from the reconstruction, rather than the concurrent surgery and that extra joint “damage” may not enlarge swelling due to the finite joint capsular volume. Surgical tunnel and graft diameter were also not correlated with knee volume differences. The size of haemarthrosis may not relate to the size of tunnels drilled or if a larger tunnel causes more haemarthrosis, this may be resorbed over the first 2 weeks. Fixation sizes also do not correlate with swelling, although the endobutton size was significant for the groups, but not the sample as a whole. This may relate to the superolateral pouch of the knee capsule, close to the endobutton tunnel exit. This part of the joint capsule may have a larger volume and less compliance and will allow greater fluid collection. Several studies have indicated the superior and superolateral capsule areas in the knee are areas where effusion frequently gathers.^{266,270,350}

BLOOD PRESSURE

Blood pressure at recovery room discharge (DBP but not SBP) did correlate with the change in knee volume pre to post op at 2 weeks. This was a strong predictor of the variance in the main outcome in the multiple regression model. The effect size however for this was not large. Blood pressure preoperatively and during the operation, however, did not correlate with the change in knee volume. The mechanism behind this is unknown but BP may influence capillary pressure in the synovium in the knee and hence may influence, both the amount of haemarthrosis and also the capillary pressure to push a fluid exudate from the plasma to the ISS or intra-articular space.

PERIOPERATIVE IV FLUID GIVEN

No RICE study in surgical cohorts, to our knowledge, has investigated the amount of perioperative IV fluid given to the patients. In this study, a significant correlation was not found between the amount of IV fluid given to the patient during the ACLR perioperative period, and the change in knee volume pre to postoperatively. But splitting cases by the number of bags of fluid given does seem to show a trend. If there is a knee volume relationship with the IV fluid given, it was expected to be very small by the time of the 2 week measurement we took. Any possible relationship may necessitate a large sample size or earlier testing of volume post operatively, a situation not possible in this study. Volumes of IV fluid given ranged from 1000ml to 3litres. The patients fasted for 12 hours before surgery, and were not permitted to drink for 6 hours before the surgery. While this may leave them dehydrated, the volumes of fluid given intravenously seem greater than their body's requirement for this short period. This may cause a fluid overload, which may have an effect on fluid extravasation and bleeding, particularly in the initial hours, and then in the 2 days after surgery. It would be expected that the fluid balance would return to normal levels within the initial 24-48 hours. The initial hours, however, may be key for the inflammatory response and bleeding into the joint and articular structures. Once proteins, fluid and cells extravasate

out of the vascular system, it may take much longer to “process” them out of the joint and back through the lymphatic system.

There has been recent attention and research into how much and what type of IV fluids are given to patients in the perioperative period for many different types of surgery. Attention has been drawn to the possible harmful effects of over-giving of fluids, with a call for fluids to be seen as drugs, with specific indications, contraindications and dose ranges.³⁵¹ The giving practice in many operating rooms may not be following evidenced guideline when it comes to elective surgery and even day surgery such as ACLR. One recent US study reviewed 5912 uncomplicated elective abdominal operations, finding very disparate amounts of perioperative fluid given. The most important factor predicting the volume of fluid given was the provider of the anaesthesia.³⁵² No study, to our knowledge has been performed to review the IV fluid given to ACLR patients.

The justification for perioperative IV giving is the long held belief that fluid shifts occur in the body during surgery, due to the body’s physiological stress response to surgery, and due to the loss of fluid to a “third space”³⁵³. The stress response, however, is much less triggered now due to less invasive and shorter surgery³⁵⁴, and the evidence for a fluid shift to a “third space” is possibly flawed according to systematic review³⁵⁵

There are consensus guidelines on giving of perioperative fluid from National Institute for Clinical Excellence (NICE)³⁵⁶ and England’s enhanced recovery partnership³⁵⁷. They recommend that maintenance fluid during surgery should be limited to <2ml/kg/hr with further fluid challenges guided by stroke volume monitoring. They suggest that fluid giving should be individualized based on need. The cohort of patients in this study had much greater levels than these recommendations, with a range of 9-68ml/kg/hr rate of fluid given.

While this study did not find a significant association. There appeared to be a trend toward correlation with our knee volume difference. In the light of the current international change

on perioperative IV fluid management, it would be worthwhile investigating perioperative IV fluid giving and ACLR outcome (particularly swelling) more closely.

RECOVERY ROOM DATA

PAIN

The recovery room pain scores showed no correlation with the affected knee volume difference pre op to 2w post op, indicating that early pain scores do not relate to 2 week swelling. This may be a further indicator that the initial swelling is different from the 2 week swelling. The poor correlation between pain and swelling may relate to joint capsule compliance which increases with a more prolonged period of intra-articular pressure. There may be some accommodation of the joint capsule with time. A change of up to 37% change in pressure has been demonstrated within the rabbit knee.¹⁰⁸ The joint also has a further mechanism to reduce pressure, the synovial microcirculation, which allows a balance of fluid exchange within the joint.³⁵⁸ The synovial micro circulation processes the postsurgical effusion, removing it from the joint cavity which subsequently decreases capsule compliance, hence reducing capsule receptor stimulation, joint afferent pain nerve fiber discharge, and, hence, pain. In a canine study, joint haemarthrosis was found to clear very quickly with clearance of red blood cells beginning by 15 minutes and 95% complete by 48hrs²⁵. Swelling is often blamed for heightening or causing pain, however in this study the presence of swelling or size of swelling did not relate to pain levels. This also raises the question of the source of pain – in an inflammatory situation. It may relate to the pressure effects swelling causing pain nerve endings to fire, however it may relate more to the chemical stimulation of nerve endings causing them to fire. There may be another culprit for pain rather than the pressure that swelling causes!

MEDICATION

Of the medications given in the recovery room, only Diclofenac came close to significance in correlating with the affected knee volume difference pre op to 2 weeks. As a stronger NSAID this could be expected, and it seems to indicate that early diclofenac may influence later swelling, however, it must be acknowledged that this correlation did not reach significance.

TIME TO MEET DISCHARGE CRITERIA

The time to discharge criteria met was better correlated in the Cryocuff group than the normal treatment group with the affected knee volume difference pre op to 2 w post operatively.

The sample as a whole did not correlate

HOME DIARY CORRELATES

HOME MEDICATION

The anti-inflammatory use, from the diary in the first 2 weeks did not correlate with 2 week affected knee volume difference pre to 2 weeks post, although this correlation was closer to significance for week 1. This would seem to indicate that the early NSAID may have some relation to the 2w swelling. Most subjects reported pain as the main reason for use. Most subjects reported a reduction in pain week 2 and subsequently reduced their diclofenac intake.

HOME KNEE COOLING

The daily time using ice or Cryocuff was not significant in correlation with affected knee volume change preoperatively to 2w to postoperatively. The daily average ice / Cryocuff use was significantly different between group, and the cryocuff group came closed to correlation in week 1. This seems to indicate that extra time using ice or Cryocuff conveys no extra benefit in controlling swelling, although the first week may be the most important. This study took no home measurement in the first 72 hrs but Barber et al²⁵² found that pain levels peaked at

36 hrs post ACLR, indicating that the early period for input may be the most important, with less further benefit after this time.

TIME IN ELEVATION

There were significant correlations between the amount of time in elevation and the 2 week volume difference for the whole sample, particularly the daily amount of elevation time in week 1. This correlation was very close to significance for week one and week two. The r value was (0.301 week 1 and 0.307 week 2), indicating reasonable effect sizes. Interestingly the correlation was in a positive direction, indicating that a longer periods of elevation corresponded to more swelling. This finding agrees with guidelines suggesting that combining compression and elevation can increase swelling.^{115,359,360} These data may point to a possible “rebound effect”, with greater knee volume differences as elevation time increases (positive correlation). Some guidelines have suggested that combining compression and elevation can cause this effect (PRICE guidelines for treatment of soft tissue injury)¹¹⁵. In the “rebound effect” the microcirculation dilates in elevation when the articular pressure in the limb drops, to ensure sufficient tissue perfusion.^{210,361} On standing, the pressure increases and vascular pooling results. This arteriolar dilatation has been documented in muscle by Murthy et al²¹¹. In a clinic study on treatment with elevation post ankle sprain, ankles were found to return to a swollen state within 5 mins after returning to the dependent position after an elevation treatment²¹². The elevation in our study was further compounded by pressure from the Cryocuff or from the ice bag used by a few of the patients in the standard treatment group. Clinical studies have documented increases in swelling when compression is combined with elevation. Rucinski et al²⁰⁸ measured ankle volume with water volumetry in patients with post-traumatic ankle edema, with finding of reduced swelling in an elevation only group but an increase in swelling in both elevation and sustained compression, and elevation and intermittent compression groups. In an acute ankle injury study, Airaksinen et al (1990) found that a sustained compression group had less edema at 1 and 4 weeks post sprain, than a once

daily intermittent compression group ²¹⁴. The acute situation post injury may produce different responses than a sub-acute or chronic phase.

The “rebound phenomenon” may have some relation to hypoxia in tissues – with tissue PO₂ levels changing in the period after injury (skin wound). Hypoxia in vitro has been found to influence increased production of vascular endothelial growth factor (VEGF)³⁶², which stimulates angiogenesis. In vivo skin wounds reach maximum PO₂ hypoxia at 5-7 days³⁶³. Compression elevation over this kind of time period and may compromise tissue perfusion in this time influencing greater angiogenesis via VEGF. The dosages of compression and elevation in our study may approach these levels for some of the patients.

Periods of stasis may also be relevant to swelling as without normal lower limb calf muscle pump venous return will lessen. This effect can be seen in intensive therapy unit (ITU) patients and Spinal cord injured patients, with some studies finding non traumatic, occult knee effusions in these groups, possibly due to stasis⁷⁶.

This cohort was not split into groups of the Cryocuff vs Standard treatment group for the correlation analyses, although this was done for some of the variables. It must be noted that the numbers were smaller and it is harder to draw stronger conclusions from a smaller correlate sample. For this reason the results have not been extensively reported split into groups, although for several variables this may be worthwhile to report. Larger studies, however, will be required to investigate the correlates in groups.

In our sample, the group with compression and elevation (Cryocuff group) did not show a correlation with the postoperative knee volume change, indicating that compression from the Cryocuff may moderate a “rebound effect”, although the trend toward more swelling with longer elevation time was present even in the Cryocuff group in the 2nd diary week. It may be that the cold effect from the Cryocuff/ice negates the negative rebound effect. There may be an interaction between compression and cold for swelling. When the ratio of time in elevation

to time using Cryocuff /ice was analyzed, there was a significant correlation in week 1 ($p=0.051$), close to significant in week 2 ($p=0.122$). This would tend to suggest that the proportion of elevation to cooling time is important, with longer elevation to cooling times giving more swelling. However, the numbers for this correlation analysis are lower and these results should be taken with caution. Larger studies are recommended with the specific aim of further investigating these results and correlations. No studies have quantified this ratio related to quantity of swelling, and this may be a possible future variable that should be investigated. It has been found that an increase in compression from a cold pack produces a lower skin temperature³⁶⁴ There may be a more complex or nonlinear relationship between compression, elevation and swelling, also with differences between acute (0-72hrs) and more sub-acute (>72hrs) swelling.

The data from this sample demonstrates close to significance in the relationship between elevation and increases in knee volume post ACLR, suggesting that prolonged periods of elevation post ACLR may be detrimental to swelling in the initial 2 weeks.

TIME STANDING

There were no significant correlations between average daily time in standing/walking and affected knee volume difference pre to post op 2, suggesting that the amount of standing or walking in the first 2 weeks is not related to the amount of swelling.

The home diary correlation data in this study point to a complex relationship between compression and elevation, ice and cooling, and swelling. Prolonged elevation may actually worsen swelling at 2 weeks, while some amount of standing and walking, rather than being detrimental, may be helpful in swelling reduction. An effect from how these variables are combined may also be important, with cooling, possibly negating the detrimental effects when elevation and compression are combined. Finally a regimen may need to change from early postoperative (0-72 hrs) to later postoperative (1-2weeks).

FUNCTION CORRELATES

QUESTIONNAIRE SCORES

Several of the functional questionnaire scores have questions on swelling (Lysholm and IKDC) and this may affect their relationship to swelling measures. Correlations between questionnaires and affected knee change in volume pre to 2 w post op, were not significant for 2w scores, indicating that swelling does not relate to function at 2 weeks. The correlations were significant for 6 week to 6 months scores for LEFS but only 6 month scores for IKDC (negative correlations). This may indicate a relationship between increased 2 week swelling and a lower IKDC and LEFS score (6weeks to 6 Moths). The other function scores, however, Lysholm and tegner showed no whole sample significant correlations with volume change at 2 weeks, suggesting swelling does not relate to function. There were some differences in function/ swelling correlations within the groups, with the standard group having stronger correlations with 6 month scores, indicating that swelling at 2 weeks, does correlate with 6 month function in a normal treatment group but not with Cryocuff group. The numbers in the standard group for 6 months were low and this result is therefore questionable.

Many knee self-assessment function questionnaires have questions relating to knee swelling, few studies have investigated the relationship between knee function and swelling. In the ankle, post-sprain, Man et al ³⁶⁵ found no relationship between self-assessed ankle function and ankle-foot swelling, measured with volumetry. This study found little relationship between knee self-assessed functional questionnaires and 2 weeks swelling.

RANGE OF MOVEMENT

Preoperative extension loss showed correlation with affected knee volume change pre to postoperatively at 2 weeks. No other significant correlations were demonstrated between ROM and swelling. Extension loss has been correlated with a poorer outcome in ACLR.³⁶⁶ It is associated with tightening of the posterior capsule. The loss of extension would be expected to coincide with a loss of whole capsule compliance, therefore it is unusual to see an increase in volume with more extension ROM loss. It may be that the knee ROM is restored in the surgery, re-establishing the normal (or a greater) capsule distensibility. This correlation may warrant further investigation.

LAXITY

The Preoperative AP laxity measured with KT1000 correlated significantly with the knee volume change pre to post op 2w. In the *affected* knee the correlation was significant in the 10 (p=0.038) and 20lb (p= 0.046)) force levels but not at the 30lb force level (p=0.142). Interestingly, in the *unaffected* knee, there was also a significant correlation at the 10 (p=0.012) and 20lb (p=0.015) KT1000 force levels but not at 30lb (p=0.099). This variable was a strong predictor of variance in the multiple regression model, however, again did not have a large effect size.

This may point to a link between swelling and laxity, but at lower force levels. The mechanism for this was not certain and was not further investigated in this study. One possible explanation may relate to connective tissue compliance/ extensibility. As connective tissue is present in vessel walls as well as joint capsule. Joint capsule compliance, may have some relation to vascular compliance. One study has found a link between BP and joint laxity as well as skin extensibility³⁶⁷. More general connective tissue

extensibility (such as found in benign joint hypermobility) may allow greater effusion (capsular stretch or compliance) before equilibrium. This has been investigated for tissue extensibility and skin³¹⁴. There may be a vascular linkage with tissue extensibility, which links with vascular compliance and hence alterations in capillary pressure and microcirculation. Hypermobility and measures of tissue or vascular compliance were not investigated in this study, however, and it is not possible to draw firm conclusions. These variables, however, warrant further investigation with larger sample size and validated measurement of vascular and tissue compliance to investigate any interrelationships in ACLR.

The affected to unaffected knee AP laxity difference is one outcome measure in ACLR patients that is frequently reported. The surgery aims to give a stiff graft, which functions with as similar stiffness as possible to the original ligament. To test the graft the AP laxity of the ACLR affected knee is normally compared with the unaffected knee. In this cohort, comparing the affected knee to the unaffected knee, the AP Laxity difference (30lb KT1000 force- ie high force level) did not correlate with 2 week swelling for the sample as a whole but the standard group showed a correlation. A possible explanation may relate to capsule tension related to Intra-articular pressure. The intra-articular pressure decreases over time with a tense effusion within the joint capsule accommodation as a possibility (There may be some accommodation of the joint capsule with time – this can be up to 37% change in pressure in the rabbit knee¹⁰⁸). This change in capsule compliance may affect laxity, however, swelling / volume did not differ between the groups and the cause of the 2W laxity difference correlation in the standard group is unknown. It should also be noted that the affected to unaffected knee laxity differences were small and caution should be exercised before drawing conclusions from this data.

LIMITATIONS

There are several limitations in this correlates study. The cohort of patients used for this study was the same as the previous study, and the data presented in this study should be read understanding the limitations discussed in the previous chapter. The patients in the sample who were lost to follow up did not have postoperative measures and the data for these patients were not used in this correlate analysis.

The cohort were also part of a randomised controlled trial of an intervention (Cryocuff v standard treatment) and the groups had different early postoperative treatment in the postoperative DSU stay and initial 2 weeks. For all of the variables the patients have been analysed as part of the groups as well as analysed as part of the whole cohort, however the smaller numbers of patients in the groups make correlation analyses more difficult and this caveat is given when viewing this data. Not all the results of these analyses have been reported but where the results of these individual group analyses showed salient findings they have been reported and discussed. For the majority of the outcomes in the correlate analysis the groups have been pooled.

Home diaries were self-reported. Although the patients were encouraged to complete the diaries daily, and their compliance was reasonable. It was not possible to force patients and relied on their accuracy. This opens the possibility of inaccuracy and recall bias. Variables that rely on these data such as the amount of standing and elevation time should be viewed with this caveat. This makes quantifying the dosage of cooling or elevation difficult while they were at home during the period from discharge from DSU to the 2 week postoperative measurement. ACLR in this unit is done as a day procedure and it was not possible to keep them admitted. The dosage of cooling was variable as we had measures of time given by patients but not of temperature. Some of the control group used ice also, and we asked them to report the amount of time used daily, but not the temperature. The Cryocuff requires

refilling regularly and the importance of this was emphasised to the patients, as was the level of elevation that was required. Compression also was not measured in this cohort and the dose of compression is not known. It was not possible, however, to get an accurate quantified dosage of the regimen applied to each patient throughout this period. These difficulties have been found in many other RICE studies on post-surgical patients and it is not possible, ethically to keep them in hospital.

The low effect size should be noted in the study with even the variables showing significant correlation, still not carrying large effect sizes. The multiple regression model showed that these variables put into the model still only accounted for 26% of the variance in the main outcome – per the R^2 value. There may be other unmeasured factors that are more responsible for outcome.

Clinically there were only very small effects from each of these variables, meaning that factors relating to swelling are likely to be multifactorial with no one factor being fully influential.

RECOMMENDATIONS FOR FUTURE WORK

This study on correlates of knee swelling raises several questions in the significant correlations shown. It would be warranted to perform further follow up studies using the perometer for larger numbers of patients, possibly with earlier postoperative measures in day 2 or the initial week.

The compliance of a home regimen is difficult to monitor and developing better methods for this would be beneficial for future studies. This may allow a quantification of dosage of RICE given to the knee, which should allow a greater understanding of the dose response

relationship (if this exists) between RICE and knee swelling after ACLR. Monitoring of the dose of compression under the Cryocuff or RJB will also be important in this dose quantification , and there have been very few studies on the level of compression that are applied to the knee by the Cryocuff, or even the normal bandaging applied after surgery .

The findings of a link between the cardiovascular variable of BP with knee volume change also raise questions, and research should further investigate this, as well as other possible contributions to fluid dynamics such as hydration and the amount of fluid given to patients during the operation and recovery room stay.

While data from home diary monitoring should be viewed with caution, the relationship found between elevation and an increase in knee volumes agreed with past studies. It may be possible, with the perometer, to investigate (and possibly quantify) this relationship. This may discover the mechanism for this increased in volume and “rebound” phenomenon. It may be possible that the explanation lies in better monitoring of the vascular and extravascular fluid dynamics in the limb.

Finally to aid this process, establishing effective methods of investigating interface pressure applied by RICE devices and their effects in the limb, could be helpful. Chapter 5 reports a study that aims to do this.

CONCLUSIONS

In summary, the most significant correlates to change in the affected knee volume pre to 2 weeks post operatively were: - Diastolic blood pressure at hospital discharge, preoperative extension loss, and Knee joint laxity from KT1000 measurement, on low force levels, and unaffected greater than affected knee.

The strongest possible predictors in the multiple regression model were – DBP in recovery room, unaffected knee laxity on KT1000 testing at 15Lb force, explaining 26 % of the variance in knee volume change. The home diary data indicate that cooling time did not relate to volume difference, but daily elevation time did, pointing to a possible “rebound effect, while some amount of standing and walking, may not be detrimental. How these variables are combined may also be important, with cooling, possibly negating the detrimental effects when elevation and compression are combined. Medication use was correlated for early Diclofenac only. The presence of swelling pre operatively may not worsen swelling response post-surgery. The change in affected knee volume pre to 2 weeks post op was not related to knee pain (either early or late), knee function, or concurrent compartmental, meniscal or ligament pathology or surgery. Surgical fixation sizes, tourniquet time and injury to surgery time, likewise, did not relate to volume in this study.

The ratio of elevation to ice time may be an important future variable. Time in standing was not a strongly significant correlate but there may be some interaction with compression, elevation and ice times, however, future work is recommended with larger cohorts of patients to investigate these relationships more fully.

CHAPTER 5– MEASUREMENT OF INTERFACE PRESSURE IN COMPRESSION OF THE KNEE

BACKGROUND

An important consideration following my previous studies was why the Cryocuff was not found to have a significant effect on knee volume beyond the normal treatment group. The explanation for this may relate to multiple factors but one mechanism may relate to fluid dynamics associated with compression. Some studies have investigated temperature under the Cryocuff device and within the underlying knee capsule^{123,124,340} but no studies have investigated the pressure distribution delivered by the Cryocuff to the knee. It is unknown whether the Cryocuff's compressive effects are distributed as anticipated by its design and whether compression has beneficial or detrimental effects on fluid exchange or perfusion around the knee.

COMPRESSION EFFECTS

Arterial blood flow can be compromised by the application of significant compression such as a surgical tourniquet applied around a limb. During knee surgery, applied tourniquet pressures applied at between 100-450mmHg³⁶⁸ (ie above arterial blood pressure). Consistent with the aim of the technique these pressures occlude arterial perfusion. Veins are much less compliant than arteries, however, and for venous occlusion, the pressures required can be significantly less. The external leg (calf) pressure for venous occlusion has been found to be 20-25mmHg (supine position), 50-60mmHg (sitting) and 70mmHg (standing)³⁶⁹. The level of compression that is required to reduce or occlude blood flow also depends on the level relative to the heart as gravity can also have an effect on arterial and venous pressure.

FLUID DYNAMICS AND POSTURE

SUPINE LYING – HEART LEVEL

In a supine position, when a body part is at heart level, pressures above systolic blood pressure will occlude arterial flow and importantly, pressures above diastolic blood pressure will compromise venous flow, which is often overlooked clinically. Venous blood pressures are normally around 5mmHg at thorax level and approximately 10mmHg at head and foot at heart height. It is conceivable that a Cryocuff or RJB could easily apply pressure above these levels, with the potential for these devices to occlude vessels even in supine positions. Flow dynamics within the popliteal artery and vein should be considered when investigating compression around the knee. The posterior straps of the Cryocuff pass across the posterior thigh and calf. These are known sites where compression effects may occlude blood flow in the popliteal artery in a large proportion of normal population³⁷⁰. Few studies have investigated the interface pressures required to occlude or compromise flow in lymphatics around the knee but they can pump against a pressure as they have contractile segments called lymphangions³⁷¹ and can pump up to 12cmH₂O to maintain flow against resistance³⁷² and may more difficult to occlude than veins, They may also require some movement to help flow and oscillatory pressures may be more helpful to lymphatic flow. This may be one way that normal movement can aid fluid dynamics (including resolution of the increased swelling post trauma). Static pressure, however, can cause larger fluid preloads and will affect lymph flow also.

STANDING – ORTHOSTASIS

When a body part is dependant, such as the ankle in standing, there is pressure exerted by the column of blood from the ankle up to the heart. This is exerted on both the arterial and the venous system, therefore, the capillary pressure greatly increases but the pressure difference across the entry-exit zones does not change and blood flow within the capillary is maintained. There is, however, a large fluid change in both the arterial and venous system. In standing the mean arterial pressure (MAP) at aortic level will be $\approx 95\text{mmHg}$ but at the foot can be as high as 183 mmHg (ie an extra 90mmHg)³². This value reflects the pressure from the column of blood $\approx 115\text{cm}$ heart to foot ($\approx 122\text{cmH}_2\text{O}$ - blood is 1.06x more dense than water/ $\approx 90\text{mmHg}$ – mercury is 13.6x more dense than water) and also relates to some very slight loss of pressure from arterial resistance to flow ($\approx 2\text{mmHg}$).

VENOUS POOLING

Much of the dynamics of fluid shift happens in the veins, they can increase or decrease their filling capacity with small increases of pressure. They are vulnerable to collapse due to their thin walls and their patency is highly affected by external compression. Together these effects dictate that veins have a wide range in their cross sectional profile, for example, at 0mmHg venous pressure they have a flat cross sectional profile, as filling pressure rises to 4mmHg the vein becomes rounder in cross section and reaches its maximum compliance. Higher filling pressures of $10\text{-}15\text{mmHg}$ give a vein profile that is fully circular and distended. These alterations allow large variations in volume and provide the capacity to act as a reservoir which accounts for the fact that veins normally carry $2/3$ of the blood volume. As the pressure rises the vessel undergoes distension causing placing tension on the vessel walls leading to

increased loading and adaptive stiffening of collagen which eventually limits further distension. At these upper volumes vein walls become less compliant than artery walls.

In the initial standing (first 30-60 seconds) the valves in the deep veins in the leg prevent any backflow. After 30-60 seconds, pressure in the veins rises and blood flows in from the arterial system and the venous valves open. This restores the pressure in the column of blood up to the heart, and raises the venous pressure in the feet. This can be raised from 10 mmHg in supine to 90mmHg in standing, causing the veins in the legs to become much distended. In a human, on rising for standing, 500ml of blood can transfer to the dependant veins (venous pooling) and explains why the level of compression required to occlude the veins in a dependant position changes.

LONGER PERIODS STANDING – FILTRATION

After standing for longer periods, up to 30 minutes, the capillary blood pressure (P_c) increases at local microcirculation level in the dependant limb. This causes microcirculation filtration of fluid out of the capillary and the dependant extremity swells. This causes a movement of fluid out of the plasma into the ISS in the dependant parts of the body. This can result in a 6-20% (≈ 375 ml) drop in plasma volume over a 15-40 minute standing period – further rise in HR helps to maintain MAP and compensatory mechanisms. The increased concentration of plasma proteins in the vascular system also raise the plasma COP (π_p) and this can be raised from 25-29mmHg over an 8 hr period of sitting. In the foot the COP in capillaries can rise from 35-44mmHg helping to reduce the amount of filtration. Given these vascular responses to standing. It would be beneficial to understand how much standing is appropriate after trauma or surgery with respect to the levels of filtration in the lower limb.

MECHANISMS FOR HOMEOSTASIS

There are some other mechanisms, however that maintain fluid in the vascular system rather than allowing it to gather in the dependant parts of the body during standing. As the filtration increases the osmotic pressure from the ISS (π_i) reduces, thus reducing the forces pulling fluid out of the capillary. Terminal arterioles in the dependant body areas also increase their tone in standing to reduce the flow through the capillary bed in dependant tissues. Thus reducing capillary BP and microcirculation filtration. This also works to maintain the body wide blood pressure in standing. The calf muscle pump is another mechanism that helps to prevent this increase in filtration in the distal limb when it is dependant. When the calf muscles contract they compress the deep veins in the lower leg. The valves in these veins prevent backflow of venous blood. The blood moves more proximally, upward against the pull of gravity. The calf pump can contribute a significant pressure to the venous system to aid venous return to the heart when upright. This is important with exercise, as it gives a mechanism whereby venous blood can be redistributed from the legs back to the heart. The calf pump also reduces the venous pressure at the foot and ankle by emptying more proximal veins, so the more peripheral veins have their pressure lowered (again the valves stop backflow). This can lower the peripheral venous pressure in the lower leg from 70-90mmHg during passive standing, down to 20-40 mmHg during walking or running. This mechanism also helps to keep veins clear to receive the outflow from the microcirculation. If the venous pressure increases, pressure gradually backlogs to the capillary level, capillary pressure rises and filtration increases. The calf muscle pump therefore helps to prevent the foot and ankle becoming swollen.

ELEVATION

When a body part is elevated above the heart the local MAP will fall. This is true for limbs raised above cardiac level – for each 1 cm raised above heart level there is a drop in arterial pressure of 0.78mmHg³². For example a MAP of 95mmHg at aortic level, gives a MAP at brain level of 60mmHg during standing i.e. the height of the head above heart is $\approx 45\text{cm}$, giving a drop in pressure of $45\text{cm blood} = \times 1.06 = 47.7 \text{ cmH}_2\text{O}$, or $45\text{cm Blood} = \times 0.78 = 35.1\text{mmHg}$. For tall animals like giraffes to maintain cerebral MAP they need an aortic MAP of $\approx 200\text{mmHg}$! When the foot is elevated by 50cm the MAP may be 40mmHg. Venous pressure will also lower in elevation. This means that both arterial and venous occlusion in the limb can occur at much lower levels of pressure. It is conceivable that the cryocuff or RJB could supply this level of pressure in an elevated position. It must also be noted that the homeostasis mechanisms operating will also help to maintain limb perfusion even in elevation by alterations in arteriolar tone as discussed.

QUANTITY OF COMPRESSION REQUIRED FOR OCCLUSION

The vascular system has mechanisms for maintaining and regulating blood pressure. To get Tamponade in the synovium of the knee some authors suggest that an intra-articular pressure of 50-60mmHg is required³⁷³. This is the irrigation fluid pressure required during arthroscopy to stop haemorrhage. For Venous occlusion, 20-25 mmHg is sufficient in the leg in a supine position, anything that occludes the limb to this level may be sufficient for venous occlusion, from a tight pair of jeans or stockings, to an occluding posture, to a cuff or bandage (such as a Cryocuff or RJB) placed around the limb. This has been shown in experiments on the upper limb with a cuff placed around the limb for 15 minutes at a pressure of 40mmHg⁵⁸. After an initial increase in volume (venous congestion in the first 2 mins), the volume of the arm continued to further slowly increase for the whole time the cuff was inflated. This was due to

capillary filtration, and the rate was measured at 0.003ml/min/mmHg per 100ml of forearm volume. In the foot the swelling rate can be $\approx$ 30ml/hr (ie unlacing shoes during a long flight or prolonged sitting).

THE CRYOCUFF-COMPRESSION AND ELEVATION

The amount of delivered compression that compression type devices like the Cryocuff actually apply to the knee is unknown. The manufacturer gives recommendations about the maximum height of the Cryocuff water chamber, but it is unclear about the evidence for this advice (Appendix 1).

If venous occlusion occurs whilst using the Cryocuff, swelling will increase in the limb due to stasis. If the device is used in different postures, there may be some postures where a much lower level of compression is required for venous occlusion. If 20-25mmHg will give venous occlusion in supine, a much lower pressure may be sufficient in elevation. It may be appropriate to avoid using these devices in these positions. For example, there is evidence that compression combined with elevation can cause an increase in swelling, due to a possible “rebound effect” when compression is released²⁰⁸. Capillary filtration with venous occlusion, however, may be sufficient to explain this swelling response, beyond just the rebound effect. Cold compressive devices such as the Cryocuff, are frequently used in leg elevation. Therefore these devices, may be detrimental to limb vascularity, with possible negative effects. It is conceivable that they could worsen swelling.

ELEVATION

Chapter 4, reports a trend in the correlation between longer home elevation time per day, and increases in knee volume after ACLR. The mechanisms behind this were unclear. Joints have normal synovial fluid exchange mechanisms, with synovium vascularity²⁷ and lymphatics⁷¹ not requiring assistance to resolve knee joint effusions or haemarthrosis (blood in the joint) post damage²⁵. Perfusion in the knee joint is maintained with many conditions of movement and posture.²⁷

TISSUE COMPLIANCE

It was also found that AP laxity measured with the KT 1000 had significant correlation with increased knee volume post ACLR. This was found for both the affected, and the unaffected knee and it was the low levels of force that had effect – (low in the force / displacement curve). The explanation and mechanisms behind this are not fully clear. It may be possible that general collagen extensibility can affect the levels of swelling and oedema. Benign joint hypermobility (BJH) may also influence this.^{374,375} The capacity of the interstitial space to increase fluid volume varies in different tissues and will partly depend on the tissue compliance. The ISF pressure P_i reaches maximum when the swelling of fluid is opposed by the connective tissue matrix components such as collagen or integrins coming under tension and limiting the expansion. Collagen and matrix extensibility and compliance vary between tissues and individuals. For example skin has much greater compliance than other tissue such as tendon or cartilage or joint capsules (skin has more elastin fibres, and a lower density of collagen fibres). This also means that skin can swell to a greater extent before the collagen matrix pushes against the expansion of fluid. This may be one reason why oedema gathers in skin, or the joint cavity, rather than the connective tissue elements that have a stronger

connective tissue matrix. Individuals with greater collagen extensibility in their body, such as those with BJH or Ehlers Danlos syndrome (EDS) may have altered fluid exchange and swelling responses.

In the previous study BP was found to correlate significantly with the change in knee volume pre to post surgery. BP will conceivably have impact on fluid exchange in the limb by altering capillary pressure in microcirculation (P_c).

MEASUREMENT OF INTERFACE PRESSURE UNDER BANDAGES AND THE CRYOCUFF

Very few measurement instruments are available to measure interface pressure between a compression device like the Cryocuff and the knee. This may be the reason why many RICE studies have measured the interface temperature (intra-articular and skin) under these devices but few studies, surprisingly, have measured the pressure these devices deliver to the knee. Many measurement instruments are used to measure pressure in the body, the most common of which is the sphygmomanometer. Current electronic BP measurement instruments monitor the oscillations in pressure from the arterial pulse to give their reading. Guidelines are available for the measurement of BP.^{376,377} Other measurement instruments have been used in the body to measure pressure from cardiac to pulmonary to cerebral. In the limbs much of the driver for this has come from research into lymphoedema, and compression stockings or garments. Venous valvular incompetence and venous ulcers also use compression in their treatment, and devices to measure interface pressure under compression bandages or stockings have been developed to quantify the pressure that they actually deliver to different regions of a limb.³⁷⁸⁻³⁸⁰ An international consensus group has also produced recommendations on optimising measurement and instruments for measurement of interface pressures.^{381,382} These devices have not been used to quantify pressure under knee bandages after surgery, or to quantify pressure delivered by compression devices like the Cryocuff.

AIMS OF THE STUDY

The aim of this study was to trial a method to measure knee to device interface pressure profiles. It was then aimed to measure and compare knee interface pressures under 2 devices, commonly used post ACLR: - the Cryocuff and the RJB, and to compare them in the different postures of - supine lying, standing and lower limb elevation

METHODS

MEASUREMENT

INTERFACE PRESSURE

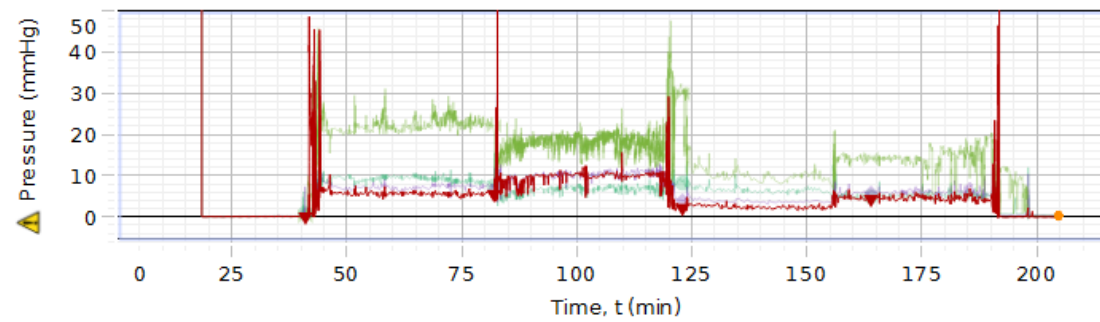
The main measured variable assessed in this study was the interface pressure (average, standard deviation, rate of change of pressure) between the compression device and the skin around the knee, with measurement values in millimetres of mercury (mmHg) for each knee. The measurement device comprised a wireless digital connection system, a universal interface device (Sparklink, Pasco, Scientific, Roseville, CA, USA) and Pasco Capstone software (Pasco Scientific, Roseville, CA, USA). Knee pressure and temperature profiles were measured with the same Pasco interface device, connected to 2 Pasco quad pressure sensors. Each quad had 4 small pillow pads attached (Microlab Ellettronica, Ponte S. Nicolo, PD, Italy). Each pad had a 2cm diameter, and connected to the quad pressure sensor with 50cm of 3mm diameter hard plastic (non-compressible) tubing.

A four way giving tap was connected 5cm from each tube attachment to the quad sensor. This allowed the introduction and removal of air into an out of the pillow pads by an empty 50ml giving syringe. Prior to application, the syringe was connected and the tap was opened to allow introduction of air. The pad and tubing was completely deflated, and then 10ml of air was introduced. The four way tap was closed and the syringe removed. This process was

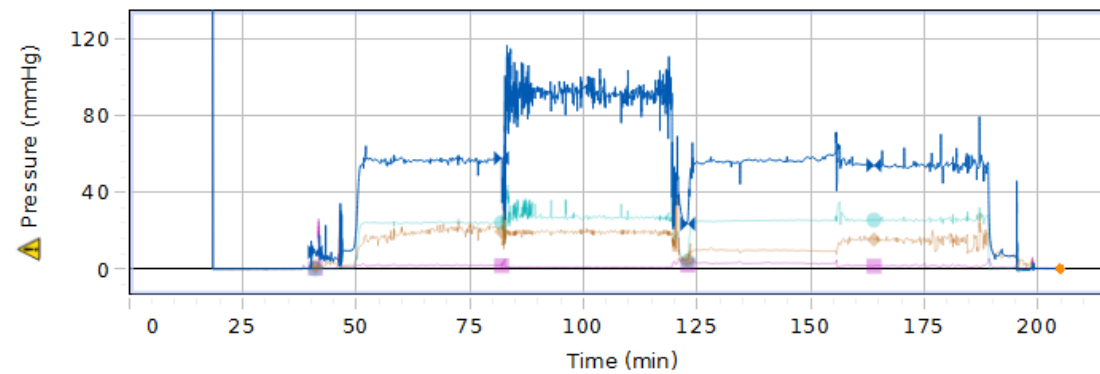
repeated for each of the 8 tubes and pad sets i.e. for all 8 channels of the quad sensor. This ensured an equal volume of air in each pad and tubing channel.

The sensors connect to software (Capstone version 3.2.1, Pasco, Roseville, CA, USA) which processed the sensor signals at a sampling rate of 20Hz and gave a continuous read out of a pressure trace. A screen shot of the software and a typical measurement trace is shown below in Figure 58.

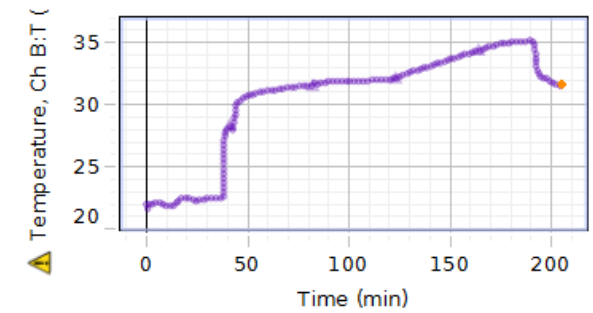
The pads were placed in a flat resting position with each tube and pad laid out flat and not touching the other tubing. A calibration was performed on the capstone software to calibrate and to zero the pressure on each channel of each quad sensor. This was performed once and all 8 channels were zeroed together. This ensures that the pressure reading on the capstone software from all pads read zero prior to their attachment onto the knee of the participant. Pads were then placed in their allocated positions around each knee. Software was started prior to the introduction of air into the pads and while calibration and zeroing took place. A period of measurement continued while the pads were still and resting on the research bench. This allowed monitoring of the zero software trace of each of the 8 channels. This was to ensure reliability and effective zeroing of the sensors, and to ensure full seal and monitor for leakage of each pad tubing channel. If there was any alterations in measurement the apparatus was emptied of air and the set up repeated, so that the calibration and zeroing could be re-performed. None of the channels during this initial period, however, were found to deviate beyond 0.4mmHg from the zero measurement.



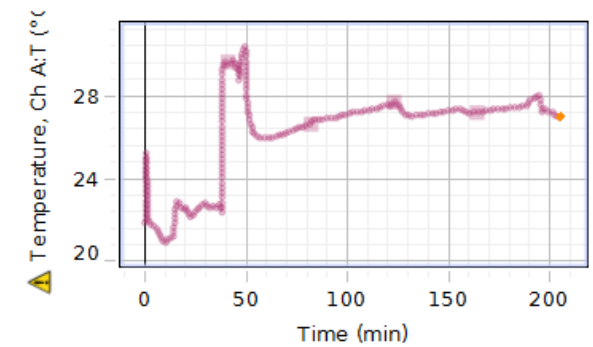
RJB R knee Run 26 TB



cryo L knee



RJB R knee



cryo L knee

Figure 58 Pasco Capstone 1.3.2 Pressure and Temperature traces of a typical 3 hour measurement session with a cryocuff and RJB knee. The four phases can be seen with each phase lasting 30 minutes. For this participant the phases were : - initial baseline + calibration 30 min , supine 30min , standing 30min , elevation 30 min, a final supine period 30 min and a final baseline phase 30 min.

RELIABILITY AND VALIDITY PILOT WORK

The Pasco Quad pressure sensor had not, to the best of our knowledge been used to measure interface pressure between the skin and any covering, a series of initial experiments were carried out on the interface pressure measurement devices to establish their reliability and validity as measures of interface pressure.

Initial pilot work was performed with static measurement periods with the pads resting on a desk at room temperature and atmospheric pressure. The pressure sensors have 8 measurement channels, and each channel was tested individually and, temperature was recorded concurrently. The knee pressure profile measurement device and pads has shown pressure differences in static state of less than 0.5mmHg over 2 hour measurement periods. The Pasco Quad sensor instruction manual (see Appendix 13) suggests that the devices are accurate to 1mmHg. Several long (2 hour) and short (10 minute) measurement sessions were performed, with the pads initially filled with 10ml of air from a syringe as the above protocol describes. The standard deviations of each trace was recorded.

Further pilot reliability and validity work took place for interface pressure under the Cryocuff and RJB. Two hard plastic cylindrical downpipes were chosen of equal length (1m), diameter (110mm) and circumference (355mm) were used to assess the measurement protocol. The piping was chosen to approximately replicate the length and circumference of a human leg. The same protocol and timings were followed and the interface pressures were measured in the 4 corresponding areas of the cylinders to the areas on the human knee of the: - pes anserine space, the superolateral to patella area, the posterior inferior area and the posterior superior area. To assess validity, a second interface pressure measurement was concurrently performed to compare the pad interface pressure with that measured by the Pasco quad sensor pads. One further devices was used to concurrently measure interface pressure. The secondary pressure measurement device used for the concurrent pressure interface testing was the PicoPress (Microlab Elettronica Bergamo, PD, Italy), which has been used and

validated for measurement of interface pressures between skin and bandages. The interface pressure measurement from the Pasco quad sensor pad superolateral to the patella was compared to the PicoPress measurement on one leg and the Kikuhime pressure measurement device on the other leg. The pads for these 2 devices were placed underneath the pads for the Pasco quad pressure sensor.

The measurement setup (see Figures 59 and 60) was similar to the protocol used for the participants with each cylinder set up in the position of the leg and the pads on initially, then the Cryocuff or RJB applied over the pads. The same protocol was followed for evaluating the RJB and the Cryocuff in different postures , with continuous interface pressure measurement during postures of initial supine, cylinders elevated, cylinders upright (standing) and a final supine position. The measurement lasted for 30 minutes in each position.



Figure 59 Reliability validity work used 2 round hard plastic pipes with the protocol repeated using the downpipes. Further pressure measurement devices were used to compare the capstone pressure measure



Figure 60 Reliability validity work also compared the Cryocuff and RJB in the different postures

RELIABILITY WORK WITH DEVICES ON PARTICIPANTS

Some final information was taken for reliability analysis during the experiments on the participants. Baseline pressure levels were recorded after the sensors were calibrated and zeroed, a period of quiet resting of the sensors on the desk was allowed to enable a 2 minute baseline to be determined. This was also done at the end of the session when the pads were removed from the participant and they were rested on the desk to establish a final baseline.

A further baseline measure of pressure was also performed after the empty Cryocuff was applied to the knee (over the pads). The baseline levels were recorded over 2-5 minutes with the participant completely rested supine and the knee in extension. Post-test baseline pressure level was recorded at the end of the session with the Cryocuff empty again, before it was removed. This allowed a comparison of the pressure that an empty Cryocuff delivers

to the knee before and after the session. The interface pressure in supine was the final baseline type measure, with interface pressures recorded in the initial and final 30 minutes of supine lying. Measures were recorded for all 8 of the sensor pads for each measurement.

SELECTION AND RECRUITMENT

21 Normal healthy volunteers were approached and questioned to determine inclusion, with recruitment taking place after informed consent.

Participants had bilateral healthy lower limbs. They were excluded if they had:- past history of injury to either limb in the last 3 months, current knee swelling or pain, a febrile illness, BP problems or medications affecting BP, diabetes, PVD, or if they smoked. Females were questioned about menses. They were asked to fast for the four hours before the test and to not exercise or consume caffeine or alcohol in the 24 hours before the testing.

MEASUREMENT PROCEDURE

The Measurement procedure is shown diagrammatically below in Figure 61



Figure 61 Flow Diagram for the course of the study

Participants attended for measurement, fasting for the 4 hours prior, without fluid or caffeine intake. They were questioned initially on the following information relating to factors that may affect lower limb blood flow including caffeine and alcohol intake, general health, BP, lower limb pathology, medication, stage of menses, exercise and activity levels. The temperature, humidity and barometric pressure in the measurement room, were recorded, and the air conditioning controlled the temperature to be as consistent as possible during each participant's measurement session. Knee joint laxity was measured with the Beighton's score (for general joint laxity) (0-9)³⁸³ and with KT1000 arthrometer for a measure of knee AP laxity. A brush test was performed on the knee to ensure no effusion was present.

Participants were asked to lie supine on a treatment couch and four pressure profile pads were attached to the same four areas on each knee. They were attached to the pes anserine area, lateral suprapatella area, inferior popliteal space and superior popliteal space. These areas were chosen as they form areas where swelling and bleeding may gather after ACLR. The pes anserine was chosen, as it is the exit area for the tibial tunnel and the harvest site of the Semitendinosus and gracilis tendons from the pes anserine. The suprapatella area was chosen, as the knee capsule extends up to this area and it is a common site where intra-capsular swelling gathers and during surgery, this is the femoral tunnel exit site for the drill and the endobutton sits in this area. The superior and inferior popliteal spaces were chosen to try to determine how much pressure the posterior aspects of the Cryocuff and RJB deliver to the posterior knee. The popliteal artery, veins, lymph vessels and tibial nerve all run in this space superficial to the posterior knee capsule. Any pressure on the capsule from behind will cause pressure to these vessels and may partially or completely occlude them. A superior and inferior pressure pad were chosen to determine if there may be a tourniquet effect established when comparing proximal versus distal pressure. It has not been determined how much pressure the proximal and distal straps of the Cryocuff exert on the posterior aspect of the knee. Each of the pressure pads was attached with micropore dressing adhesive tape.

Figure 62 shows the set-up of the participant with the interface pressure pads and tubing attached to the quad pressure sensors.

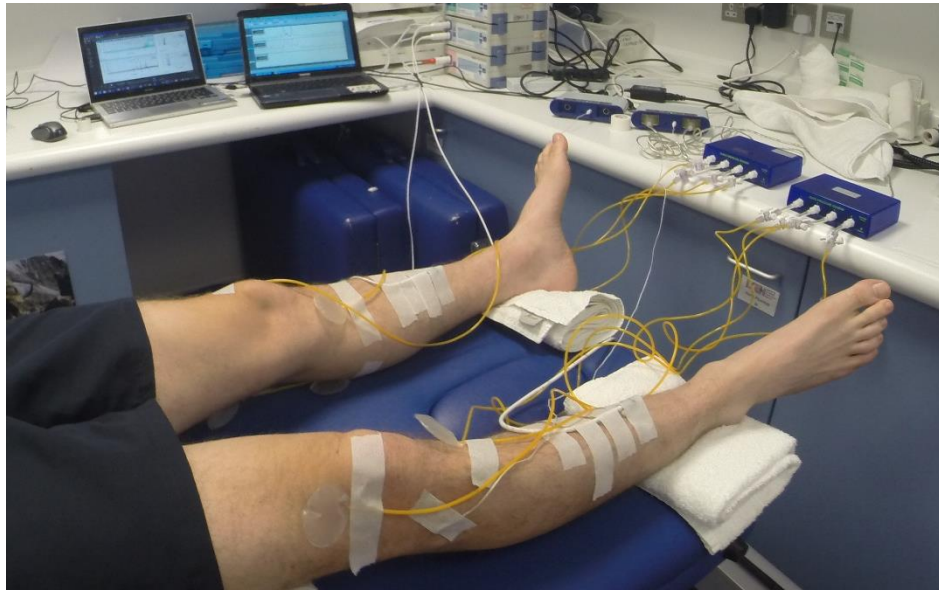


Figure 62 interface pressure pads attached to participant and connected to the quad pressure sensors via plastic tubing

The tape was attached to the plastic base of the pad, taking care not to apply direct pressure to it and the hard plastic tube connected to each pad, and not over the actual pad. This was to ensure that there was no pressure applied by the tape to the air filled section of the pad. The tubes were plastic and were 2.5mm wide with 1mm thick walls. They were made from hard plastic and were not compressible. This ensured that any pressure applied to the tubes did not affect the pressure reading from the pads. The pressure readings on the computer software were due only to the pressures applied to the pads. Along with the pads, one temperature thermistor was applied to each knee also and temperature readings were taken with pressure readings. The thermistors were attached to the anterolateral knee skin just at the superior border of the lateral tibia, ie at the base of the anterolateral joint capsule attachment. This position was chosen as it was away from the pressure pads but gave a temperature under the RJB and Cryocuff for a consistent part of the knee. The heels were rested on towels and a blanket was placed under the thighs near the hip. This ensured that the posterior interface pressure pads did not rest on the bed. This ensured that the

pressure from the posterior straps did not come from the leg resting weight on the posterior pads.

RESTING BLOOD PRESSURE

Resting BP and mean arterial pressure (MAP) was measured with a blood pressure and pulse wave analysis monitor (IEM Mobil-O-Graph® GmbH, IEM, Stärkt Internationale Top-Position, Germany) which the participant wore on the Left brachial area of the arm for measurement. BP was taken after 20 minutes of quiet lying in supine, which the participant did while the tests were being prepared.

BASELINE LIMB MEASURES

Recordings were then taken after the devices were applied to each knee, with continuous recording throughout the 4 phases of the measurement session.

INTERVENTION

Measurement of interface pressure took place in both knees, in 4 different postures for a 30 minute period in each posture- Supine lying, leg elevation, quiet standing, and then a final second supine period. Block randomisation took place to decide the order (second or third) of the standing or elevation periods for each subject. The supine periods were always first and fourth. Block randomisation in blocks of four also took place to decide which knee received the Cryocuff and which knee received the RJB. These randomisations were performed with statistical software, to ensure that there were not order effects or interaction effects between the 4 periods.

PHASE 1 - REST SUPINE

The RJB and Cryocuff were applied to their respective knee over the interface pads. Figure 63 shows the initial application in supine.



Figure 63 Supine position set with Cryocuff and RJB over respective knees on top of the pressure pads, with tubing connected to the Pasco quad pressure sensors and the Sparklink connecting them to the software on the laptop

The Cryocuff cooler water container was filled with room temperature water to a consistent level for every session (2800ml) and raised, to a consistent height of 14cm above the cuff. This was maintained for each phase/position of the intervention. This height was chosen, to try to keep the pressure of the water from the chamber to the cuff as consistent as possible, throughout the experiment. This ensured that any changes in interface pressure in between the cuff and the knee were monitored for each posture, independently of any changes in pressure from the height of the cooler container. The cooler container was not put higher than 38cm (15inches), as per the manufacturer's instructions. The size of the cuff was medium and the same cuff was used for all the subjects to ensure consistency. The amount of water in the cuff varied between participants but in the reliability trials on the inert cylinders, it was found that 1070 ml of water flowed from the cooler container into the cuff. The water in the

cooler was at room temperature. The RJB was applied to the opposite knee in a consistent manner between participants. It was applied in the same manner as the normal postsurgical RJB (see Chapter 3), which patients receive immediately after ACLR surgery. Coban wrap was applied over the skin and then a crepe bandage applied over this. There was no tension applied to the Coban and crepe bandage wraps as they were laid on the skin and the same researcher (BP) applied each RJB with a consistent method. A period of pilot training took place using the Kikuhime for pressure feedback to ensure a consistent application and bandage tension between participants. This followed a similar method to Keller et al³⁸⁴ but with lower target pressures. Application of the Coban and crepe bandage commenced distally and moved proximally, overlapping each previous turn by half the bandage width, until the knee was covered from mid-shin to mid-thigh. This also covered the pressure pads and temperature thermistors that had previously been applied to their positions around each knee. The Cryocuff straps were also attached without tension and the knee was held in 0° extension to ensure the angle is consistent between the phases, and subjects will be asked to relax as much as possible to ensure no muscle activity. Participants were asked not to move and to rest as still as possible throughout the whole measurement period. Once the pads were set up, the participant remained quiet, not talking or moving. Baseline measurement was taken with the participant in a supine position, with 20 minutes lying to ensure blood pressure stabilisation. Measurements of the above interface pressures were taken continuously and the software continued collecting data from each of the pressure pads throughout the whole of each phase.

PHASE 2- ELEVATION

After the initial 30 minutes supine, the participant was either moved for the standing or leg elevation phase (30minutes), depending on their randomisation. The elevation phase (30 minutes) involved elevating the back of the plinth and lifting this up to a 50 cm height from the plinth base as shown in Figure 64. The towels were placed under the heels again to ensure the leg and the posterior pads did not rest on the plinth.



Figure 64 Elevation with head of the plinth raised to maximum height and Cryocuff and RJB in place over the interface pressure measurement pads

PHASE 3- STANDING

After 30 minutes of elevation, the next phase involved 30 minutes of relaxed standing, with knees in comfortable extension, with the Cryocuff and RJB still on and the pads and software connected. The participants stood on a step to make it easier to slide off the desk end of the plinth gently and so the knees were close to level with the Quad pressure sensors as possible. The pads were roughly at the same height as the sensor. This aimed to avoid any pressure difference from the height of the pad and tubing above or below the Quad sensor. The participants were asked to relax as much as possible, with a minimum of muscle activity and movement. This was often difficult as they required some calf and thigh activity to maintain stance over the full 30 minute period. The setup can be seen in Figure 65.



Figure 65 standing phase 30 mins with Cryocuff and RJB and the interface pressure measurement pads visible posteriorly (posterior inferior and posterior superior pads)

PHASE 4 -FINAL SUPINE

The final supine phase, involved moving back onto the plinth in supine lying again for 30 minutes with Cryocuff and RJB on. The same measurements were recorded.

FINAL BASELINE

A final baseline phase of measurement finished the session, with pressure monitoring continuing as the cooler container connected to the Cryocuff was lowered. The cuff emptied its water back into the cooler container, and was deflated. When this was complete, it was disconnected from the cooler and, with the participant remaining supine and still, a follow up baseline pressure measurement period was allowed with the cuff on but deflated (empty). The RJB was removed first, followed by the Cryocuff, then the pads were removed one by one, however the temperature thermistors were left on to get a baseline temperature of the knee. The final pressure measurement period took place with pressure pads off the participant and on the desk next to the quad sensors. A period of measurement with the pads off allowed a comparison with the pre-session initial pad pressure measurement period taken after the calibration. This also allowed a measure for test-retest reliability analysis. A flow diagram can be found in Figure 77 which summarises the steps in the experiment.

SOFTWARE CAPTURE AND ISOLATION

Data was recorded from the software from the pressure and temperature traces. Timings of each event were recorded during the session from the capstone software. The periods of interest were highlighted with the highlighter tool and the software trace was enlarged to make this as accurate as possible. The data recorded for pressure and temperature were mean interface pressure (mmHg) , standard deviation of the interface pressure (mmHg), the mean gradient or incline of the trace in the period of interest (mmHg/min $\times 10^{-4}$), and the SD of this gradient (mmHg/min $\times 10^{-4}$).

ANALYSIS

Comparisons were made between legs for knee interface pressure profiles and BP – (mmHg), temperature (degrees Celsius (°C)). The data were tested for normality of distribution and either paired T tests or a non-parametric test was used to compare differences between legs, and between the phases of measurement respectively. The statistical tests performed for assessing the reliability of the interface pressure measurement with the Pasco quad sensors, were the Intra class correlation $ICC(3, 2)$, as only one rater was evaluated. This was done in the measurements from the 21 participants to give a measure of test- retest reliability. The initial and final supine measurements were chosen for this, as supine was physiologically the measure where the participants could relax most, and hence standardise the measurement. It was harder for the participants to relax in standing or elevation and there tended to be more variability in the pressure interface data.

The ICC could not be used for the other measures because the Pasco equipment sampled at a rate of 20Hz which gave a large volume of data for any measurement period and the level of variance in this data was very low. The ICC could not be calculated accurately with this level of variance. The other baseline levels were reported and assessed for comparison. Response stability was measured using the method error (ME) and coefficient of variation of the Method error (CV_{ME}). Validity was assessed using the concurrent interface measurement device-the PicoPress, using the Pearson correlation coefficient.

SAMPLE SIZE CALCULATIONS

Sample size has been calculated on the main outcome of the knee pad pressure profile. Based on a predicted difference of 10mmHg between limbs and between postures and a standard deviation of 10 mmHg. A further 10% has been added for possible drop out, giving 18 knees in each group. Considering that each knee was its own control, we aimed to recruit 18 participants with 36 healthy knees for the study.

ETHICS

The Kings College ethical application was submitted under number BDM/11/12-123, and approval was given, with a risk assessment performed, however, the research took place at only one site – the human physiology laboratory at the institute of sport exercise and health at University College London. An ethics application was, therefore, made to UCL and the study received data protection and ethical approval from the UCL ethic office (certificate, reference No Z6364106/2014/10/70) (see Appendix 11)

RESULTS

SAMPLE

BASELINE DEMOGRAPHICS

Tables 22- 24 reports the baseline demographic and outcome variables for this cohort. Some baseline data on alcohol and caffeine intake, hydration, body composition, normal exercise, sedentary time and some variables associated with the lab environment at the time of testing.

Table 22 Baseline demographic, exercise, nutrition, body composition and Lab atmospheric data

Mean (SD, 95%CI)	Mean (SD)	95% confidence interval
Number	21	
Male	13	
Female	8	
Mean Age (years)	30.1(8.56)	(26.1, 34.0)
Body Height (centimetres)	174.65 (9.68)	(170.11,179.18)
Body Mass (Kilograms)	69.57 (10.08)	(64.86, 74.29)
Body Mass Index (Kilograms per metre squared)	22.74 (2.36)	(21.63, 23.84)

Table 23 Baseline data for participants with means SD and CI

Mean (SD, 95%CI)		Mean (SD)	95% confidence interval
Caffeine intake (cups/day)		2.1 (1.66)	(1.2, 2.9)
Alcohol intake (Units/week)		9.0 (10.7)	(3.8, 14.1)
Lab Variables	Temperature (°C)	23.6 (1.3)	(22.9, 24.3)
	Humidity (%)	30.6 (4.8)	(28.1, 33.0)
	Atmospheric Pressure (Mbar)	997.9 (52.6))	(970.8, 1024.9)
Blood Pressure (mmHg)	Systolic	114.0 (10.6)	(109.1, 118.8)
	Diastolic	68.5 (6.8)	(65.4, 71.6)
	Mean Arterial Pressure	89.4 ()	(85.7, 93.1)
Hydration variables / Body composition	Total body water (%)	60.4 (5.1)	(58.1, 62.7)
	Total body fat (%)	14.4 (7.2)	(11.1, 17.7)
	Total body muscle (%)	79.2 (6.8)	(76.1, 82.2)
	Extracellular water (kg)	15.5(2.0)	(14.6, 16.5)
	Extracellular water (% of TBW)	37.1 (1.5)	(36.4, 37.7)
	Intracellular water (kg)	26.6 (4.5)	(24.6, 28.6)
Exercise	Frequency (sessions/week)	5.1 (2.2)	(4.0, 6.2)
	Intensity (% maximum)	68.1(16.7)	(60.0, 76.2)
	Duration (minutes)	63.76 (34.9)	(46.9, 80.6)
Sedentary time / day (hours)		7.6 (3.3)	(5.6, 9.1)

The baseline data collected for each leg in each participant are recorded below in Table 34

Only AP laxity was significantly different on testing, and only for one force level. The reasons for this are uncertain, as the side of the Cryocuff was block randomised to different legs and, therefore, leg dominance should not have affected this.

Table 24 Baseline leg data – circumference (cm) and Knee AP laxity measured with the KT1000 dynamometer (mm)

Mean (SD, 95%CI)		Cryocuff leg	RJB leg	P-values
Leg circumference (cm)	Calf	37.4 (1.9) (36.5, 38.2)	37.5 (1.8) (36.6, 38.4)	0.872
	Ankle	22.8 (2.5) (21.6, 24.0)	22.3 (1.2) (21.7, 22.9)	0.876
	Knee	39.3 (2.3) (38.2, 40.4)	39.2 (2.2) (38.1, 40.3)	1.000
Knee AP Laxity (mm) (KT1000 arthrometer)	15lb force	1.7 (0.7) (1.4, 2.0)	2.0 (0.7) (1.7, 2.4)	0.048 *
	20lb force	2.9 (0.7) (2.5, 3.2)	3.0 (0.7) (2.7, 3.4)	0.102
	30lb force	5.0 (1.3) (4.4, 5.7)	5.4 (1.6) (4.6, 6.1)	0.205
	Manual Maximum Test	5.8 (1.3) (5.2, 6.4)	6.0 (1.6) (5.3, 6.8)	0.274

Note data was not found to be normally distributed on normality testing (Shapiro Wilk tests). Non parametric tests used were the Wilcoxon signed rank test unless stated * P<0.05 indicates a significant difference.

INTERFACE PRESSURE

RELIABILITY AND VALIDITY

Initial reliability and validity testing for the Pasco Quad pressure sensors with the interface pads took place with pads initially resting and zeroed in room air.

STATIC MEASUREMENT

Two (2 x 2) two hour sessions were performed and ten (10 x 10) ten minute sessions. The mean standard deviation of the static zeroed measurement sessions were found to be very low, indicating that there is little drift or noise in the sensors, even over a 2 hr period.. The standard deviations through the sessions were equivalent between pads and were found to range between 0.00444 to 0.00486 mmHg for the ten minute sessions, and between 0.0147 to 0.0215 mmHg for the 2 hour sessions.

INTERFACE PRESSURE MEASUREMENT CYLINDERS - BASELINE RELIABILITY VALIDITY

The results with means and standard deviations of the interface pressure measurements with the two cylinders are shown below. The initial and final baseline measures were taken with pads off the cylinders, again placed on a desk, and the means and standard deviations of interface pressures are shown below in Table 25.

Table 25 baseline Cylinder reliability measures with pads on desk (interface pressures in each pad pre and post session) (mmHg)

Knee interface Pressure (mmHg)	Site of the interface pressure pad	Initial baseline w pads on the desk	Final Baseline With pads on desk
Cryocuff knee mean(SD)	Pes anserine	-0.07 (0.03)	-0.83 (0.03)
	Superolateral to patella	0.001 (0.02)	-0.32 (0.03)
	Inferior posterior	-0.03 (0.03)	-0.48 (0.03)
	Superior posterior	-0.06 (0.03)	-0.65 (0.03)
Robert Jones Bandage knee mean (SD)	Pes anserine	-0.03 (0.03)	-0.71 (0.03)
	Superolateral to patella	-0.04 (0.02)	-0.64 (0.03)
	Inferior posterior	-0.02 (0.03)	-0.18 (0.04)
	Superior posterior	-0.04 (0.03)	-0.57 (0.02)

In each of the interface pressure pads, the final baseline pressure levels with the pads off and quiet and resting on a desk were lower than the initial baseline. The mean difference, however was low, between the initial to final measurements (-0.51mmHg). The standard deviation in the measures was almost exactly equal from initial to baseline and remained below 0.05mmHg for all the measurements initial and final. This indicated that, again, each

of the sensors showed very little variability in the measurement trace. The change in mean, without a subsequent change in standard deviation, would not seem to indicate drift in the sensors. The measurement session lasted 3 hours

INTERFACE PRESSURE MEASUREMENT CYLINDERS – POSTURES

The cylinders were used to give a measure of the interface pressure in the different postures as a pilot measurement prior to measuring participants. The mean pressure values and standard deviations for each of the positions are given below in Table 26.

Table 26 baseline reliability/ Cylinder measures with devices applied in 4 positions (interface pressures in each pad (mmHg))

Cylinder interface Pressure (mmHg)	Site of pad	Cryocuff knee	Robert Jones Bandage knee
Initial Supine (mean (SD)) (95%CI)	Pes anserine	20.09(0.24)	12.08(0.12)
	superolateral to patella	19.17(0.18)	11.48(0.11)
	Inferior posterior	17.48(0.26)	9.1(0.2)
	Superior posterior	10.79(0.06)	8.78(0.2)
Elevation (mean (SD)) (95%CI)	Pes anserine	13.15(0.1)	11.7(0.12)
	superolateral to patella	17(0.07)	10.88(0.14)
	Inferior posterior	11.08(0.13)	8.26(0.16)
	Superior posterior	12.17(0.05)	8.3(0.11)
Standing (mean (SD)) (95%CI)	Pes anserine	24.49(0.24)	10.97(0.11)
	superolateral to patella	24.3(0.04)	10.34(0.08)
	Inferior posterior	16.05(0.15)	8.06(0.14)
	Superior posterior	18.06(0.08)	8.3(0.06)
Final supine (mean (SD)) (95%CI)	Pes anserine	15.28(0.14)	10.48(0.08)
	superolateral to patella	20.21(0.18)	9.9(0.13)
	Inferior posterior	10.82(0.09)	8.43(0.21)
	Superior posterior	15.46(0.27)	8.54(0.15)

*** Statistically significant difference to $p < 0.001$ shaded dark grey / ** significant difference to $p < 0.01$ /

*significant difference to $p < 0.05$

The reliability statistics are below. The data from the initial and final supine measures was compared. The response stability was assessed with the Method error (ME) and the coefficient of variation of the method error (CV_{ME}). The variance of these measures was very low and it was not possible to use the ICC in table 27.

Table 27 Reliability - Response stability statistics for Cylinder measures initial vs final supine periods (mmHg)

Interface pressure pad	Statistical measures	Cryocuff knee	RJB knee
Pes anserine	ME	0.47	0.01
	CV _{ME}	19%	1%
superolateral to patella	ME	0.63	0.01
	CV _{ME}	27%	1%
Inferior posterior	ME	0.43	0.01
	CV _{ME}	19%	1%
Superior posterior	ME	0.50	0.01
	CV _{ME}	21%	1%

VALIDITY - CORRELATION WITH SECOND PRESSURE MEASUREMENT DEVICE

The results are reported below from the measures using the 2 identical cylinders for Cryocuff and RJB knee, and using the other pressure measurement devices –the PicoPress.

The correlation plots are below in Figure 66 for the correlation between the PicoPress and the Pasco quad pressure sensor for the cylinder trial (the superolateral to the patella pad was used).

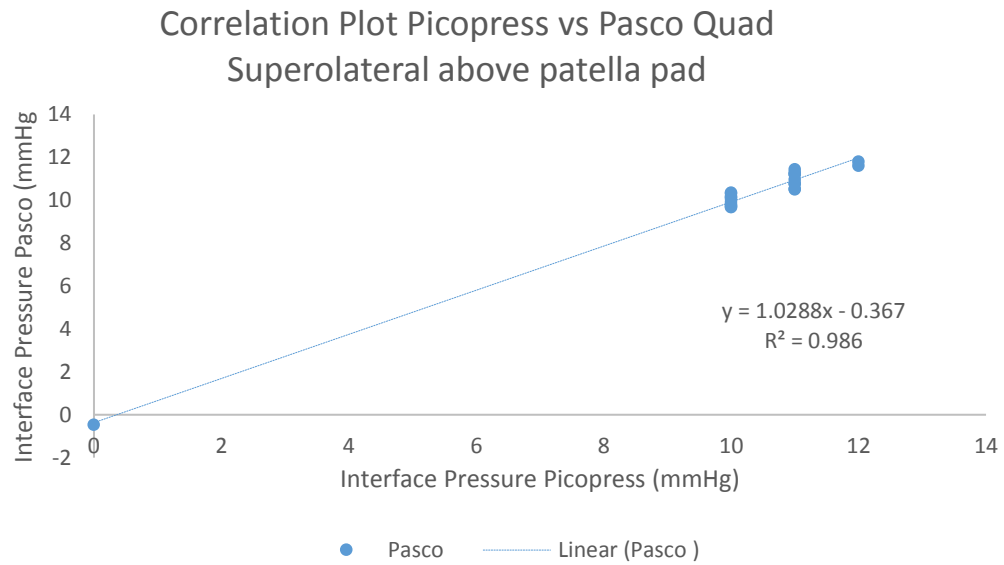


Figure 66 Correlation between the interface pressure measurements of the PicoPress and the Pasco quad sensor during the cylinder measurement session

Good agreement was found between the measures, with the PicoPress results the same as the quad sensor pad ($R^2=0.986$), indicating that the quad pressure sensor interface pressure measurement has a very close correlation with the PicoPress measure. Indeed they were the same for all measures, however the PicoPress can only read in full units of 1mmHg and cannot read fractions or decimals, meaning that the Pasco device was able to discriminate more closely. The limits of agreement, using an interval $\pm$ two SDs from the mean. The measures were very close with lower limit -0.657 with upper limit of 0.508 mmHg, which shows the measures correspond to within less than 1mmHg. This represents a good level of validity for the Pasco pressure sensor device.

MEASUREMENT OF VARIABILITY DURING THE RELIABILITY MEASURE

The Pasco software gave a mean and standard deviation of the interface pressure trace for each pad and each posture period (Region of interest (ROI)) (see Figure 57) but the software also allowed analysis of the slope of the trace – enabling analysis of the rate of increase or decrease of interface pressure. This allowed an analysis of the baseline periods to investigate for any possible drift.

CHANGE IN PRESSURE / GRADIENT OF TRACE

There was a very slight change in the pressure traces during the cylinder experiment during some of the baseline phases. There was also some difference in this behaviour between the Cryocuff cylinder and the RJB. The incline of the pressure trace (or rate of change in pressure (Δ/t pressure)) was recorded for each 30 minute episode and it gave a positive or negative gradient of the pressure trace line, depending on whether the pressure increased or decreased during the 30 minute interval.

RELATIONSHIP WITH TEMPERATURE

The temperatures were also recorded from thermistors attached to the lateral knee under each device (RJB or CC) and they are shown for the cylinder experiment, for each side and for each position below in figure 67.

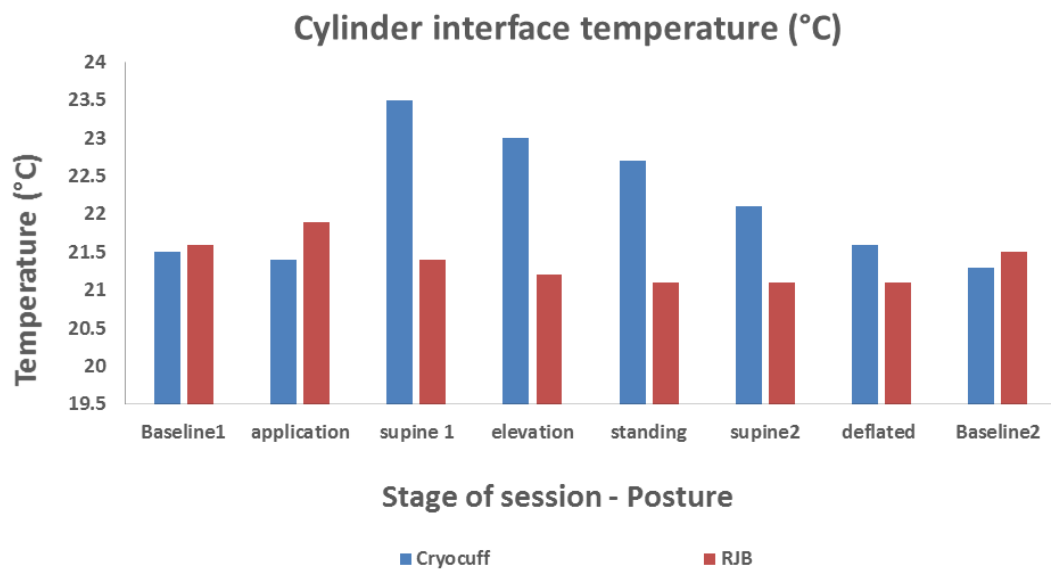


Figure 67 Cylinder experiment Interface temperature between device and cylinder (°C)

The temperatures were found to change during the experiments. (see Figure 68 and temperature traces on Figure 57) The rate of change in temperature (Δ Temperature/ time) was also recorded from the incline gradients on the capstone graphs. When the change in temperature was graphed against the change in pressure – it was found to correlate for each pad. Indicating, as expected, that there is some relationship between the pad pressure and the temperature of the pad.

Cylinder rate of change interface pressure vs rate of change interface temperature

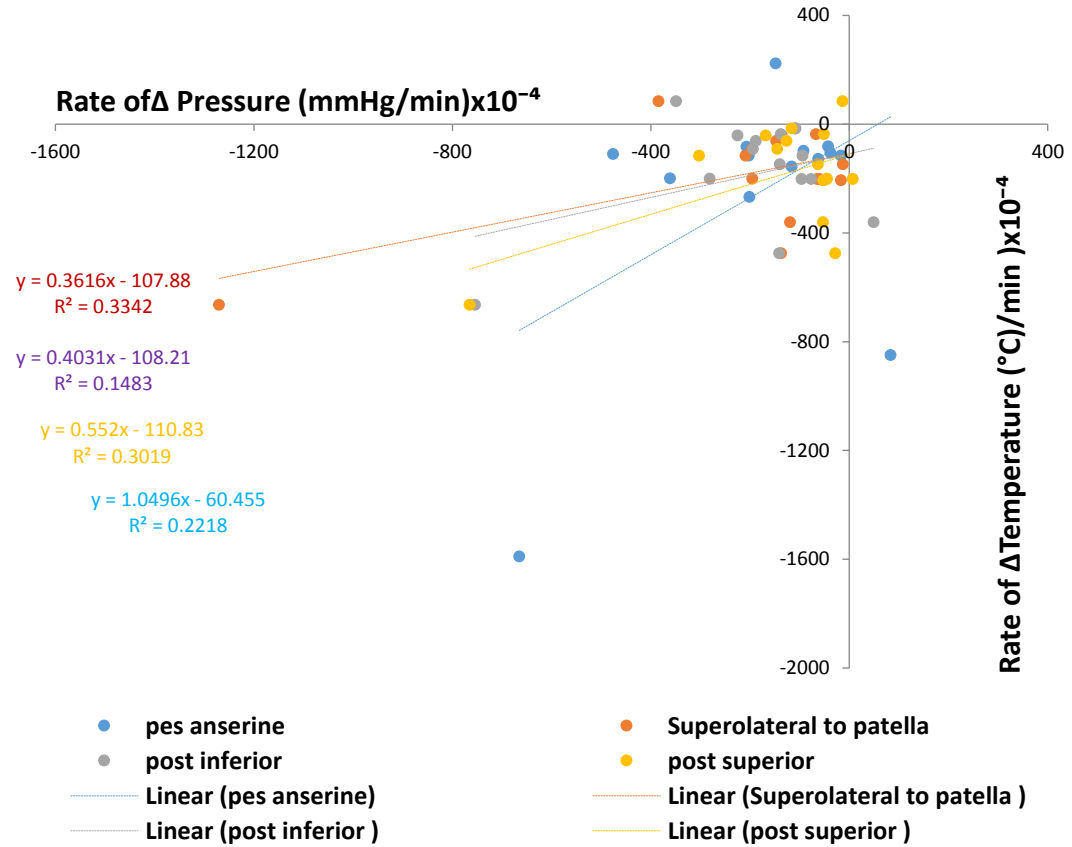


Figure 68 Rate of change of temperature ($^{\circ}\text{C}/\text{min} \times 10^{-4}$) versus rate of change of pressure (mmHg/min $\times 10^{-4}$)

MEASUREMENTS ON PARTICIPANTS - BASELINE EQUIVALENCE

PARTICIPANTS - BASELINE 1 PADS RESTING

The initial and final baseline readings of pad pressure were taken with the pads on the desk, before being placed on the participant's knee (after calibration and zeroing), and also once they had been removed from the participant, see Table 28 below.

Table 28 Final baseline pad pressure (mmHg) taken with the pads placed flat on a desk and off the participant

Knee interface Pressure (mmHg)	Site of pad	Cryocuff knee (n=21)	Robert Jones Bandage knee (n=21)	P value for significance
Final Baseline With pads on desk (mean (SD)) (95%CI)	Pes anserine	-0.17 (1.10) (-0.71, 0.36)	-0.19 (0.93) (-0.62, 0.24)	0.339
	Superolateral to patella	-0.11 (1.17) (-0.68, 0.45)	-0.08 (0.98) (-0.53, 0.38)	0.980
	Inferior posterior	-0.22 (1.42) (-0.91, 0.46)	0.05 (1.17) (-0.49, 0.60)	0.249
	Superior posterior	-0.37 (1.62) (-1.15, 0.41)	-0.38 (1.75) (-1.20, 0.44)	0.389

Nb data was not found to be normal on normality testing (Shapiro Wilk tests). Non parametric tests used were the Wilcoxon signed rank test unless stated * P<0.05 indicates a significant difference

The mean pressures were very close to zero and the means of these measures were taken and compared within and between groups. The results are reported in table below. There were no statistically significant differences, indicating that the baseline final measures were equivalent between pads.

PARTICIPANTS - BASELINE 2 INITIAL APPLICATION OF DEVICES – CUFF AND BANDAGE

A baseline was also taken when the devices were first placed on the knees, before filling.

The Cryocuff was initially placed on the knee, over the pressure pads, and a baseline pressure was measured from each pad. This was also repeated after the final supine stage, once the cooler container was lowered and the water was drained from the cuff. This gave an interface pressure of the unfilled (or deflated) cuff, both initially on application and just before removal. This is presented in table 29.

Table 29 Mean interface pressures (mmHg) in the knee pressure pads during initial and final baseline periods when the Cryocuff was deflated

Knee interface Pressure (mmHg)	Site of pad	Initial deflated (mean (SD)) (95%CI)	Final deflated (mean (SD)) (95%CI)	P value for significance
Cryocuff	Pes anserine	2.02 (1.50) (1.34, 2.70)	7.61 (5.75) (4.92, 10.30)	0.004**
	superolateral to patella	21.52 (3.26) (20.00, 23.05))	0.70 (1.69) (-0.12, 1.51)	P < 0.001***
	Inferior posterior	11.46 (4.97) (9.20, 13.73)	12.98 (6.94) (9.64, 16.33)	0.433
	Superior posterior	4.94 (4.04) (3.10, 6.78)	4.79 (4.85) (2.45, 7.12)	0.390
Robert Jones Bandage knee	Pes anserine	8.55 (3.90) (6.77, 10.33)	4.98 (2.83) (3.69, 6.27)	P < 0.001***
	superolateral to patella	6.77 (1.41) (6.13, 7.41)	4.09 (1.74) (3.29, 4.88)	P < 0.001***
	Inferior posterior	12.21 (8.56) (8.31, 16.10)	12.46 (5.46) (9.97, 14.95)	P < 0.001***
	Superior posterior	13.43 (5.27) (11.03, 15.82)	18.66 (6.15) (5.86, 11.45)	P < 0.001***

***Statistically significant difference to p< 0.001 shaded dark grey /** significant difference to p< 0.01/* *significant difference to p < 0.05.Nb data was not found to be normal on normality testing (Shapiro Wilk tests). Non parametric tests used were the Wilcoxon signed rank test unless stated

PARTICIPANTS - BASELINE 3 - INITIAL AND FINAL 30 MINUTE SUPINE POSITIONS

The initial and final supine postures were also used as a baseline and the mean interface pressures were compared (initial to final) in each pad during the 30 minutes in supine. See table 30 below.

Table 30 Baseline initial supine and final supine postures with mean interface pressure (mmHg) of the participant cohort from each of the pads in both knees

Knee interface Pressure (mmHg)	Site of pad	Initial Supine (mean (SD)) (95%CI)	Final supine (mean (SD)) (95%CI)	P value for significance
Cryocuff	Pes anserine	9.90 (6.29) (6.95, 12.84)	7.61 (5.75) (4.92, 10.30)	0.002**
	Superolateral to patella	21.52 (3.26) (20.00, 23.05))	21.33 (4.41) (19.27, 23.39)	0.751
	Inferior posterior	21.71 (6.49) (18.68, 24.75)	23.61 (5.69) (20.95, 26.28)	0.520
	Superior posterior	22.89 (10.57) (17.94, 27.84)	24.92 (10.36) (20.08, 29.77)	0.092
Robert Jones Bandage knee	Pes anserine	7.22 (3.36) (5.69, 8.75)	4.98 (2.83) (3.69, 6.27)	P<0.001***
	Superolateral to patella	5.55 (1.23) (4.99, 6.11)	4.09 (1.74) (3.29, 4.88)	P<0.01***
	Inferior posterior	12.21 (8.56) (8.31, 16.10)	12.46 (5.46) (9.97, 14.95)	0.768
	Superior posterior	11.65 (4.30) (9.69, 13.61)	18.66 (6.15) (5.86, 11.45)	0.01*

*** Statistically significant difference to $p < 0.001$ shaded dark grey / ** significant difference to $p < 0.01$ /

* significant difference to $p < 0.05$. Nb data was not found to be normal on normality testing (Shapiro Wilk tests). Non parametric tests used were the Wilcoxon signed rank test unless stated * $P < 0.05$ indicates a significant difference

Half of the pads showed non-significant differences in mean interface pressures, indicating that, for the second supine period, the pressure in 4 of the pads did not return to baseline.

This was more marked in the RJB pads anteriorly, with high statistical significance. In the

Cryocuff pads the pes anserine pad and posterior superior pad did not return to baseline.

This indicated that half of the pressures altered between the initial and final supine periods.

Table 31 summarises the reliability analysis of the initial and final supine lying baseline of the participants. The Intraclass correlation was a model 3 mixed model investigating just one rater.

Table 31 Initial and Final supine comparisons statistical tests of reliability

Interface pressure pad Supine subjects	Statistical measures	Cryocuff knee	RJB knee
Pes anserine	ICC (3,2)	0.927	0.894
	ME	2.16	1.36
	CVME	25%	22%
Superolateral to patella	ICC (3,2)	0.806	0.664
	ME	2.15	1.07
	CVME	10%	22%
Inferior posterior	ICC (3,2)	0.716	0.571
	ME	4.36	5.61
	CVME	19%	45%
Superior posterior	ICC (3,2)	0.933	0.588
	ME	3.64	4.05
	CVME	15%	4%

MEASUREMENTS ON PARTICIPANTS - INTERFACE PRESSURE IN PADS

The interface pressures at each pad around each knee in mmHg are shown in table 32 below. The P values are given for the T tests performed between the knees comparing pressures under the Cryocuff and the RJB at each of the 4 pads.

Table 32 Mean knee interface pressures (mmHg) in interface pads at 4 sites around the knee under RJB and Cryocuff

Knee interface Pressure (mmHg) (mean (SD)) (95%CI)	Site of pad	Cryocuff knee (n=21)	Robert Jones Bandage knee (n=21)	P value for significance
Initial Pressure after application (Cryocuff unfilled)	Pes anserine	2.02 (1.50) (1.34, 2.70)	8.55 (3.90) (6.77, 10.33)	P < 0.001***
	superolateral to patella	1.18 (0.78) (0.82, 1.53)	6.77 (1.41) (6.13, 7.41)	P < 0.001***
	Inferior posterior	11.46 (4.97) (9.20, 13.73)	14.50 (6.76) (11.42, 17.58)	0.128
	Superior posterior	4.94 (4.04) (3.10, 6.78)	13.43 (5.27) (11.03, 15.82)	P < 0.001***
Initial Supine	Pes anserine	9.90 (6.29) (6.95, 12.84)	7.22 (3.36) (5.69, 8.75)	0.096
	superolateral to patella	21.52 (3.26) (20.00, 23.05)	5.55 (1.23) (4.99, 6.11)	P < 0.001***
	Inferior posterior	21.71 (6.49) (18.68, 24.75)	12.21 (8.56) (8.31, 16.10)	0.002**
	Superior posterior	22.89 (10.57) (17.94, 27.84)	11.65 (4.30) (9.69, 13.61)	P < 0.001***
Elevation	Pes anserine	6.70 (4.28) (4.70, 8.71)	5.27 (2.38) (4.19, 6.35)	0.195
	superolateral to patella	17.17 (3.76) (15.41, 18.93)	3.90 (1.33) (3.29, 4.51)	P < 0.001***
	Inferior posterior	22.36 (10.16) (17.60, 27.11)	11.77 (8.06) (8.11, 15.45)	P < 0.001***
	Superior posterior	18.66 (9.95) (14.00, 23.31)	4.70 (4.21) (2.79, 6.62)	P < 0.001***
Standing	Pes anserine	6.22 (6.94) (2.97, 9.47)	6.16 (3.36) (4.63, 7.69)	0.871
	superolateral to patella	25.76 (4.40) (23.70, 27.82)	8.53 (3.37) (7.01, 10.04)	P < 0.001***
	Inferior posterior	31.52 (8.55) (27.52, 35.53)	13.49 (10.13) (8.87, 18.10)	P < 0.001***
	Superior posterior	39.38 (16.96) (31.44, 47.32)	15.25 (9.70) (10.83, 19.66)	P < 0.001***
Final supine	Pes anserine	7.61 (5.75) (4.92, 10.30)	4.98 (2.83) (3.69, 6.27)	0.067
	superolateral to patella	21.33 (4.41) (19.27, 23.39)	4.09 (1.74) (3.29, 4.88)	P < 0.001***
	Inferior posterior	23.61 (5.69) (20.95, 26.28)	12.46 (5.46) (9.97, 14.95)	P < 0.001***
	Superior posterior	24.92 (10.36) (20.08, 29.77)	18.66 (6.15) (5.86, 11.45)	P < 0.001***

*** Statistically significant difference to p< 0.001 shaded dark grey/** significant difference to p< 0.01/

* significant difference to p < 0.05. Nb data was not found to be normal on normality testing (Shapiro Wilk tests). Non parametric tests used were the Wilcoxon signed rank test unless stated * P<0.05 indicates a significant difference

COMPARING THE INTERFACE PRESSURES BETWEEN KNEES - RJB AND CRYOCUFF

The levels of interface pressure for each of the pressure pads is given above. There was a highly significant difference between the mean pressures delivered by the Cryocuff versus those delivered by the RJB. This demonstrates that the Cryocuff delivers a different pressure profile to the knee than the RJB. This difference held for most of the parts of the knee, although notably, the pes anserine area did not show difference in pressure between the devices, except for post initial application. The levels of pressure were greater for the Cryocuff at each of the locations in the knee except for the pes anserine. In many postures the mean pressure delivered by the Cryocuff was close to double or beyond this in comparison to the mean pressures delivered by the RJB.

REGIONS OF PRESSURE AROUND THE KNEE

Both the RJB and the Cryocuff delivered greater mean pressures to the posterior aspects of the knee than to the anterior aspects (see Figure 69), although there was more variability with higher standard deviations for the posterior pad pressures, particularly the superior pad. The superior pads (both anterior and posterior) delivered more mean pressure than the inferior pads in standing. In elevation this was reversed, in both the Cryocuff and the RJB, with the greater pressures in the inferior pads than the superior pads. In supine the mean Superior / inferior pressures were equivalent posteriorly. Again there was more variability in the posterior superior pad. Anteriorly, however, in the Cryocuff knee the superolateral to patella pad was always greater than the pes anserine pad in every posture.

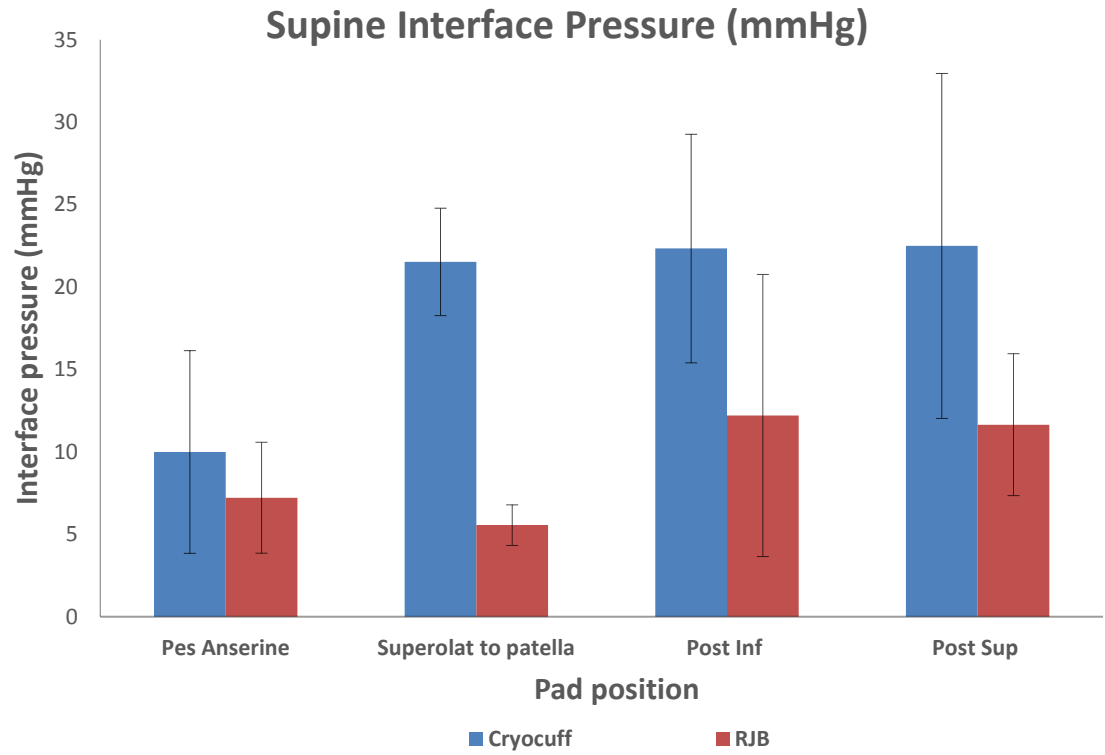


Figure 69 Mean Pad interface pressure (mmHg) on Cryocuff and RJB knee for initial supine posture

(NB for all figures Error bars are 1 Standard deviation above and below the mean)

BETWEEN POSTURES

Within the groups, with both the cryocuff and the RJB, there were significant differences in interface pressures found between the different postures in most of the pads

This is represented in graphs below in figure 70.

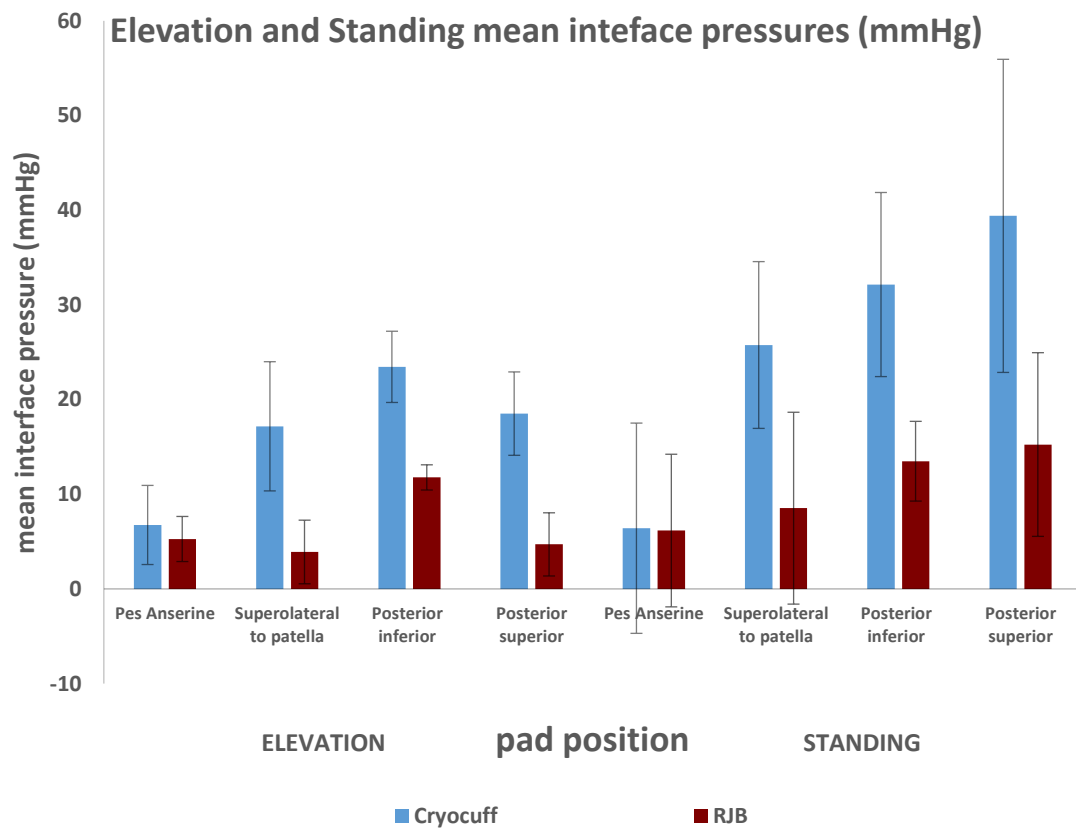


Figure 70 Mean interface pressures (mmHg) in each of the knee pads during Elevation and Standing

VARIABILITY WITHIN EACH POSTURAL STAGE

The pressures did not fully remain static throughout each 30 minute postural stage. They showed slight increases or decreases. There was also some movement from the participants and this affected the pressure trace. Note was made of this variability and both the inclines and the standard deviation of the pressure traces were noted from the capstone software.

The mean standard deviations of each 30 min measurement period are given below in

Figure 71.

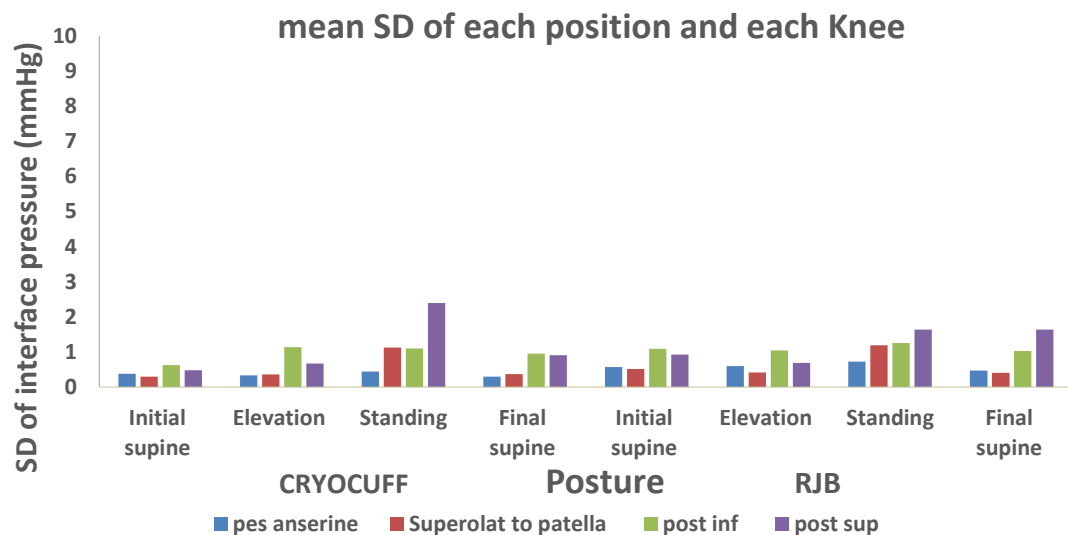


Figure 71 Mean standard deviations of the pressure measurement trace (mmHg) during each 30 min phase of the experiments

This shows that there is a small amount of variability during each phase of the measurement. The standing phases and the posterior pressure pads have the most variability as expected. The standard deviations are mostly less than 1mmHg with most below 0.5mmHg. This, however, is high in comparison with the reliability experiments with the cylinder represented in Figure 72. The mean SDs were generally below 0.25 mmHg.

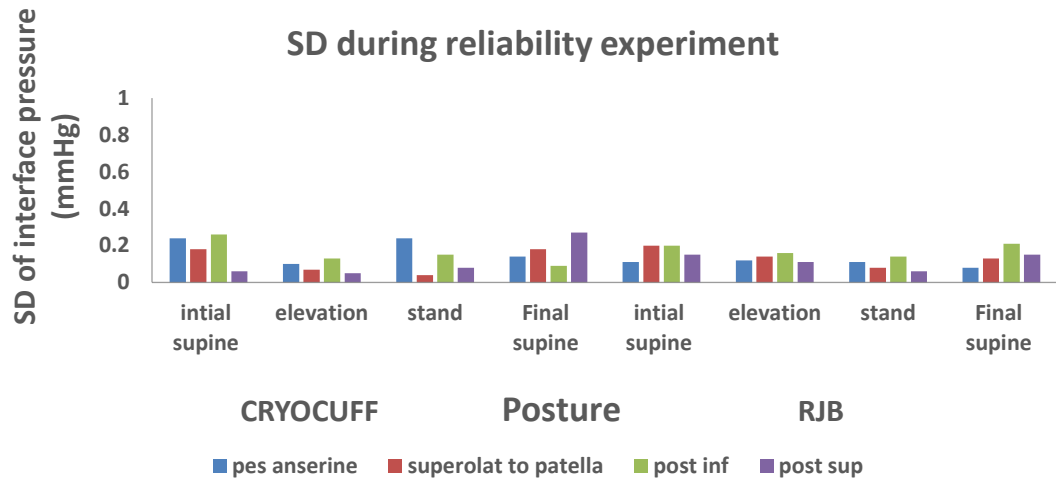


Figure 72 Mean Standard Deviation for pressure pad measures during the reliability experiment on 2 Cylinders for each knee and each 30 minute position (initial supine, elevation, standing, and final supine)

During the experiment, some of the traces showed a gradual increase or decrease. The incline of slope of the increase was measured by the software and this was recorded for each 30 minute phase for each knee the mean slopes are presented in Figure 73. The results are very variable for the Cryocuff, however the RJB seemed to show trends in the same direction for each phase, with increases in pressure during the 30 min standing phase but decreases in pressure in the supine and elevation phases.

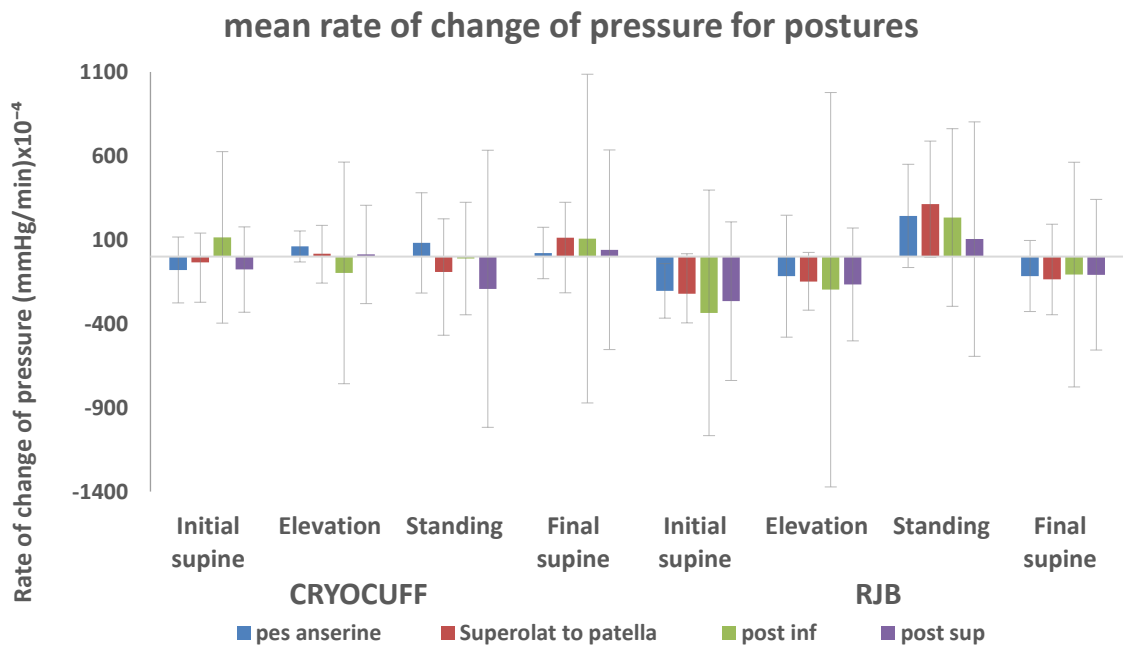


Figure 73 mean rate of change of the pressure trace for each knee and each position during the 30 min measurement of each phase

ELEVATION FIRST OR STANDING FIRST

The order of standing and elevation was block randomised and this gave two further groupings. The participants that stood first, and those who elevated first. The data are displayed split by this grouping for both the RJB and Cryocuff knees in Figures 74 and 75.

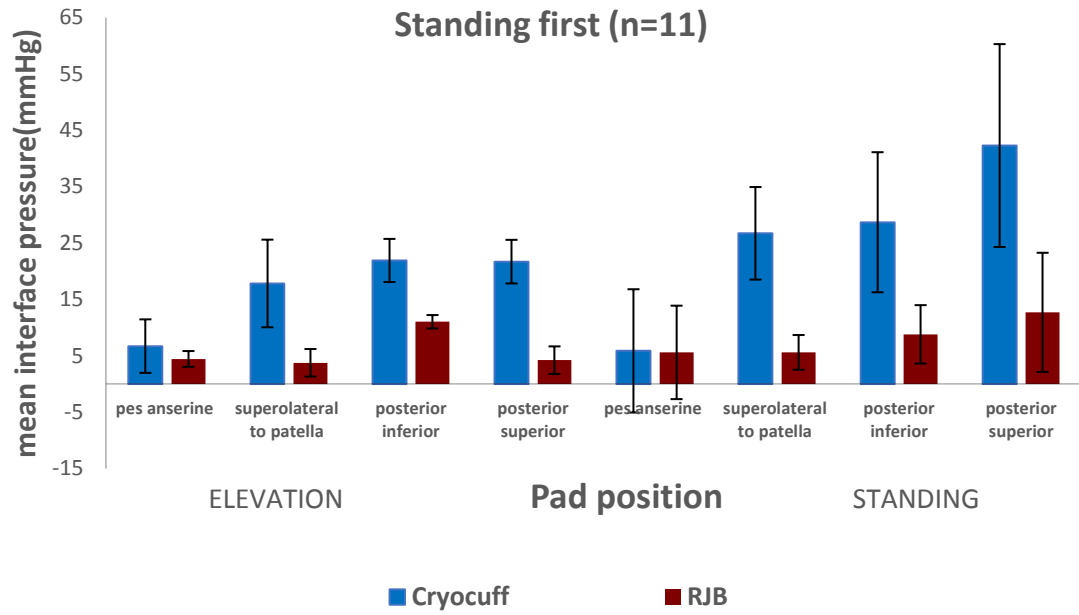


Figure 74 Mean interface pressures (mmHg) in each of the knee pads during Elevation and Standing – Standing first position

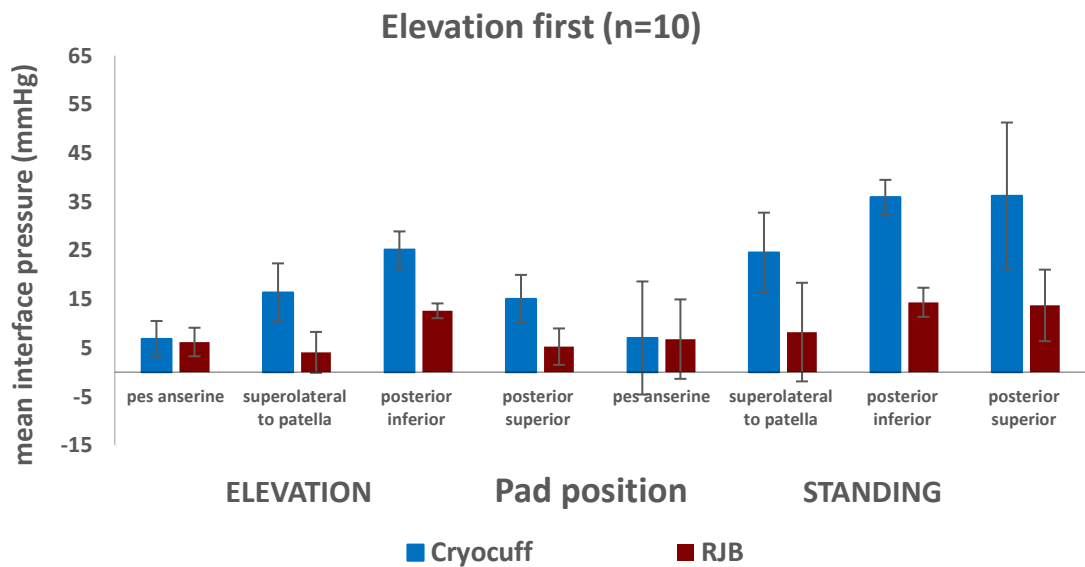


Figure 75 Mean interface pressures (mmHg) in each of the knee pads during Elevation and Standing – Elevation first position

The values were different if Elevation or Standing was performed first. Pressure levels in the subsequent 30 minute period were influenced to either be greater (standing first) or lower (elevation first) . When analysis was performed on the slope of the pressure trace with the cohort of participants was split into those who elevated versus stood first, the same trends were found as for the whole sample, with the Cryocuff more variable than the RJB knee.

TEMPERATURE

Temperature may be a variable that has a relation to the pressure in the pads The temperatures at the knee during the phases of the experiment are shown below for the Cryocuff and RJB knee (see figure 76)

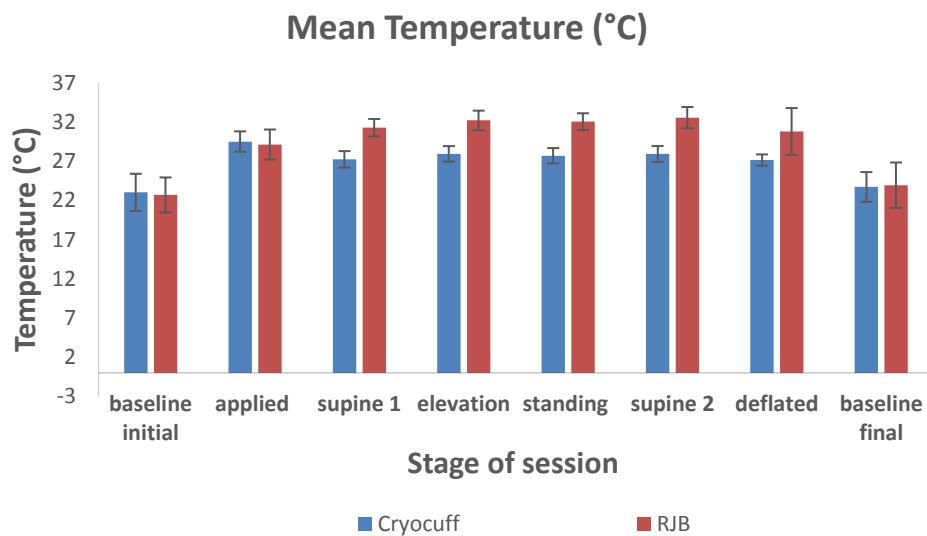


Figure 76 Mean temperature participants for the sessions

DISCUSSION

RELIABILITY AND VALIDITY OF INTERFACE PRESSURE MEASUREMENT

No significant baseline differences were found between the initial and final baseline pressure pad readings, with the pads, resting on the desk. The readings were close to zero, indicating that the device maintains its calibration throughout the 3 hour measurement session. There was very little drift in the pressure reading from the pads. With mean pressure readings being within 0.4mmHg of zero for each quad pressure sensors each of their four channels. The small amounts of drift were not significant and may relate to slight alterations in temperature, as the majority of pads moved in the same direction. Device error, or loss of air seal at the pads, the joins of the tubing and the pads, the 3 way taps, the outflow pipe at the Quad sensor, or within the sensor itself may also account for this. The device specifications report that it is accurate to 1mmHg, however, this study would indicate it is accurate to 0.4mmHg over a 2 hour measurement session. The lack of significant difference between the initial and final measurements meant that the measures are consistent. As a measure of test / retest reliability the pads showed little error. The standard deviation of these readings was small.

Investigating the pressure profiles from the inert objects, there is more discrimination in the pads to slight changes in pressure than to the PicoPress, which was used to test validity this suggests that the Quad pressure sensor and capstone software has good validity in comparison with the PicoPress. The limits of agreement were low and this suggests that the Pasco quad sensor pads give a valid measurement of interface pressure. The PicoPress sensor measurement was equal to the Pasco capstone measure throughout the 3 hour measurement, although it was not able to discriminate between numbers less than whole

mmHg and would round a pressure up or down to a whole number of ml, where the Pasco device allows display of fractions of an mmHg.

When the pads were attached to the cylinder, the standard deviations in the interface pressure measurement traces were low, indicating little variability in measures. The minimal difference in baseline levels indicates that the pads keep their calibration throughout a measurement session. There may be a very minimal drift that could relate to slight changes in temperature.

The cylinders testing also showed difference between the Cryocuff and RJB in the interface pressure profile that they delivered, in all the positions that were tested. The pressure trace did also show some change throughout each of the measurement phases, with this quantified in the assessment of gradient/ or slope of the trace. This occurred more on the RJB side than the Cryocuff side, and this may relate to stretch or accommodation of the Coban and crepe bandage in the RJB, and some stretch of the Cryocuff materials. If accommodation occurs like this in an inanimate object, the levels in a moving patient will be greater, and the RJB will drop its level of compression to the knee, even with little movement. There were some very minor fluctuations in temperature and there was a finding of significant correlation of the slope of the temperature trace with the slope of the pressure trace. This may mean that the pads show very minor pressure alterations in response to temperature. These were typically within 0.5 mmHg with temperature changes within 1 °C. Temperature changes were expected with measurement on participants, due to body heat and the differing insulation properties of the RJB and Cryocuff, but some alterations in the temperature trace were also found in the cylinder measurement sessions, however this may relate to some sensor noise.

In the baseline measures in the participants there was finding of ICC (3,2) lower in the RJB than the Cryocuff side and with the posterior pads lower than anterior. This may indicate,

that for human participants, the supine interface pressure profiles change sufficiently during a session, such that baseline supine measures on human participants are not ideal for test retest reliability with these interface pressure devices. Reliability study with repeat measures on inert objects will be more helpful.

INTERFACE PRESSURE PROFILES

THE CRYOCUFF VERSUS THE ROBERT JONES BANDAGE

When unfilled, the Cryocuff delivered less pressure to the knee than the RJB. The Cryocuff, however, when filled, delivered more mean pressure to the knee than the RJB for all of pad positions around the knee and in all postures tested. This was statistically significant for all the pads except the mean pressure on the pes anserine pad. The mean interface pressures in this pad were lower than the other pads around the knee. The pads with the greatest mean pressure difference between Cryocuff and RJB were the superolateral to the patella pad, and the two posterior pads. This indicates that the Cryocuff delivers more pressure to these area of the knee. But the RJB was also found to deliver greater posterior pressure. The difference in mean interface pressures to these areas when the Cryocuff was inflated were great, and these differences were highly statistically significant. This may mean that the Cryocuff delivers its greatest pressure to the posterior structures of the knee (above and below the knee). This area does not encompass the knee joint capsule and the only pad in this study that was delivering compression to areas of the knee joint capsule may be the superolateral to the patella pad. The posterior straps may also deliver compression to the popliteal artery and veins. There may also be some compression delivered to the Lymphatic veins and nodes posteriorly to the knee.

REGIONAL PRESSURE AROUND THE KNEE

The shape and design of the cryocuff, mean that the water filling component of the cuff is anteriorly around the patella, presumably with the aim of compressing the anterior aspects of the knee. Presumably this aims to focus more compression around the knee capsule anteriorly, which has a larger extent anteriorly, extending superiorly from 10-12 cm above the patella to the inferior portion adjacent the tibial tubercle. The capsule has large extent superolateral and medially also. The Cryocuff fills more on this anterior aspect, and would be expected to deliver more pressure in these areas. This is not demonstrated in this study. The Cryocuff was found to deliver greater pressures posteriorly than anteriorly. This was in spite of the lack of water compartments in the Cryocuff posteriorly and, more likely, represented the tension on the superior and inferior Cryocuff straps. This tension rose as the Cryocuff inflated with water, and reached a mean of 21mmHg in supine , with 30-40 mmHg in standing, but in some participants this went as high as 70-90mmHg . This means that the Cryocuff exerts a circumferential force on the leg, and this may represent a tourniquet effect. This was found to be greater in the proximal strap than the distal strap, having implications for arterial flow and venous return. This tourniquet effect is applied above and below the knee and this may be a mechanism that will “trap” fluid in the knee region (subcutaneous/ vascular and articular). These pressure levels have been found to be sufficient for vascular compromise or occlusion in some people may be sufficient for vascular compromise and occlusion. Interestingly the posterior pressure was greater in both the RJB and in the Cryocuff. This raises the possibility that both of these devices may compromise venous return, trap fluid, cause more distal filtration and increase swelling. This may be one explanation for the lack of finding of a difference between RJB and the Cryocuff in knee volume change in the experiment reported in chapter 3. As well as their possible tourniquet effects, the greater posterior pressure values delivered by the RJB and Cryocuff

have implications for compression of the popliteal artery and veins. The inferior strap ran very close to the point where the popliteal artery enters the soleus, and this has been a site implicated for compromise or occlusion of the popliteal artery flow, even in a proportion of the normal population³⁷⁰.

The cylinder session showed difference in comparison with the measures on participants' knees. This was expected due to the irregular shape of the knee, and the patella anteriorly and the design of the Cryocuff to fit around the irregular shape of the knee. The pads anteriorly under the Cryocuff measured high pressure levels under the superolateral to the patella area, however much lower interface pressures delivered to the pes anserine area. In ACLR with a hamstring graft, this area of the knee inflames and swells due to the harvest site wounds, the tibial tunnel exit and the fixation put into bone in this area. Reducing pain and swelling in this area would be desirable. It would be anticipated from the design of the Cryocuff, that it would be ideal to apply cooling and compression to this area particularly. This study however indicates, that in all postural positions this area of the knee receives less compression from the Cryocuff than other parts of the knee posteriorly or superolaterally to the patella. This may be a further reason for the lack of effect on knee volume (beyond that of RBJ) shown by the Cryocuff in chapter 3.

CHANGES WITH POSTURE

STANDING AND ELEVATION

Mean interface pressures were different in different postures. This applied for both the Cryocuff and the RJB. ANOVA testing found significant differences both between groups and within groups, indicating that the mean interface pressure levels were significantly different between postures.

Taking all pad mean interface pressures together, the greatest interface pressures were found in standing, for both the RJB and the Cryocuff. Taking each pad separately the interface pressure did not alter greatly in the pes anserine area between different postures. The greatest changes were seen in the posterior pads of the Cryocuff, then the RJB with standing, when the interface pressures in these areas elevated greatly, particularly under the Cryocuff and the superior strap greater than that inferiorly. This pressure increase was large and under the superior strap the mean interface pressure was close to double that of the pressure in supine.

In elevation there was a drop in mean pressure, however, this occurred to a greater extent in the RJB knee. The Cryocuff did not drop mean pressure in elevation, particularly maintaining the mean interface pressure in the posterior inferior pad. This may have been a function of the pressure exerted by the cooler container of water at the consistent 14cm height above the knee (ie there was a consistent 14cmH₂O pressure exerted by the water remaining in the cooler container). This may have been the reason for the lack of attenuation of the mean interface pressure seen in elevation in the Cryocuff versus the attenuation seen in the RJB on elevation. This shows that the Cryocuff still exerts a strong interface pressure to both the anterior and posterior aspects of the knee, even in elevation. There may be greater venous or arterial compromise in elevation if these levels of posterior pressure are applied by the Cryocuff straps in elevation. The straps apply circumferential pressure and this also raises the possibility of a greater tourniquet effect applied by the Cryocuff in elevation, than in supine. This may also have been a reason for the findings in chapter 3 of a lack of effect of the Cryocuff. This may also have contributed to the finding in Chapter 4 of a correlation between the daily average elevation time, and an increase in knee volume difference.

CONSIDERATIONS, LIMITATIONS, AND IDEAS FOR FURTHER STUDY

There are several limitations to the study with implications for its findings. In this study the Cryocuff was used with the knee cuff connected to the cooler container. This meant that there was always pressure exerted from a column of fluid above the knee. The Cryocuff may exert different pressures with the cuff disconnected from the cooler. The instruction manual suggests this as a method of use, with reconnection only to refill the cuff with cold water. In this study the cuff was not investigated with this method. A consistent height of the cooler was maintained to try to keep the water pressure within the cuff at as constant a level as possible, with a consistent column of water at a consistent height above the cuff in all postures. It is not known what pressure profile exists under the Cryocuff if the container disconnected. It would be envisaged that the pressures may also differ in the cuff, depending on how high the cooler is above the cuff at the time of filling. A higher cooler means a greater filling pressure (cmH₂O) and hence a greater volume of fluid filling up the cuff with a greater subsequent pressure applied by the Cryocuff once disconnected. This however has not been tested, and warrants further investigation.

The manufactures of the Cryocuff give no recommendation of the optimum height of the cooler. But they caution against going too high and they give a maximum height of 38cm (15inches) beyond which to avoid. The container needs to be above the cuff to allow filling. In this study 14cm was chosen as a level between these two heights. The amount of pressure exerted by the filled Cryocuff, however, was still significant at this height of cooler and may be too great. It may be that a very low height is sufficient to fill the cuff to provide an appropriate pressure. It should be noted however, that it is not known what the interface pressure effects are on the knee of heights above or below this, while a greater height is expected to give a greater interface pressure, this may not be the case.

Often the Cryocuff is used in a resting position with the leg resting flat and the calf (and the posterior strap) resting on a surface. This would further increase the posterior strap pressure due to the pressure applied by the weight of the leg. In this study, this confounding addition to the interface pressure under posterior strap, was eliminated by resting the leg on a towel with heels on small hand towels to ensure the calf did not rest on the surface of the plinth. It was difficult with several participants who had greater knee hyperextension. The towel under the thighs may also have had an influence lower down the leg, however this was standardised for all participants and equal between legs. In elevation and standing the towel under the thigh was not required and the calf was clear of any external pressure from the resting position.

The tension put on the bandage and Cryocuff straps during application was not measured. It may be possible that this differed between participants. Efforts were made, however, to standardise this, with the same researcher applying all the devices (BP). No tension or stretch was put on the Cryocuff straps and they were attached via Velcro lightly. The RJB was applied rolling the Coban and bandage on, rather than pulling against the skin, to ensure no stretch of the Coban or Crepe. This standardised the application but may have allowed some accommodation of the bandage in the different positions as the interface pressure under the RJB was found to decline in certain positions

There was a significant correlation between the rate of change in interface pressure and the rate of change of temperature. This means that the pressure in the pads could have been influenced by alterations in temperature. Temperature will have an effect on the volume of gas contained within the pad, as well as the elasticity of the plastic material in the pad and tubing. The Cryocuff and RJB also have different insulating properties and this meant that there were temperature differences between them. In human knees the body warmth tends to warm the air within the Coban and crepe bandage of the RJB and it warms faster.

Whereas the Cryocuff had a period of cooling after application before starting to warm up. This may have accounted for some of the pressure difference observed in this study between the RJB and the Cryocuff. The participants may also have had different core temperature and the knee temperature response may have been different between them.

This study used the Cryocuff with room temperature water and ice was not used in the cooler. It is not known if the interface pressures will differ when the Cryocuff is used at low temperature. This would also be a recommended future piece of research work.

There are many devices that apply intermittent compression, which have not been investigated in this work. These devices have become used more widely over the last several years and future work would ideally investigate the interface pressures under these devices during their treatment. It would be useful to have an understanding of how intermittent compression affects the knee tissues differently from static compression, and the differing arterial, venous and lymphatic responses.

Some sources of error relate to our participants. Firstly it was very difficult for them to remain fully still for the 30minute measurement period of each position (3hr total). It was not possible for them to remain motionless in standing for 30minutes and there was some muscle activity in the calf, quadriceps and hamstrings that affected the pressure traces (see Figure 57). This can be seen in the standard deviations of the interface pressure which are greater for each pad in standing (see figure 87)and they are much greater than the standard deviations found when using the cylinders (see Figure 88). This adds error to the pressure trace readings.

CONCLUSIONS

Both the Cryocuff and RJB delivered pressure to the aspects of the knee measured in this study and this is the first study to outline the mean levels of interface pressure (pressure profile) around the knee delivered by these devices.

Mean interface pressures in the RJB range from approximately 5mmHg to 19mmHg (pes anserine and posterior thigh) in supine and for the Cryocuff they range from approximately 6mmHg to 40mmHg (pes anserine and posterior thigh) in standing. In this study, the Cryocuff was found to deliver significantly more interface pressure in most postures and areas of the knee than the RJB.

The RJB showed some loss of pressure with time, even on an inert object like a cylinder, and the Coban and crepe bandage material may accommodate and stretch quickly, with a subsequent loss of pressure. There may be fluid exchange factors, however, such as capillary filtration in the limb that could account for this change in pressure.

Investigating the pressure profile of the knee, this study found that both the RJB and Cryocuff deliver greater pressures to the posterior aspects of the knee than anteriorly. This has implication for vascularity running in the posterior aspect of the knee.

Interface pressures were greater in standing than in elevation, however the posterior and proximal pressures delivered by the Cryocuff were more maintained in elevation than those of the RJB.

For the Cryocuff, the pes anserine area had the lowest mean interface pressure delivered, in spite of the Cryocuff having water filling sections in this area. The posterior superior aspect of the knee had the greatest mean interface pressure delivered, in spite of the Cryocuff having no water chambers in this area, and only an elastic strap.

Mean interface pressures between the knee and the Cryocuff, when it is inflated, were found to be greater proximally than distally, raising the possibility that the Cryocuff may have a tourniquet-like effect on the leg.

These results raise questions about the mechanism of action of these devices and the possibility of detrimental effects, and further investigation of interface pressures would be warranted, to provide recommendation of optimum and hazard-free use.

The Pasco quad sensor was found to be effective and efficient for measuring interface pressure underneath the RJB and Cryocuff in the knee. It was found to have good reliability and validity in comparison to another commercially available interface pressure measurement device. The Pasco quad sensor proved easy to use and sensitive measure of interface pressure but there are sources of error and these should be controlled as much as possible. The measurement of interface pressure is sensitive to temperature, and consideration and monitoring of temperature is important when evaluating interface pressures.

The above findings may give explanation for why the Cryocuff device was not found to be effective to lessen swelling in our study reported in chapter 3 and why the Cryocuff has not been found to be effective to reduce knee swelling in other studies after ACLR.

CHAPTER 6 GENERAL SUMMARY

GENERAL DISCUSSION – THESIS

MAIN FINDINGS AND CONTRIBUTION OF THIS BODY OF WORK

The main findings of this body of work are summarised below: -

Chapter 2: The perometer is an effective and reliable tool for measuring knee volume.

Chapter 3: There was no difference between a regimen of elevation, cooling and compression applied daily for two weeks post ACLR via a Cryocuff compared with standard treatment for swelling – the RJB applied for 48 hours post ACLR.

Chapter 4: The pre to postoperatively change in knee volume correlates with, knee joint AP laxity and loss of extension range of motion preoperatively, diastolic blood pressure perioperatively and early dosing with Diclofenac postoperatively. This change in knee volume did not correlate with outcome.

Chapter 5: There is a greater knee interface pressure with a Cryocuff than RJB but the pattern and distribution of pressure is potentially detrimental to the reduction of knee joint swelling

These findings will be discussed in more detail and their implications for practice and further research considered in order to place the work within a clinical reasoning framework.

CHAPTER 2

The perometer is an effective and reliable tool for measuring knee volume

This is the first study to test the use and reliability of the perometer in a clinical orthopaedic population after knee and ACLR surgery. Because swelling (including haemarthrosis and effusion) after ACLR is enclosed in the irregularly shaped knee capsule it has proved difficult to find a convenient and accurate measure of knee capsular volume and exact fluid content within it. This difficulty is further compounded by the fact that this is not the only region that swells post ACLR, swelling also occurs at both the Pes anserine graft harvest site and the site of tibial tunnel exit and fixation. Fluid often collects subcutaneously affecting overall knee joint volume. Prior to this study, the methods for measurement of knee swelling were considered inadequate which may explain why many studies did not attempt measure knee swelling. Where knee swelling was measured, simple methods were employed with inherent imprecision. Measurement of volume has typically been measured across the whole limb and measurement normally consists of a series of circumferential tape measurements, mathematically extrapolated to a whole segment volume. Whilst this is a rapid and convenient clinical measure it is inaccurate. Measuring swelling across the whole knee was desirable and a measure was required that was able to assess all the regions where swelling is likely to occur. Knee volume has been measured effectively with the horizontal perometer 350s and gives valid reliable measure of knee volume. The knee volume measure of the perometer, therefore, is currently the most ideal method for measurement of knee swelling. This work confirmed its reliability pre and post ACLR and it is suggested should be considered the gold standard method of measuring swelling currently. It is however acknowledge that the use of 'high-tech' measurement tools such as the perometer is seriously limited for practical reasons (such as cost, availability and time) in clinical settings. Here we were able to show that the brush or stroke test may be a rapid easy complimentary clinical test to use to assess for the presence

of an Intra-articular effusion, as it correlates well to the perometer result but the test is limited to the extent to which it can differentiate between anything other than small or large volumes.

CHAPTER 3

There was no difference between a regimen of elevation, cooling and compression applied daily for two weeks post ACLR via a Cryocuff compared with standard treatment for swelling – the RJB applied for 48 hours post ACLR

The results presented in chapter 3 are consistent with the limited number of studies that have assessed the treatment of swelling post ACLR that directed and continued (2weeks in this study) treatment of swelling has no significant effect and fails to demonstrate improved outcomes compared to treatment as usual. This raises the important question of whether it should be considered necessary to treat swelling at all?

Swelling is considered maladaptive and undesirable by the majority of clinicians but we suggest that this view is a best limited and that swelling should be considered adaptive and helpful in ACLR until proven otherwise.

The failure to observe any differences between Cryocuff versus the standard care group in our study suggests either that the Cryocuff elevation (RICE) routine is ineffective to reduce swelling, or that the RJB alone has an effect on swelling which is equal to the Cryocuff. Unfortunately the study design did not allow differentiation of effects of between the Cryocuff and RJB. In retrospect it would have been advantageous to seek ethics for and include a control group that received no compression or elevation treatment at all and this would form the basis of a future study.

The risk exists of type 2 error by falsely accepting the Null Hypothesis of no difference between the groups in this study sample. Every effort has been made in this study to control confounding and extraneous variables to avoid this error but this is a risk in any RCT and particularly in studies investigating swelling. This is due to difficulties such as:-

- 1/ measuring swelling, and detecting the levels of change that can be clinically significant,
- 2/ Physiological systems for fluid exchange, blood flow and inflammation (which all influence swelling) are controlled by multiple variables and it is impossible to control all of these, particularly in a clinical randomised controlled trial. It is notoriously difficult to control for confounding physiological effects in clinical RCTs.
- 3/ Interventions for control of swelling encompass multiple effects on these physiological systems and it is impossible to separate the effects completely in RCT studies in humans.

For these reasons there will always be risk of type 2 error in this type of RCT.

CHAPTER 4

The pre to postoperative change in knee volume correlates with knee joint AP laxity and loss of extension range of motion - preoperatively, blood pressure perioperatively and early dosing with diclofenac postoperatively.

This work was also the first to attempt to establish the pre, peri or postoperative factors that correlate with swelling post ACLR. Importantly I found that knee swelling did not correlate with “gold standard” outcomes including the self-reported outcome measures (IKDC form, Lysholm).

Postoperative BP measured in the recovery room was found to correlate significantly with the change in knee volume in the first 2 weeks. It has been suggested that perioperative factors that affect fluid exchange such as BP or perioperative intravenous fluid delivery are

associated with change in knee volume, these have not previously been investigated in ACLR and warrant investigation in future studies investigating swelling. There may be questions around monitoring BP and fluid giving perioperatively to not just affect recovery from the anaesthetic but to assess their influence on the capillary fluid exchange in the knee.

Knee joint pre-operative AP laxity from KT1000 measurement, was also correlated significantly with the change in knee volume after ACLR in the first 2 weeks. The exact reason for this remains unclear, it may relate to either the extent of the original injury and subsequent tissue loading and/or to an increase in tissue extensibility. The latter is supported to some degree by the finding that the correlation was true for both knees both affected and unaffected. Further investigation would be warranted of the relationship between knee laxity and swelling in the knee. It may be worthwhile in future studies investigating the reasons for this correlation and the possible mechanisms behind it.

Preoperative loss of knee range of movement in Extension was found to correlate with the change in knee volume pre to 2 weeks postoperatively. Regaining full knee hyperextension is a landmark goal preoperatively. The knee has a screwing home mechanism that will not function effectively without full hyperextension. The reason for the correlation with volume change is not fully known but may relate to capsule volume alteration with stiffness in extension, or possibly forcible restoration of this range of movement during the surgery. The implication of this finding further strengthens the importance of regaining full knee hyperextension preoperatively.

We also assessed for the impact of the use of medication including analgesics and NSAIDs. The only compound that demonstrated a positive correlation with alterations in knee volume was the delivery of early post-operative Diclofenac the exact mechanism for this remains unclear but is likely to involve effects on inflammation as there was no correlation with post-operative pain scores. Further work would warrant investigating the influence of anti-

inflammatory medication on swelling although this again may represent an unnecessary intervention if, as suggested, swelling should be considered adaptive.

Several of our findings are counter intuitive and oppose commonly held clinical assumptions. The presence of swelling preoperatively did not correlate with worse swelling post-surgery. Likewise a more involved and extensive surgical procedure surgery or concurrent pathology were not found to relate to the change in affected knee volume pre to postoperatively in this study. The finding that there was no relationship between pain and swelling questions the traditional perspective that increased pressure from swelling is a significant cause of nociception.

The home diary data indicate that cooling time did not relate to a reduction in volume, indicating that the length of cooling time did not have any relationship to swelling. Daily elevation time, however, did show a trend toward correlation, pointing to a possible “rebound effect”, but there may also be an explanation related to venous occlusion in the limb in elevation and subsequent increase in limb volume as more distal capillary filtration occurs.

Furthermore we did not find correlation of change in knee volume with the daily amount of standing and walking, suggesting that walking and standing in the initial 2 weeks does not seem to be any effect on knee swelling and should perhaps be encouraged to its beneficial effects on other physiological systems. Early mobilisation and optimising loading in the early stages have been themes in rehabilitation of soft tissue injury³⁸⁵.

This work did not investigate the effect of loading or movement on swelling post ACLR and several components of the RICE regimen relate to protection and rest. It must be noted that the home diaries related to the self-reported compliance and adherence of our patients and while they adhered to the regimen this was not monitored by an in-hospital stay and caution is advised when evaluating the strength these findings.

CHAPTER 5

There is a greater knee interface pressure with a Cryocuff than RJB but the pattern and distribution of pressure is potentially detrimental to the reduction of knee joint swelling.

It is suggested by the manufacturer that the Cryocuff applies cooling and compression to a knee. The level of cooling it supplies to the interface with the skin and within the joint itself has been investigated but the level of compression the Cryocuff actually delivers to the skin interface and within the joint had not been measured to the best of our knowledge. It was unclear how this pressure is distributed regionally around the knee. This was the first investigation, to our knowledge to outline the knee interface pressure profiles that are produced by the Cryocuff alone and that compared these pressures with those produced by a RJB.

My results suggest that the interface pressure profile delivered by the Cryocuff and the RJB was distributed in a pattern different to that suggested by their proponents. Some of the observed pressures raise the possibility of a selective 'tourniquet like' effect from the Cryocuff. There appears to be a major compression effect to the posterior aspect of the knee complex. The potential ramifications of these pressures are deleterious in terms of blood flow and venous and lymphatic drainage as the major arterial, venous and lymph vessels that perfuse and drain the knee are located on its posterior aspect. In addition the pressure differential across the knee proximal to distal was also revealing. Some areas e.g. pes anserine area demonstrated a low interface pressure, compared to suprapatellar measures, which suggests that there is a greater pressure proximal than distal. The likely effect of which, is to impede/constrain venous return and lymphatic drainage. By comparison the RJB delivered less interface pressure to the knee than the Cryocuff but it in a similar distribution.

These results raise questions about the mechanism of action of these devices and the possibility of detrimental effects on vascular, venous and lymphatic flow dynamics. I propose that these effects may also explain either fully or in-part, the results obtained in Chapter 2 of this study and in other studies which measured swelling post ACLR.

This research raises the possibility that there are inherent design problems with the Cryocuff (and possibly other cold compressive devices) that compromise their effectiveness to achieve their intended effects. Further work is warranted, investigating in more detail the direct compressive effects, their mechanism of action on vasculature and fluid exchange, and the possibility that the Cryocuff and possibly other cold compression devices, have detrimental effects on fluid dynamics.

CLINICAL IMPLICATIONS

On the back of this work there may be some clinical applications with respect to measuring swelling and the use of the Cryocuff. The Perometer would seem a useful tool for follow up clinical research studies after ACLR or other knee surgery but there may be a little more reliability with the horizontal rather than the vertical perometer. It is also important to note the caveats mentioned above about the use of 'high-tech' measures in the clinic.

This study suggests that the Cryocuff is not a useful modality to reduce swelling in the knee after ACLR. The efficacy and cost effectiveness of the Cryocuff, therefore should be questioned if it is not effective beyond a much cheaper treatment. The Cryocuff is considerably more expensive than a RJB. Considering its use globally and the significant number of orthopaedic units that use these devices, a considerable cost to the NHS and other health systems could be avoided for a potentially ineffective treatment (although it should be pointed out that the Cryocuff has been shown to have an effect on pain, and this may still justify its use)

The main question remains should we try and effect swelling, as there are no differences in outcomes between the groups in these studies and the proposition that it is in the majority of cases adaptive. Chapter 3 has suggested potential correlates to increased swelling following ACLR and further studies are required to investigate the potential for the development of a screening tool that would potentially identify those at risk of excessive swelling and to investigate volume change that may be consider maladaptive.

If and when necessary it may be possible to treat or prevent swelling by focussing on cardiovascular factors. There may be the potential to impact on swelling by controlling blood pressure in the immediate postoperative period particularly. Caution should be exercised by the anaesthetist with respect to the volume of IV fluid given. The ACLR surgery is relatively short and these volumes of fluid must be appropriate for this short period. The rationales behind IV giving of fluid should be re-evaluated for shorter (and possibly also longer) orthopaedic operations such as ACLR.

FUTURE WORK

The perometer opens a validated reliable and rapid method for more accurately and precisely assessing knee volume in clinical orthopaedic situations. It could be a useful tool to evaluate knee swelling in both acute situations post trauma and surgery, particularly other types of knee surgery, but also in pathologies such as inflammatory arthropathies and osteoarthritis. It would be worthwhile assessing the limb volume response after ACLR to different postures or exercise.

The perometer opens the possibility of more accurately assessing the natural history of knee swelling after injury or surgery to understand when (or if) it requires treatment. The effectiveness and optimisation of interventions for swelling may also be investigated more easily with a more reliable measurement method.

Further research is needed to investigate the interface pressure internally within the joint itself during application of the Cryocuff. This work investigated normal healthy population but future work would ideally investigate interface pressure in a clinical population post ACLR, as well as utilising the Cryocuff at its normal cold temperature ranges. Considering the questions raised in this work, it is important to investigate any possible inherent design aspects of these devices that could be detrimental to fluid exchange and to provide best recommendations for its optimum safe and effective use. This may also be warranted for other cold compression type devices that are growing in popularity and use, including those that provide intermittent compression. A research approach is suggested that assesses both clinical and physiological variables, particularly those associated with vascular pressures, fluid exchange dynamics, perioperative blood pressure and IV fluid giving.

Swelling in ACLR is part of an inflammatory response and it is acknowledged that this work has not focused on the vascular features of the inflammatory response. It is therefore essential that future work would also focus on the vascular components of the inflammatory response.

This work has specifically investigated the knee in ACLR and swelling, however many of the reviews on RICE report the existence of larger numbers of studies investigating cooling and ice post injury or surgery than on compression and elevation. There are also a larger number of primary research studies focused on pain than on swelling. Further studies are required on the elevation and compression components of the RICE regimen to enable future recommendations on optimising regimens of elevation and compression. There has been a move toward optimising movement and loading after injury (POLICE). Future studies should also investigate the effects of optimising movement on fluid exchange. It would be interesting in the future if studies discover that optimising movement also optimises fluid exchange

CONCLUSION

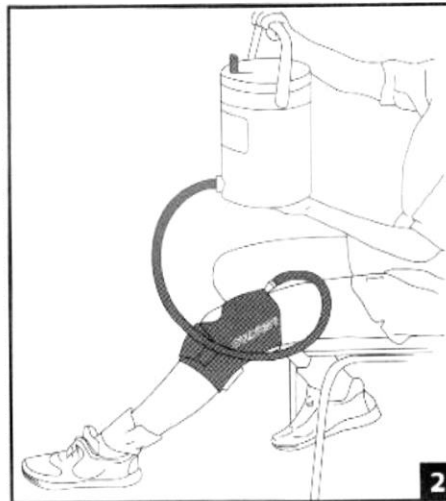
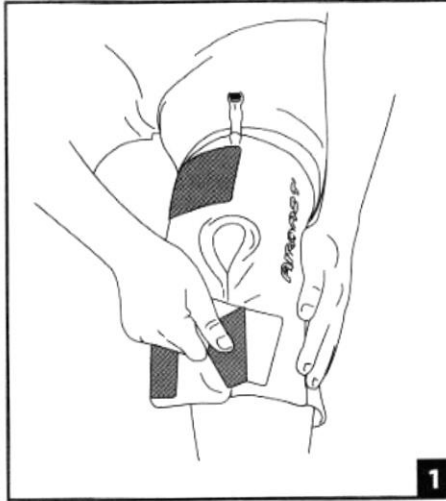
This thesis brings some questions regarding current practice regarding knee swelling in ACLR. This has come out of observing a career's worth of patients go through this procedure and rehabilitation, and undergoing knee surgery, with my own experience of knee swelling!

The hope of this research is that clinicians will take in its findings and it will help them reevaluate their practice, make them more effective for their patients and have the curiosity to ask the question?

Should swelling be treated or left alone?

APPENDICES

APPENDIX 1 - CRYOCUFF OPERATING INSTRUCTIONS AND CE COMPLIANCE STATEMENTS



ENGLISH

BEFORE USING THE DEVICE, PLEASE READ THE FOLLOWING INSTRUCTIONS COMPLETELY AND CAREFULLY. CORRECT APPLICATION IS VITAL TO THE PROPER FUNCTIONING OF THE DEVICE.

INTENDED USE/INDICATIONS:

The Aircast Cryo/Cuff combines focal compression with cold to provide optimal control of swelling, edema, hematoma, hemarthrosis, and pain. The length of use and frequency of use of the Cryo/Cuff are determined by the healthcare professional depending on individual patient's needs.

CONTRAINDICATIONS:

Cryotherapy should not be used on persons with Raynaud's or other vasospastic diseases, cold hypersensitivity, decreased skin sensitivity, or compromised local circulation.

WARNINGS AND PRECAUTIONS:

- Do not use an elastic wrap in conjunction with the Cryo/Cuff.
- Dressings used under the Cryo/Cuff should be applied lightly.
- Patient's skin should be observed frequently due to individual sensitivity and susceptibility to cold.
- When filling the Cryo/Cuff, do not raise the cooler higher than 15 inches (38 cm) above the cuff to avoid excessive pressure.
- Reduce pressure with any sense of discomfort, numbness or tingling of the limb.
- The Cryo/Cuff is designed for single patient use only and may be used on the same patient for the length of treatment. The device should be cleaned if it is used on the same patient for an extended period of time (see cleaning instructions).

APPLICATION INFORMATION:

- 1) Prepare cooler: Connect blue tube to cooler. Add water to line inside cooler, then add ice. For 6-8 hour treatment add ice to top of cooler. Lay the insulation disk on top of ice. Attach cooler lid snugly. Allow 5 minutes with occasional shaking to chill water.
- 2) Apply the empty cuff: Lay cuff on front of knee and secure the top strap, snug but not tight. Adjust front opening so cuff conforms to slightly flexed knee – knee cap should appear through opening. Secure bottom strap loosely – do not stretch the elastic. During continuous passive motion therapy (CPM) the bottom strap should be very loose.
- 3) Fill Cuff: Connect blue tube to cuff. Open air vent on cooler lid and raise cooler no more than 15 inches (38 cm) above the cuff. (If the cooler is raised more than 15 inches (38 cm), the cuff will increase in volume and in weight). Hold raised cooler for about 30 seconds while cuff fills. Close air vent on cooler lid. If not using an Aircast Autochill System, the cooler can now be disconnected from cuff by pressing the metal tab on the quick-disconnect while the cooler is raised.
- 4) Recharge water: At first, recharge the water in the cuff after 15-30 minutes, then once an hour or as needed. Reconnect the blue tube to cuff, lower the cooler below cuff, and the warmed water will drain from the cuff into the cooler. Allow a minute or two for the water to mix with the ice and recharge, then raise the cooler and repeat the filling process.

The Autochill System can be used with the Cryo/Cuff to automatically recycle the water from cooler to cuff (contact Aircast customer service for more information).

CLEANING INSTRUCTIONS:

After use completely drain water from cuff, tube, and cooler. (To drain tube, elevate tube while pressing tip of quick-disconnect). Store cooler with top off to allow drying. Periodically clean cuff, tube, and cooler using a few ounces of liquid soap added to hot water in cooler. Recycle soap/water mixture between cooler/cuff a few times, then repeat with warm water only. Rinse completely.

WARRANTY: DJO, LLC will repair or replace all or part of the unit and its accessories for material or workmanship defects for a period of six months from the date of sale.

RX ONLY

LATEX FREE

AIRCRAFT[®]

Cryo/Cuff[®]

for cold and compression



⚠ Before using, read all instructions supplied with cooler, cuff and Auto Chill pump.

Cautions:

1. Federal Law (U.S.A.) restricts this device to sale by or on the order of a licensed health care practitioner.
2. A licensed health care practitioner must select the appropriate treatment protocol to meet the patient's individualized needs. Users must follow these treatment guidelines.
3. Users who experience continued discomfort, redness of the skin, tingling, or numbness should discontinue use and contact their health care professional immediately. Any cold products may cause frostbite if not properly used.

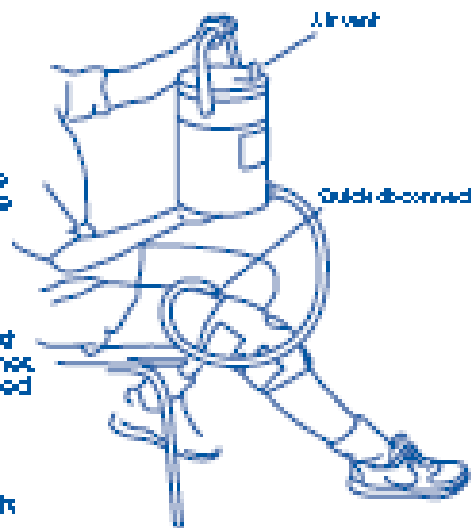


Illustration © AirCrest Cryo/Cuff

Fill cooler. Apply and fill cuff:

- Connect tube to empty cooler.
- Fill cooler with water to line, then add ice.
- Apply empty cuff per instruction sheet.
- Connect tube to cuff.
- Open cooler air vent
- Raise cooler above cuff until cuff is full. Do not raise higher than 15 inches above cuff.
- Close cooler air vent
- Disconnect tube from cuff by pressing quick-disconnect on tube.

Rechill water when cuff becomes warm:

- Reconnect tube to cuff.
- Open cooler air vent
- Lower cooler below cuff and drain cuff.
- After water rechills, raise cooler and refill cuff.

When using the AutoChill[®] system:

- After initial set-up, keep air vent closed and cooler level with cuff.

2 of 2 pages

Certificate of Registration



This is to certify that the quality management system of

DJO, LLC

Main Site: 1430 Decision Street Vista, California, 92081, USA

Additional sites

8151 Scott Street, Vista, CA 92081

dj Orthopedics de México, S.A. de C.V.: Carretera Libre Tijuana Tecate #202 30 Submetropoli El Florido, Tijuana B.C. México 22244

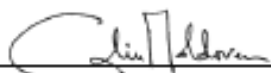
has been assessed and registered by Intertek, a CMD CAS recognized registrar, as conforming to the requirements of

ISO 13485:2003

The quality management system is applicable to

Main: Design, Manufacture and Distribution of Rigid and Soft Orthopedic Braces, Cold Therapy Systems, Bone Growth Stimulators (Active Device), CQM (Custom Contour Measurement Instrument), Cuffs, Bands, Wraps, Intermittent Pneumatic Compression Medical Devices, Exosuits, Ultrasonic Diathermy Units, Neuromuscular Stimulator and Electrodes, Powered Traction Units, Iontophoresis, Cutaneous Electrodes, Lead Wires/Cables, Ultrasonic Applicators, Electromyography, Continuous Passive Motion, Shortwave Diathermy, Paraffin Bath, Cryotherapy Compression, Fluidotherapy (Dry Heat Whirlpool), Powered Heating Pads, and Therapeutic Laser and applicators, Radial Pressure Wave Generator and Applicators, and Heating Units.
Scott Street: Manufacture and Distribution of Rigid Orthopedic Braces, Bone Growth Stimulators (Active Device), Intermittent Pneumatic Compression Medical Devices, Neuromuscular Stimulator, Ultrasonic Applicators and Manufacture, Distribution and Service of Therapeutic Laser applications.
Tijuana: Manufacture and Distribution of Rigid and Soft Orthopedic Braces, Cold Therapy Systems, CQM (Custom Contour Measurement Instrument), Cuffs, Bands, Wraps, Intermittent Pneumatic Compression Medical Devices, Exosuits, Ultrasonic Diathermy Units, Neuromuscular Stimulator and Electrodes, Powered Traction Units, Iontophoresis, Cutaneous Electrodes, Lead Wires/Cables, Ultrasonic Applicator, Electromyography, Continuous Passive Motion, Shortwave Diathermy, Paraffin Bath, Cryotherapy Compression, Fluidotherapy (Dry Heat Whirlpool), Powered Heating Pads, and Therapeutic Laser, Radial Pressure Wave Generator and Applicators, and Heating Units.

Certificate Number: MED-0078g
Initial Certification Date: November 8, 2002
Certificate Effective Date: September 28, 2014
Certificate Expiry Date: September 27, 2017


Christopher An, President
Intertek Testing Services NA, Ltd. - Lachine, QC, Canada



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Technical File – TF-DJO-006-2 – Declaration of Conformity – Rev A

DECLARATION OF CONFORMITY	
MANUFACTURER	DJO, LLC 1430 Decision Street Vista, CA 92081-8553 U.S.A.
EU AUTHORIZED REPRESENTATIVE	MDSS GmbH Schiffgraben 41 30175 Hannover, Germany
PRODUCT	Level 2 Category Code 800 (Item Group) Specialty (Cryo/Cuff™ and Accessories)
CLASSIFICATION	Class I, by Rule 1
CONFORMITY ASSESSMENT ROUTE	Annex VII
GMDN CODE	42463 Cold Therapy Unit, Water
WE HEREWITH DECLARE UNDER SOLE RESPONSIBILITY THAT THE ITEM GROUP TO WHICH THIS DECLARATION IS RELATED IS IN CONFORMITY WITH ALL RELEVANT PROVISIONS OUTLINED IN THE OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITY COUNCIL DIRECTIVE 93/42/EEC CONCERNING MEDICAL DEVICES. THE ITEM GROUP COMPLIES WITH ALL RELEVANT PROVISIONS OF THE ANNEX I ESSENTIAL REQUIREMENTS.	
STANDARDS APPLIED	ISO 13485:2003 (Applied in full) Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes ISO 14971:2007 Application of Risk Management to Medical Devices ISO 10993-1:2003 Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing EN 1041:1998 Information Supplied by the Manufacturer with Medical Devices ISO 15223-1:2012 Medical devices – Symbols to be used with medical device labels, labeling and information to be supplied ISO 15223-2:2010 Medical devices – Symbols to be used with medical device labels, labeling and information to be supplied
NOTIFIED BODY	N/A – Class I without sterility or measuring function.
EC CERTIFICATE(S)	N/A – Class I without sterility or measuring function.
SIGNATURE	 5.2.13 Jeff Monroe, Quality Director & Management Representative Date

Technical File – TF-DJO-006-2 – Declaration of Conformity – Rev A

DECLARATION OF CONFORMITY	
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PRODUCT	Level 2 Category Code 800 (Item Group) Specialty (Cryo/Cuff™ IC and Accessories)
CLASSIFICATION	Class I, by Rule 12
CONFORMITY ASSESSMENT ROUTE	Annex VII
GMDN CODE	42463 Cold Therapy Unit, Water
WE HEREWITH DECLARE UNDER SOLE RESPONSIBILITY THAT THE ITEM GROUP TO WHICH THIS DECLARATION IS RELATED IS IN CONFORMITY WITH ALL RELEVANT PROVISIONS OUTLINED IN THE OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITY COUNCIL DIRECTIVE 93/42/EEC CONCERNING MEDICAL DEVICES. THE ITEM GROUP COMPLIES WITH ALL RELEVANT PROVISIONS OF THE ANNEX I ESSENTIAL REQUIREMENTS.	
STANDARDS APPLIED	ISO 13485:2003 (Applied in full) Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes ISO 14971:2007 Application of Risk Management to Medical Devices ISO 10993-1:2003 Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing EN 1041:1998 Information Supplied by the Manufacturer with Medical Devices ISO 15223-1:2012 Medical devices – Symbols to be used with medical device labels, labeling and information to be supplied ISO 15223-2:2010 Medical devices – Symbols to be used with medical device labels, labeling and information to be supplied IEC 60601-1 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance
NOTIFIED BODY	N/A – Class I without sterility or measuring function.
EC CERTIFICATE(S)	N/A – Class I without sterility or measuring function.
SIGNATURE	 5.2.13 Jeff Monroe, Quality Director & Management Representative Date

APPENDIX 2 - ACLR REHABILITATION PROTOCOL

Phase	WB	Brace	ROM	Exercise	Precaution
Phase 1 0- 2 W	WBAT Crutches Working to FWB wean crutches by 10-14days	No brace if uncomplicated ACLR May require Cricket pad / Zimmer splint if Q weak ++ Remove Compression Bandage at 48hrs	Ework to full Hyper E gentle F (can use X bike)	Q SLR C raises or theraband Hip E standing Flexion Gentle prone	NO resisted HS until week 6 post operatively Wounds clean dry covered
Phase 2 2 - 6 Weeks	FWB No Crutches	No Brace	Full E / hyper E Full F (Nb. swelling tends to restrict full F)	Q closed chain mini Squat 2L to lunge to Single Leg Squat & leg press Gait re-education C raise 2L Gluteus medius work Hamstrings prone Proprioception Pool – no breast stroke and straight leg kick (wounds closed) scar massage	NO resisted HS until week 6 post operatively Return to work graded as increase pain + swelling
Phase 3 6-12 Weeks	FWB Normal gait pattern	No Brace	Gain Full Pain free	Q closed chain S L Squat + leg press progress HS resisted X bike – seat high no clips Cross trainer / stepper / inclined treadmill walk in prep for running Proprioception	No running until 3 months post operatively Phased increases in gym loads Control swelling
Phase 4 12-26 Weeks	FWB	No Brace		Running and progress time and speed Q continue leg press progress Start open chain Agility and gentle impact introduced grad Progressing to sport specific drills and returned to training when ready	Paced increases in running
Phase 5 26-38 Weeks	FWB	No Brace		Phased return to sport Training paced increases in time if all well. paced return to Games – 1/4, Half, 3/4, full	Caution return to training , low impact , non- contact initially Phased increase in contact

Wk=weeks/ WB=weight bearing/FWB=full weight bearing/ WBAT=weight bearing as tolerated / Q=Quadriceps/ HS=hamstrings/ C=calf/ SLR=straight leg raise/ 2L=2 legs/ SL=single leg/ X =exercise/ E=extension/ F=flexion/ hrs=hours

APPENDIX 3 ETHICAL APPROVAL LETTER

Ethical approval letters

The Joint UCL/UCLH Committee on the Ethics of Human Research (Committee A)

Research & Development Directorate
1st Floor Maple House, 149 Tottenham Court Road
London W1P 9LL
020 7600 6000
c/o Ground Floor, Roseham Wing Postroom
25 Grafton Way, London
WC1E 6DB

Telephone: 020 7250 8977
Facsimile: 020 7250 9937

GS/05/06/120

9th June 2006

Mr Fares Haddad
Consultant Orthopaedic surgeon
Orthopaedic department
UCH
235 Euston Rd
London NW1 2BU

Dear Mr Haddad

Full title of study: Investigation into patient characteristics and treatment factors associated with short-term and medium-term outcome following Anterior Cruciate Ligament Reconstruction.
REC reference number: 05/G0505/120

Thank you for your letter of 1st June 2006, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation (as revised).

Ethical review of research sites

The ethical opinion refers to the sites in the accompanying attachment.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Application	S.1 - Parts A, B, C	31 May 2006
Investigator CV	Fares Haddad	
Protocol	3	01 April 2006
Covering Letter		16 December 2005
Statistician Comments	Gareth Ambler, UCLH	01 December 2005

05/G0505/120

Page 2

	R&D	
GPI/Consultant Information Sheets	1	01 December 2005
Participant Information Sheet	5	15 April 2006
Participant Consent Form	3	01 November 2005
Response to Request for Further Information		01 June 2006
Flowchart		
Profile of Prof. Martin Ferguson-Pell		16 December 2005
Summary Patient Information Sheet	5	15 April 2006

Research governance approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final research governance approval from the R&D Department for the relevant NHS care organisation.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/G0505/120 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Dr. Geoff Scott
Chair

Email: caroline.williams@uclh.nhs.uk

Enclosures: Standard approval conditions
Site approval form

Copy to: R&D, University College Hospitals London Foundation Trust

SP1 list of approved sites

APPENDIX 4 PARTICIPANT INFORMATION LEAFLET

Participant Information Leaflet

Version: 9

Date: 15/4/06

Project ID:

Bruce Paton
Clinical Specialist Physiotherapist
Therapies and Rehabilitation
Lower Ground Floor
University college hospital
235 Euston Rd
NW1 2BU
Telephone: 08451 555 000
Ext 73821
Fax: 0207 691 5818 ext 73880
Email: Bruce.Paton@uclh.nhs.uk

Investigation into patient and treatment characteristics associated with short-term and medium-term outcome following Anterior Cruciate Ligament Reconstruction

Invitation

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.



UCL Hospitals is an NHS Trust incorporating the Euston Dental Hospital, Elizabeth Garrett Anderson & Obstetric Hospital, The Moat Hospital, Hospital for Tropical Diseases, The Middlesex Hospital, National Hospital for Neurology & Neurosurgery, The Royal London Homoeopathic Hospital and University College Hospital.

1. What is the purpose of the study

We are interested in trying to improve the outcome following cruciate ligament surgery. In order to do this, we first need to identify those characteristics that make some people have a better outcome than others. This process involves us carefully assessing your knee, as well as some of your attitudes to the injury, your social support network and sport. We will also be looking at whether the amount of swelling you experience after surgery affects your outcome, and whether we can influence this.

Swelling and bleeding into the knee joint is very common after arthroscopic knee surgery. Swelling can also effect pain and muscle contraction, which can slow the recovery of a normal walking pattern.

Sometimes this swelling takes a long time to resolve, and most patients find their knee swells intermittently through the months of rehabilitation, making rehabilitation slower.

In this study we are investigating the effect of trying to control this swelling in the very early stage after surgery. This may give less pain, better muscle function and faster recovery and rehabilitation.

We are also investigating the effect of your attitudes to your injury, sport, social support and motivation on your rehabilitation.

2. Why have I been chosen?

The study is being undertaken in the knee unit at UCLH with subjects recruited through clinics run by Mr Fares Haddad. The study has been put together with his approval & guidance

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.



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4. What is involved in the study?

a. What will happen to me if I take part?

If you decide to take part you will be asked to fill in some questionnaires to measure both your knee function and some of your attitudes. We will also take careful measurements of the knee as part of our examination. Once you have been admitted for surgery, usually the day before the operation, you will be put into one of two groups. Using numbered envelopes (similar to tossing a coin).

The first group

Patients allocated to this group receive normal treatment post surgery with admission to hospital for the day of surgery only, and possibly one night, as previously planned.

As we do normally after surgery, the knee will be placed in a bandage & you will be asked to keep it on for 24 hours.

Exercises will commence the evening after surgery on waking up then every waking hour through the first 2 weeks as is the normal practice

There will be no restriction on getting up /moving around/ walking (as long as the knee does not feel like giving way) & just as you feel comfortable, with crutches in first 5 days if you feel you need them.

The 2nd group

Patients allocated to the second group will stay in hospital for the day of surgery only, and possibly one night, as previously planned. Their treatment will differ only slightly, in the first evening and the first 2 weeks after the operation.



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Two extra measures to control swelling will be used immediately after the operation in the recovery room. These are:

1. The leg will be elevated to a 45 Degree angle or slightly greater than (with the knee held straight)
2. A cryocuff cooling device. This is a plastic sleeve placed around the knee which contains iced water. This will be refilled regularly giving gentle cooling to the knee

Exercises are the same in the 2 groups and will be started the evening after surgery, on waking and then performed gently each waking hour over the next 2 weeks.

The Cryocuff (2nd Group only)

You will be provided with your own cryocuff for the first two weeks after surgery. This is a plastic sleeve that wraps around your knee. It is connected to a container filled with ice and water. It will be taken home with you and filled each day with ice and water from your fridge. It is to be worn for as much of the day as possible over the next 2 weeks, removing it only to perform exercises.

The knee is to be kept straight and elevated more than 45 degrees for as much of the day as possible over the first 2 weeks. It should be lowered only to perform exercises.

This second group is allowed up to walk around a little (with crutches if required), but will rest / getting up for toilet privileges & very short periods only (less than 10 minutes).

The cryocuff should be kept on with the knee elevated (more than 45 degrees with knee straight) for the rest of the day in those first 2 weeks.

Diary (Both groups)

In order to monitor any other factors that might affect your recovery, we will ask you to fill in part of a diary sheet each day for the first 6 weeks. This is a simple sheet for each week, where you can write the amount of pain medication take, the amount of activity you have undertaken, the number of times you have been able to do your exercises and the amount of swelling around the knee. This should take about 5 minutes each day and is very important for us to check the results of this study.



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After the first 2 weeks, the rehabilitation and physiotherapy procedure will be the same for both groups

Measurement / Testing (Both groups)

Pre operative and Follow up appointments are made in the orthopaedic clinic to see your surgeon at 2 weeks / 6 weeks / 12 weeks / 6 months and 9 months after the operation.

After each of these appointments you will see the researcher and will undergo a series of tests including, measurements of swelling, knee laxity, movement and strength in the knee. When your knee is ready (in the later stages of rehabilitation) we will also perform some functional tests, such as hopping and jumping tests. You will also be asked to complete some written questionnaires, which ask questions on physical function of the knee and psychological aspects and attitudes to the knee injury and sport, such as motivation, anxiety, social support, sense of control and motivation for rehabilitation. (Psychological counselling can be organised with psychologists in local mental health and social care trust if you feel you require this). At the last follow-up appointment we will re-measure the knee and, once again, ask you to fill in these same questionnaires.

It is anticipated that each of these measurement sessions will take approximately 1½ hours.

b. What will I be required to do?

If you take part in the study you will be required to:

- Stick with the routine over the first 2 weeks. This includes elevating the leg with knee straight and using the cryocuff (cooling).
- Fill in your quick daily diary each day over the first 6 weeks.
- Give us your time after the orthopaedic appointments, before and after the operation, for the Questionnaires and measurement procedure

(It is anticipated this will take approximately 1½ hr)



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5. What is the procedure that is being tested?

There are few treatments available that can reduce swelling once it has gathered. Traditionally we have waited for the knee joint to absorb it, slowing your recovery. By preventing the swelling in the first hours after surgery we feel that it will allow the rehabilitation to start with less knee swelling allowing you to move on more quickly. Normal practice involves using a tight bandage after surgery to control the swelling. We feel that the addition of the cooling device and strict elevation will improve your recovery.

6. What are known risks of the study or the side effects of any treatment received?

There are some risks with any knee surgery including infection / and leg blood clots (deep vein thrombosis – DVT). There will be some risk for both groups as in any normal knee arthroscopy operation. These risks associated with the operation will be explained to you before the surgery, when you consent to having the procedure done. With the swelling control regimen, there may be a slightly increased risk of deep venous thrombosis. However the risk of these complications may actually decrease if swelling is reduced.

Two measures we have put in place, with more frequent observations of your leg in recovery room by recovery nurses & staff and the regular ankle and knee exercises we ask you to do (Taught to you in preadmission clinic). These staff will be on hand to advise & help you during this period. We have also placed our contact number on this form should you need to contact us at any time with questions/ concerns you have regarding this, either before or during your rehabilitation. It may also be uncomfortable keeping the leg in elevation & cooling the knee, however hourly exercises & some toilet breaks through the day should help prevent discomfort.

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.



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University College London Hospitals

NHS Foundation Trust

Also, on receiving new information your research doctor might consider it to be in your best interest to withdraw you from the study. He will explain the reasons and arrange for your care to continue.

7. What are the possible benefits of taking part?

We anticipate a smooth recovery after your knee surgery, with the efforts you make in the initial 2 weeks greatly helping your recovery. We hope that both the treatments will help you. However, this cannot be guaranteed. The information we get from this study will help us to improve the treatment we give people after arthroscopic knee surgery.

8. What information will be held about you?

On your hospital visits the researcher will assess you. They will make some measurements including swelling measurements /knee mobility and laxity measures / strength / walking and several other measures such as hopping & jumping tests (when your knee is ready for these tests).

They will ask you some questions about your activity levels and medication use and collect your daily diary sheets for that period

They will also hold the results of the written questionnaires

The information will be stored on several databases by the researchers and stored and handled at UCLH/ UCL. The information will be stored safely and only those involved in the study will have access to it.

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address, date of birth and all identifiable information (including patient/hospital/NHS number) removed so that you cannot be recognised from it. We will also write to your GP explaining that you have been entered in this study so that he/ she can be aware to look out for any problems if they arise.



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University College London Hospitals

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9. What happens when the research study stops?

If the research study stops it will in no way effect the treatment or rehabilitation you get. This will carry on regardless of your participation in the study.

10. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns of this study, the normal National Health Service/ UCLH complaints mechanisms should be available to you.

11. What will happen to the results of the research study?

The results of the study will be analysed & hopefully published in a relevant scientific journal in 2-4 years time. If you would like to know the outcome you can maintain contact with us on the above address.

It may be easy for you to know which of the 2 groups you are in, but we would ask that you do not communicate this to the researcher assessing your knee (he does not know) or to your surgeon. Again, you will not be identified in any report/publication.

12. Who is organising and funding the research?

The study is organised by the orthopaedic and physiotherapy department of UCLH, specifically the orthopaedic team of Mr Fares Haddad. It has been organised in an effort to improve outcome for our patients after knee surgery.

The study is currently not funded and we are seeking funding from UCLH and various grant bodies to cover costs of our equipment such as the cryocuff.



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13. Withdrawal from the project

Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. If you choose not to enter the trial, or to withdraw once entered, this will in no way affect your future medical care. All information regarding your medical records will be treated as strictly confidential and will only be used for medical purposes. Your medical records may be inspected by competent authorities and properly authorised persons, but if any information is released this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

14. Who has reviewed the study?

The study has been reviewed and registered by the research and ethics committee of UCLH under the framework of the NHS advice on Research and ethics committees

15. Contact for further information

If you have any other questions or would like to discuss any aspect of the study, our contact details are on the front page of this leaflet. We would be very happy to speak with you.

If you decide to take part you will be given a copy of this information sheet and a consent form to sign and keep

16. Note for those seeking Compensation for knee injury following an accident

If you are seeking compensation, or have a legal claim in process for your knee injury, we would suggest you seek advice from your legal advisor prior to taking part in this study as it may have implications for your claim.

Thank you for taking part in this study! We very much appreciate your help.



UCL Hospitals is an NHS Trust incorporating the Eastman Dental Hospital, Elizabeth Garrett Anderson & Obstetric Hospital, The Heart Hospital, Hospital for Tropical Diseases, The Middlesex Hospital, National Hospital for Neurology & Neurosurgery, The Royal London Homoeopathic Hospital and University College Hospital.

Group 1 - The Normal Intervention Group

Normal treatment post surgery with admission to hospital for the day of surgery only, and possibly one night, as previously planned.

The knee will be placed in a bandage & you will be asked to keep it on for 24 hours.

Exercises will commence the evening after surgery on waking up then every waking hour through the first 2 weeks as is the normal practice

There will be no restriction on **getting up /moving around/ walking** (as long as the knee does not feel like giving way) & just as you feel comfortable, with crutches in first 5 days if you feel you need them.

Group 2 - The Swelling Control Group

Initial treatment is as above. In addition two extra measures to control swelling will be used immediately after the operation in the recovery room and in the first 2 weeks after going home.

These are:

1. **The leg will be elevated** to a 45 Degree angle or slightly greater (with the knee held straight)
2. **A Cryocuff cooling device.** This is a plastic sleeve placed around the knee which contains iced water. This will be refilled regularly giving gentle cooling to the knee

At home in the first 2 weeks:

- **Cryocuff to be worn most of the day for the first two weeks** after surgery, removing it only to perform exercises, and refilling with iced water through the day.
- **The knee is to be kept elevated and straight** more than 45 degrees for as much of the day as possible over the first 2 weeks. It should be lowered only to perform exercises.
- **Rest for most of the day / getting up for toilet privileges & very short periods only** (less than 10 minutes). You are allowed to walk around with crutches if required.

Both Groups

Will complete a daily diary sheet writing down:-

The amount of daily time in elevation

The number of daily exercises

The amount of daily medication use.

Exercises are the same in the 2 groups and will be started the evening after surgery, on waking and then performed gently each waking hour over the next 2 weeks.

Will complete questionnaires and measurement sessions after their clinic visits – taking about 1 hr each time.



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APPENDIX 5 CONSENT FORM

University College London Hospitals
NHS Foundation Trust

Centre Number:
UCLH Project ID number:
Participant Identification Number for this study:
Form version: 3
Nov 2005

Bruce Paton
Clinical Specialist Physiotherapist
Therapies and Rehabilitation
Lower Ground Floor
University college hospital
235 Euston Rd
NW1 2BU
Telephone: 08451 555 000
Ext 73621
Fax: 020 7380 9572
Email: Bruce.Paton@uclh.nhs.uk

CONSENT FORM

Title of project:

Investigation into patient and treatment characteristics
associated with short-term and medium-term outcome following
Anterior Cruciate Ligament Reconstruction

Name of Principal Investigator: Mr Fares Haddad (C/O address and contact details above)



Please
initial box

1. I confirm that I have read and understood the information sheet dated 15/04/06, (Version 9) for the above study and have had the opportunity to ask questions.

☐

2. I confirm that I have had sufficient time to consider whether or not want to be included in the study

☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

☐

4. I understand that sections of any of my medical notes may be looked at by responsible individuals from UCL and UCLH or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

☐

5. I agree to take part in the above study.

☐


1 form for Patient;
1 to be kept as part of the study documentation,
1 to be kept with hospital notes



UCL Hospitals is an NHS Trust incorporating the Eastman Dental Hospital, Elizabeth Garrett Anderson & Obstetric Hospital, The Heart Hospital, Hospital for Tropical Diseases, The Middlesex Hospital, National Hospital for Neurology & Neurosurgery, The Royal London Homoeopathic Hospital and University College Hospital.

Centre Number:
UCLH Project ID number:
Participant Identification Number for this study:
Form version: 3
Nov 2005

CONSENT FORM

Title of project:
Investigation into patient and treatment characteristics
associated with short-term and medium-term outcome following
Anterior Cruciate Ligament Reconstruction

Name of Principal Investigator: Mr Fares Haddad

Name of patient

Date

Signature

Name of Person taking consent
(if different from researcher)

Date

Signature

Name of the research to be contacted if there are any problems

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL hospitals. Please quote the UCLH project number at the top of this consent form.

1 form for Patient;
1 to be kept as part of the study documentation,
1 to be kept with hospital notes

APPENDIX 6 QUESTIONNAIRE - IKDC FORM

University College London Hospitals **NHS**
NHS Foundation Trust

2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

Your Full Name: _____

Today's Date: ____/____/____ Date of Injury: ____/____/____ Date of Surgery: ____/____/____
Day Month Year Day Month Year Day Month Year

SYMPTOMS*:
*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?

☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
☐ Strenuous activities like heavy physical work, skiing or tennis
☐ Moderate activities like moderate physical work, running or jogging
☐ Light activities like walking, housework or yard work
☐ Unable to perform any of the above activities due to knee pain

2. During the past days, how often have you had pain?

10 9 8 7 6 5 4 3 2 1 0
Never ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Constant

3. If you have pain, how severe is it?

10 9 8 7 6 5 4 3 2 1 0
No pain ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Worst pain Imaginable

4. During the past days, how stiff or swollen was your knee?

☐ Not at all
☐ Mildly
☐ Moderately
☐ Very
☐ Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?

☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
☐ Strenuous activities like heavy physical work, skiing or tennis
☐ Moderate activities like moderate physical work, running or jogging
☐ Light activities like walking, housework, or yard work
☐ Unable to perform any of the above activities due to knee swelling

6. During the past days, did your knee lock or catch?

☐ Yes ☐ No

7. What is the highest level of activity you can perform without significant giving way in your knee?

☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
☐ Strenuous activities like heavy physical work, skiing or tennis
☐ Moderate activities like moderate physical work, running or jogging
☐ Light activities like walking, housework or yard work
☐ Unable to perform any of the above activities due to giving way of the knee

University College London Hospitals **NHS**
NHS Foundation Trust

Page 2 – 2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

SPORTS ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis right now?

- ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
☐ Strenuous activities like heavy physical work, skiing or tennis
☐ Moderate activities like moderate physical work, running or jogging
☐ Light activities like walking, housework or yard work
☐ Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately difficult	Extremely difficult	Unable to do
a.	Go up stairs	☐	☐	☐	☐	☐
b.	Go down stairs	☐	☐	☐	☐	☐
c.	Kneel on the front of your knee	☐	☐	☐	☐	☐
d.	Squat	☐	☐	☐	☐	☐
e.	Sit with your knee bent	☐	☐	☐	☐	☐
f.	Rise from a chair	☐	☐	☐	☐	☐
g.	Run straight ahead	☐	☐	☐	☐	☐
h.	Jump and land on your involved leg	☐	☐	☐	☐	☐
i.	Stop and start quickly	☐	☐	☐	☐	☐

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

Couldn't perform Daily activities

0 1 2 3 4 5 6 7 8 9 10
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No limitation in daily Activities

CURRENT FUNCTION OF YOUR KNEE:

Cannot perform Daily activities

0 1 2 3 4 5 6 7 8 9 10
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No limitation in daily Activities

APPENDIX 7 QUESTIONNAIRES - TEGNER AND LYSHOLM

University College London Hospitals 
NHS Foundation Trust

Name Date

The Tegner Activity scale

On the scale from 0 – 10, Please place a circle “O” around the level of activity you are currently undertaking

10	Competitive sports	Soccer – national or international
9	Competitive sports	Soccer – lower divisions Ice hockey Wrestling Gymnastics
8	Competitive sports	Bandy Squash or badminton Athletics (jumping etc) Downhill skiing
7	Competitive sports Recreational sports	Tennis Athletics (running) Motor cross or speedway Handball or Basketball Soccer Bandy or ice hockey Squash Athletics (jumping) Cross country track finding (orienteeing both recreational and competitive)
6	Recreational sports	Tennis or badminton Handball or basketball Downhill skiing Jogging, at least 5 times weekly
5	Work Competitive sports Recreational Sports	Heavy labour Cycling Cross-country skiing Jogging on uneven ground at least twice weekly
4	Work Recreational sports	Moderately heavy work (e.g., truck driving, scrubbing floors) Cycling Cross-country skiing Jogging on even ground at least twice weekly
3	Work Competitive & recreational sports	Light work Swimming Walking in rough forest terrain
2	Work	Light work Walking on uneven ground
1	Work	Sedentary work Walking on even ground
0	Sick leave or disability pension because of knee problems	

On the scale from 0 – 10, Please ALSO place a CROSS “X” around your PRE INJURY level of activity


HOSPITALS

UCL Hospitals is an NHS Foundation Trust comprising: The Eastman Dental Hospital, The Heart Hospital, Hospital for Tropical Diseases, National Hospital for Neurology and Neurosurgery, The Royal London Homeopathic Hospital and University College Hospital (incorporating the former Middlesex and Elizabeth Garrett Anderson Hospitals).

University College London Hospitals 
NHS Foundation Trust



Name Pre Post Date

THE LYSHOLM SCORE

Please circle the most appropriate answer to each section

How much do you notice yourself limping?	
None	5
Slight or periodic	3
Severe or constant	0
Do you require a crutch or stick for support?	
None	5
Stick or crutch	2
Weight bearing impossible	0
Does your knee lock on you? (i.e. unable to straighten from bent position)	
No locking or catching sensation	15
Catching sensation but no locking	10
Locking occasionally	5
Locking frequently	2
Locked now	0
Does your knee ever give way?	
Never gives way	25
Rarely gives way during sport or severe exertion	20
Frequently gives way during sport/unable to do sport	15
Occasionally gives way during ADL	10
Often gives way during ADL	5
Gives way every step	0
How much pain do you have?	
None	25
Inconstant and slight	20
Marked during severe exertion	15
Marked on or after walking >2km	10
Marked on or after walking <2km	5
Constant	0
How much do you notice your knee swelling?	
None	25
On severe exertion	20
On ordinary exertion	15
Constant	10
Describe your knee function with stair climbing	
No problems	25
Slightly impaired	20
One step at a time	15
Impossible	10
Describe your knee function with squatting	
No problems	25
Slightly impaired	20
Not beyond 90 degrees	15
Impossible	10
Total	


HOSPITALS

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APPENDIX 8 QUESTIONNAIRE – LOWER EXTREMITY FUNCTIONAL SCALE

University College London Hospitals
NHS Foundation Trust

Name		Date	

LOWER EXTREMITY FUNCTIONAL SCALE

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your lower limb problem for which you are currently seeking attention
Please provide an answer for each activity

Today do you, or would you have any difficulty at all with :- (Circle one number on each line)

Activities	Extreme Difficulty Or unable To perform	Quite a bit of difficulty	Moderate difficulty	a little bit of difficulty	no difficulty
A Any of your usual work, house work, or school activities	0	1	2	3	4
B Your usual hobbies, recreational or sporting activities	0	1	2	3	4
C getting into or out of the bath	0	1	2	3	4
D walking between rooms	0	1	2	3	4
E putting on your shoes & socks	0	1	2	3	4
F squatting	0	1	2	3	4
G lifting an object, like a bag of groceries from the floor	0	1	2	3	4
H Performing light activities around your home	0	1	2	3	4
I Performing heavy activities around your home	0	1	2	3	4
J Getting into or out of a car	0	1	2	3	4
K Walking 2 street blocks	0	1	2	3	4
L walking a mile	0	1	2	3	4
M Going up or down 10 stairs (about 1 flight of stairs)	0	1	2	3	4
N Standing or 1 hour	0	1	2	3	4
O sitting for 1 hour	0	1	2	3	4
P Running on even ground	0	1	2	3	4
Q Running on uneven ground	0	1	2	3	4
R Making sharp turns while running fast	0	1	2	3	4
S Hopping	0	1	2	3	4
T Rolling over in bed	0	1	2	3	4

Column totals

SCORE _____/80



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APPENDIX 9 – DIARY SHEET

University College London Hospitals

NHS Foundation Trust

DATE:**ACTIVITY / MEDICATION / EXERCISE DIARY**

Thank You for taking part in the knee swelling study

We are interested in your amount of activity over the first 6 weeks after your operation

Thank you for completing this short diary each day

Have you used any medication today ?

Name of medication :

Dose taken today (ie
number of tablets) :

How active have you been today ?

Briefly list your activities for the day :

Amount of time spent
standing :Amount of time spent walking
:Amount of time out of
elevation :Amount of time without
cryocuff on :

Have you done exercises today ?

Amount of times :

Total time for exercises :

Thank you for your time today completing this diary



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Bruce Paton
Clinical Specialist Physiotherapist
Therapy Outpatient Services
Physiotherapy Outpatients
Therapies and Rehabilitation
Lower Ground Floor
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NW1 2BU
Tel: 08451 555 000
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Fax: 020 7380 9572
Email : Bruce.Paton@uclh.nhs.uk

APPENDIX 10 PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

INFORMATION SHEET FOR PARTICIPANTS in research study :- Investigating the vascular and pressure effects of devices claiming to speed recovery after knee surgery  We would like to invite you to participate in this postgraduate research project. You should only take part if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. What is this study about? Ice and cooling is commonly applied after knee injuries or surgery to decrease pain and swelling. Many devices are used to give a dry cooling to the knee after injury or surgery. Four commonly used devices are the Cryocuff and the "Game ready" and the "bodyflow" device and finally a simple bandage. They involve a cuff or bandage around the knee, sometimes containing cooled water moved in and out of a pump/container and they affect the knee by cooling and/or compression. There is currently a lack of evidence as to optimal use of these devices for the knee. While temperature changes have been measured under the cuffs or bandages, the pressure at points under the cuffs or bandages has not been investigated. Why is this study being done? We want to measure the pressure at several points under the cuff/ bandage when they are filled. We aim to measure in 3 positions - standing / lying flat and lying with the leg in 60° elevation. If we know how these devices work better, we hope to help people experience less knee pain after injuries or operations. Who can take part in this study? We are looking for healthy volunteers over the age of 18. You should not have experienced any leg injury or surgery over the last six months, or have any pain or swelling in your knees, or have any conditions that would affect blood flow in the legs. You should not smoke or have diabetes, or be pregnant. You should not have had any history of leg blood clots. What will you have to do if you take part in this study? You will be required to come to a laboratory at the Institute of Sport Exercise and Health - 170 Tottenham Court Road W1T 7HA for approximately 2 hours on two occasions. On each occasion the same procedure will be followed. Before testing, you will have some measurements taken of - height, weight, current activity levels, diet, hydration, will be gathered using a questionnaire. A choice of 2 envelopes will be provided for you to pick one, which will determine the knee side which has the cuff device or bandage. You will then be required to change into shorts with shoes and socks removed. After sitting quietly for 15 minutes your blood pressure will be taken from both arm and leg. A	researcher will place pressure and temperature probes on your skin on pre-determined areas of the knee and lower leg and foot. The blood pressure cuffs will be left on your arm and each leg, and will be inflated only occasionally during the study to take blood pressure. During measurement you will wear one of the cuff devices on one knee, and a Bandage on the other knee for a total of 90 minutes including 30 minutes lying flat / 30 minutes lying flat with the legs elevated at 60° angle and 30 minutes in standing. There will be a final 15 minutes lying flat. While you are in these positions with the measuring probes on, measurements will be noted every 5 minutes of temperature and pressure, as well as arm and leg blood pressure. There is a theoretical risk of some discomfort as the blood pressure cuffs expand and shrink however these will be short lasting and only every 5 minutes. There may be risk of decreased circulation to your foot but the researchers will monitor your circulation regularly and will adjust the knee cuff if you experience discomfort. You will be given a contact number (below) to call if you have any concerns about your leg before or after the testing. There is also some risk of discomfort from keeping still for 30mins with the knee cooling cuffs inflated - We ask you to tell us if this is the case and we will adjust your position. There will be a qualified physiotherapists and doctors present during the testing. Following the data collection, we will organise another date at your convenience to re-attend the laboratory to repeat the same process with a different type of knee cuff similar to the cryocuff. Personal information may be retained or shared with fellow researchers after the trial. This data will be completely anonymous and no one will contact you regarding your participation. We will be happy to give you a copy of the final report if you request this on the consent form. If you agree we will keep your contact details for possible involvement in future studies that you may be suitable for. If you decide you would rather not be contacted, this will not affect your participation in this study. It is up to you to decide whether you take part or not. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. In addition to withdrawing yourself from the study, you may also withdraw any data/information you have already provided if you so choose. If you decide to take part you will be given this information sheet to keep, and be asked to sign a consent form. Will information about me be available to anyone? All information collected from you during the course of this research will be kept strictly confidential. Who will have access to the research records? Only members of our research team will be able to look at the information we collect. Our study complies with the Data Protection Act of 1998 (DPA). The DPA makes sure the information we collect and keep is well protected. How to contact the researchers You can ask any questions that you have about the study. If you have a question that you didn't think of now, you can ask it later. You can contact me at 0203 447 2820 or by

email at b.paton@ucl.ac.uk if you need any more information about the study. You can check more about the ISEH on www.iseh.co.uk. Contact details can also be found on the web site.

THANK YOU FOR TAKING THE TIME TO READ THIS INFORMATION SHEET.
Your help makes our research possible!

If this study has harmed you in any way you can contact University College London through Professor FS Haddad - director of the Institute of Sport Exercise and Health for further advice or information by email care of the ISEH

Address
Professor FS Haddad
Research and Development
Institute of Sport Exercise and Health
170 Tottenham Court Road
London
W1T 7HA
02034472800

INFORMATION SHEET FOR PARTICIPANTS in research study:-

Investigating the vascular and pressure effects of devices
claiming to speed recovery after knee surgery



CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

- I understand that if I decide at any time during the research that I no longer wish to participate in this project, I can notify the researchers involved and withdraw from it immediately without giving any reason. Furthermore, I understand that I will be able to withdraw my data
- I consent to the processing of my personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the Data Protection Act 1998.

Please tick
or initial

☐
☐

Participant's Statement:

I -

Agree that the research project named above has been explained to me to my satisfaction and I agree to take part in the study. I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves.

Signed

Date

Investigator's Statement:

I _____

Confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the participant.

Signed

Date

- The information you have submitted will be published as a report and you will be sent a copy. Please note that confidentiality and anonymity will be maintained and it will not be possible to identify you from any publications.
- I agree to be contacted in the future by King's College London researchers who would like to invite me to participate in follow up studies to this project, or in future studies of a similar nature. ☐
- I agree that the research team may use my data for future research and understand that any such use of identifiable data would be reviewed and approved by a research ethics committee. (In such cases, as with this project, data would not be identifiable in any report). ☐

For health related research, additional points are important

- I understand that I must not take part if I :- ☐
 - have a past history of injury to either leg in the last 3 months
 - have current knee swelling or pain
 - have ever had a deep vein thrombosis or leg blood clot
 - Currently have a temperature and illness
 - have blood pressure problems or take medications affecting blood pressure
 - are pregnant, or may be pregnant.
 - have peripheral vascular disease
 - if you consume greater than 14 units of alcohol a week if you are female, or greater than 28 units of alcohol a week if you are male
 - use recreational drugs
- I agree that my GP may be contacted if any unexpected results are found in relation to my health. ☐
- Please inform the researcher if you are currently involved or have been involved in any other research studies in the last 12 months. ☐

APPENDIX 11 UNIVERSITY COLLEGE LONDON- ETHICAL APPROVAL LETTER

UCL RESEARCH ETHICS COMMITTEE
ACADEMIC SERVICES



Mr Bruce Paton
Institute of Sport Exercise and Health
UCL

28 November 2014

Dear Mr Paton

Notification of Ethical Approval

Project ID5938/01: Investigating the vascular and pressure effects of devices claiming to speed recovery after knee surgery

In my capacity as Chair of the UCL Research Ethics Committee (REC) I am pleased to confirm that I have approved your study for the duration of the project i.e. until December 2015.

Approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form': <http://ethics.grad.ucl.ac.uk/responsibilities.php>
2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

Reporting Non-Serious Adverse Events

For non-serious adverse events you will need to inform Helen Dorgal, Ethics Committee Administrator (hicks@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Reporting Serious Adverse Events

The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information sheet and/or study protocol.

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.

APPENDIX 12 INSURANCE FORM



Joint Research Office

Office Location:

1st Floor Maple House
149 Tottenham Court Road
London W1T 7DN

Postal Address:

UCL,
Gower Street
London WC1E 6BT

Email: david.wilson@ucl.ac.uk Tel No. 020 3447 5199 Fax No 020 7380 9937
Web-sites: www.uclh.nhs.uk www.ucl.ac.uk/jro

4th November 2014

Bruce Paton
UCL Institute of Sport Exercise and Health
170 Tottenham Court Rd
London
W1T 7 HA

Dear Bruce,

Chief Investigator: Bruce Paton

Study/Trial Title: Investigating vascular and pressure effects of devices claiming to speed recovery after knee surgery

Funder: UCL

UCL Project ID No: 14/0738 (UCL REC Ref: 5938/001)

Re: Insurance for studies not involving a Clinical Trial of an Investigational Medicinal Product (non-CTIMP) sponsored by UCL

Thank you for completing UCL Insurance Registration Form of 4th November 2014. I am pleased to inform you that the above study, as described in the registration form, is now insured under UCL's Policy. A copy of the current insurance summary (Certificate of Currency) is attached to this letter.

The policy provides for the legal liabilities (negligence) of UCL and its employees or agents.

The UCL insurance policy is renewed annually but studies included in the UCL insurance portfolio will be automatically rolled over into subsequent insurance period(s) until the study terminates. Indemnity and insurance arrangements for any participating sites will be detailed in individual Site Agreements.

Director UCL SLMS Research Support Centre, Director R&D UCLH – Professor Monty Mythen
Managing Director UCL SLMS Research Support Centre – Dr Nick McNally

Version 12 9th August 2011

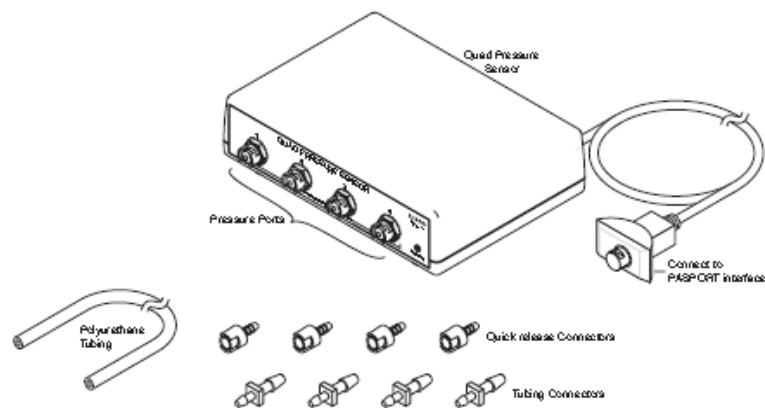
APPENDIX 13 PASCO QUAD PRESSURE SENSOR INSTRUCTION MANUAL



Instruction Sheet
012-090 12A

Quad Pressure Sensor

PS-2164



Included Equipment	Part Number
Quad Pressure Sensor	PS-2164
Polyethylene Tubing (length 2.4 m)	640-028
Quick-release Connectors (qty. 4)	640-021
Tubing Connectors (qty. 4)	640-020
Required Equipment	
PASPORT Interface ¹	See PASCO Catalog or www.pasco.com

¹PASPORT Interfaces include the ALiLink (MW-4100 or PS-2009), Xplorer GLX (PS-2002), Xplorer (PS-2000), PowerLink (PS-2001), and USB Link (PS-2103).

Introduction

The four-port Quad Pressure Sensor is a multi-sensor capable of reading up to four absolute pressures, or two differential pressures, or two gauge pressures. Dynamic variable over-sampling automatically reduces measurement noise at low sampling rates. Sample rates up to 1000 Hz make studies of both transient and steady-state pressure possible. The sensor measures pressure in units of kPa, N/m², and pounds per square inch (psi).

Setup

Types of Pressure Measurements

To measure pressure in an apparatus, connect one or more of the four pressure ports using the included tubing and connectors. The way that you connect the Quad Pressure Sensor

Model No. PS-2164

Setup

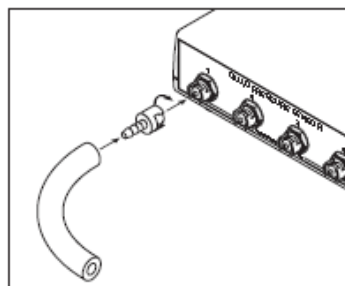
depends on whether you will measure absolute pressure, differential pressure, or gauge pressure:

Absolute Pressure The multi-sensor can measure up to four absolute pressures simultaneously. One connection is required for each measurement, and any of the pressure ports may be used.

Differential Pressure The multi-sensor measures differential pressure by determining the pressure difference between two ports. It can measure one or two differential pressures simultaneously, with two connections required for each measurement. Differential pressure can be measured between ports 1 and 2 or between ports 3 and 4 (or both).

Gauge Pressure Gauge pressure is a special case of differential pressure in which the second port of the pair is left unconnected. The multi-sensor measures the pressure difference between the first port (connected to the apparatus) and the second port (left open to the atmosphere). It can measure up to two gauge pressures simultaneously with one connection required for each measurement. Gauge pressure can be measured by port 1 (with port 2 left open) and by port 3 (with port 4 left open).

Sensor Setup



1. Cut a piece (or pieces) of tubing to the desired length.
2. Insert a quick-release connector into each piece of tubing.
3. Connect each piece of tubing to the multi-sensor or by inserting the quick-release connector into one of the pressure ports and twisting clockwise.
4. Connect the free ends of the tubing to the apparatus using connectors supplied with the apparatus or the tubing connectors included with the Quad Pressure Sensor.

You can use the included tubing connectors to connect to a 5/16" (16 mm) hole in a rubber stopper.

5. Connect the multi-sensor's cable to your PASPORT interface.

DataStudio Setup

If you are using a computer, connect the PASPORT interface to the computer and start DataStudio. Refer to the documentation that came with your PASPORT interface for instructions on connecting it to your computer. In DataStudio, click the Start button to begin data collection; click the Stop button to stop data collection.

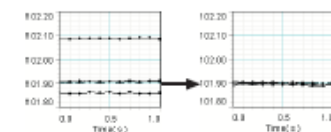
By default, DataStudio displays the absolute pressures measured by all four ports in a Graph display. To make the differential measurements available for display, click the Setup button to open the Experiment Setup window; in that window, select 1-2 Differential Pressure or 3-4 Differential Pressure. There you can also change the sampling rate (up to 1000 Hz) and select different units of measure. For more instructions on using DataStudio, press F1 to open DataStudio's on-line help.

Xplorer GLX Setup

If you are using an Xplorer GLX in standalone mode, press **▶** to start data collection. By default, the GLX displays the absolute pressures from port 1 (Absolute Pressure 1) in units of kPa, but you can select any of the other absolute or differential measurements for display. For more instructions on using the Xplorer GLX, refer to the GLX Users' Guide.

Multiple-measurement Alignment

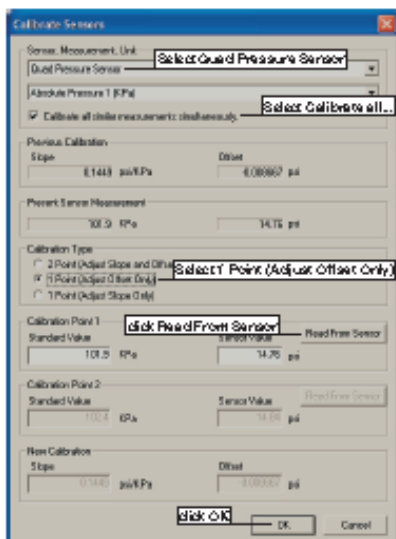
When you are using multiple pressure ports, you may find that their readings differ slightly when they are measuring the same thing. In the example illustrated below, measurements from four ports open to the atmosphere vary by about 0.2 kPa. The multiple-measurement alignment procedure adjusts the calibrations of the measurements so they agree more closely.



The procedure described here for DataStudio can also be performed on the Xplorer GLX. See the Xplorer GLX Users' Guide for detailed instructions.

1. Click the Setup button to open the Experiment Setup window. Click Calibrate Sensors to open the calibration dialog box.

- From the Sensor field, select the Quad Pressure Sensor. (See screenshot below.)



- Select the Calibrate all similar measurements simultaneously option.
- From the Calibration Type menu, select 1 Point (Adjust Offset Only).
- Apply the same pressure to all four ports (for instance by opening them to the atmosphere).
- Click the Read From Sensor button for Point 1.
- Click OK to accept the new calibration.

One-point and Two-point Calibrations

Though it is usually not necessary, a one-point or two-point calibration can be performed on any of the absolute or relative measurements to make them more accurate. To do so, you must have a very accurate independent means of measuring pressure, such as a barometer. For step-by-step instructions refer to the documentation for DataStudio version 1.9.5, the Xplorer, or the Xplorer GLX.

Over-sampling

The Quad Pressure Sensor uses dynamic variable over-sampling to reduce noise, produce smoother data, and improve the

measurement resolution. This effect is especially noticeable when very small pressure changes or differences are measured. The degree of dynamic variable over-sampling that takes place within the Quad Pressure Sensor depends on the sample rate. To maximize the over-sampling, set the sample rate as low as possible for a given application. Maximum over-sampling occurs at sampling rates of 1 Hz or slower.

Specifications

Range	Absolute pressure: 0 to 200 kPa Differential pressure: -100 kPa to +100 kPa
Resolution	0.01 kPa at 10 Hz
Repeatability	1 kPa
Units of Measure	kPa, N/m ² , psi
Max. Sample Rate	1000 Hz
Included tubing	Material: polyurethane Inside diameter: 3.2 mm (1/8 inch) Length: 2.4 m (8 feet)

Technical Support

For assistance with any PASCO product, contact PASCO at:

Address: PASCO scientific
10101 Foothills Blvd.
Roseville, CA 95747-7100
Phone: 916-786-3800 (worldwide)
800-772-8700 (U.S.)
Fax: (916) 786-3292
Web: www.pasco.com
Email: support@pasco.com

Limited Warranty

For a description of the product warranty, see the PASCO Catalog.

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