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Robust and practical non-invasive estimation of local arterial wave speed and mean blood velocity waveforms

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Abstract

Objective. Local arterial wave speed, a surrogate of vessel stiffness, can be estimated via the pressure-velocity (PU) and diameter-velocity (ln(D)U) loop methods. These assume negligible early-systolic reflected waves (RWes) and require measurement of cross-sectionally averaged velocity (U_{mean}), which is related to volumetric blood flow. However, RWes may not always be negligible and Doppler ultrasound typically provides maximum velocity waveforms or estimates of mean velocity that are subject to various errors (U_{raw}). This study investigates how these issues affect wave speed estimation and explores more robust methods for obtaining local wave speed and U_{mean} .

Approach. Using aortic phase-contrast MRI (PCMRI) and a simulated virtual cohort, we assessed errors in calculated wave speed caused by RWes and use of U_{raw} rather than true U_{mean} . By combining PU_{raw} and $\ln(D)U_{\text{raw}}$ loop wave speed values, (i) a corrected wave speed ($\ln(D)P$), insensitive to RWes and velocity errors, was derived; and (ii) a novel method for estimating U_{mean} from U_{raw} was proposed (where U_{raw} can be any scaled version of U_{mean}).

Main results. Proof-of-principle was established via PCMRI data and in the ascending aorta, carotid, brachial and femoral arteries of the virtual cohort, with acceptably low wave speed and U_{mean} errors obtained even when local pressure was estimated from diameter and mean/diastolic brachial pressures.

Significance. Given a locally-measured diameter waveform and brachial cuff pressures, (i) the velocity- and RWes-independent $\ln(D)P$ method can be applied non-invasively and is likely more robust than $\ln(D)U$ and PU loop methods; and (ii) U_{mean} can be estimated from routinely-acquired U_{raw} .

Keywords: pulse wave velocity; wave analysis; echocardiography; Doppler; flow

Introduction

Arterial stiffness is a major biomechanical factor that modulates blood pressure and cardiovascular risk (Laurent *et al.*, 2001; Blacher *et al.*, 1999). Although large artery stiffness is often assessed as regional pulse wave velocity (Laurent *et al.*, 2006), it is also possible to calculate local pulse wave velocity (or ‘wave speed’) using the pressure-velocity relation (PU loop), which utilizes local blood velocity (U) and pressure (P) signals (Khir *et al.*, 2001). Experimental studies have generally applied this method using invasive measurements, but non-invasive approaches have also been described, e.g. with U from echocardiography and P from applanation tonometry (Zambanini *et al.*, 2005) or diameter calibrated to systolic and diastolic brachial pressure (Niki *et al.*, 2002). An alternative non-invasive approach not requiring estimation of pressure is to calculate wave speed from the loop of the natural logarithm of vessel luminal diameter (D) and velocity (ln(D)U method) (Feng and Khir, 2010; Li and Khir, 2009).

A current barrier to robust non-invasive application of both the PU and ln(D)U methods, however, is that they both rely on an accurate *mean* (i.e. cross-sectional average) velocity waveform. Mean velocity (U_{mean}) is an important quantity in its own right, being closely related to volumetric blood flow ($Q = U_{\text{mean}}A$, where A is cross-sectional area). However, mean velocity (and flow) are notoriously difficult to measure accurately with ultrasound, despite several techniques being available (Hoskins, 2011; [Borlotti *et al.*, 2012](#)), and clinicians typically measure only the maximum velocity envelope from the Doppler spectrum (Figure 1). Importantly, the accuracy of measured mean or maximum velocity may be confounded by non-uniform insonation, various sources of spectral broadening, imprecise angle correction, presence of secondary flow, inappropriate gain settings, inaccurate sample volume placement and operator dependence (Mynard and Steinman, 2013; Winkler *et al.*, 1995; Hoskins, 2011; Corriveau and Johnston, 2004; Mikkonen *et al.*, 1996; Cobbold, 2006).

Even where an accurately-measured mean velocity is available, recent work has highlighted that significant errors in estimated wave speed may be encountered with the PU and $\ln(D)U$ methods in the presence of early systolic wave reflection, particularly in the carotid artery (Segers *et al.*, 2014; Swillens *et al.*, 2013; Willemet *et al.*, 2016). Improved non-invasive estimation of both wave speed and mean velocity would thus be valuable for studying arterial stiffness and would also increase the applicability, accuracy and reproducibility of state-of-the-art analyses of arterial hemodynamics and ventricular-vascular interactions, such as wave separation and wave intensity analysis (Parker, 2009; Westerhof *et al.*, 1972; Mynard and Smolich, 2016; Alastruey *et al.*, 2014).

The aims of this study were therefore to 1) evaluate the magnitude of errors likely to be encountered with PU and $\ln(D)U$ wave speed estimation due to measurement errors and early-systolic wave reflection; 2) derive a method for estimating wave speed that is immune to velocity errors and early-systolic wave reflection, and can be robustly applied non-invasively (i.e. considering expected errors in measured diameter and pressure); and 3) develop and verify a robust and practical method for estimating mean velocity from an acquired maximum or mean velocity waveform that may contain substantial biases.

After developing the necessary mathematical foundation, the accuracy and reliability of the wave speed and mean velocity estimation methods were tested. Given the lack of a reliable gold-standard reference to compare with echocardiographic data, we instead provide proof-of-principle using (i) phase contrast magnetic resonance imaging (PCMRI) in which gold-standard maximum and mean aortic velocities were obtained simultaneously, and (ii) a computational modeling study involving a virtual cohort of 3325 patients simulating a large range of normal physiological variability (Willemet *et al.*, 2015), with systematic investigation of the influence of errors expected to be encountered in a clinical setting.

Methods

In this section, we first explain the pitfalls of estimating wave speed with the PU and ln(D)U loop methods related to wave reflection and velocity measurement in practice. We then derive a corrected wave speed that is insensitive to wave reflection and velocity scale errors. We then show that, as a byproduct of this correction procedure, it is possible to estimate mean velocity from a measured velocity waveform that contains any amount of scaling error. Methods for validating these techniques are then described.

Wave speed

In the absence of any wave reflection, and in the setting of perfectly accurate recordings of pressure (P), mean (i.e. cross-sectionally averaged) velocity (U_{mean}) and diameter (D), wave speed derived from the PU (c_{PUmean}) and ln(D)U ($c_{\text{ln(D)Umean}}$) loop methods are identical, with

$$c_{\text{PUmean}} = \frac{1}{\rho} \frac{dP}{dU_{\text{mean}}} = c_{\text{ln(D)Umean}} = \frac{1}{2} \frac{dU_{\text{mean}}}{d \ln D} \quad (1)$$

where dX is a change in variable X, and ρ is blood density. In practice, maximum velocity is often acquired from a standard Doppler recording (see Figure 1). If this is used instead of mean velocity in the wave speed calculation (a methodological error), and/or if this is accompanied by measurement errors (or alternatively, if an estimate of mean velocity using a variety of available methods involves error), the acquired or ‘raw’ velocity (U_{raw}) may differ from U_{mean} . From Eq (1), it is clear that if U_{mean} is overestimated (e.g. if maximum velocity is used), c_{PUmean} will be underestimated and $c_{\text{ln(D)Umean}}$ will be overestimated. Under most circumstances, maximum and mean velocity waveforms have a similar shape and common measurement errors are likely to lead primarily to an incorrectly scaled velocity. We therefore assume that the overall error (combined methodological and measurement error) is a constant scaling error α , such that $U_{\text{raw}} = U_{\text{mean}} / \alpha$. Then, a correction can be applied as follows:

$$\frac{1}{\rho} \frac{dP}{\alpha dU_{\text{raw}}} = \frac{1}{2} \frac{\alpha dU_{\text{raw}}}{d \ln D} \quad (2)$$

In the absence of measurement errors, use of maximum velocity leads to $\alpha = 0.5$ for a parabolic velocity profile and $\alpha = 1$ for a flat velocity profile. However, in general the shape of the velocity profile is unknown, measurement errors are non-zero and hence the value of α is unknown. Nevertheless, rearranging Eq. (2) yields an estimate of α as follows:

$$\alpha = \sqrt{\frac{2}{\rho} \frac{dP d \ln D}{dU_{\text{raw}}^2}} \quad (3)$$

This can also be expressed as a ratio of uncorrected loop-based wave speeds, with

$$\alpha = \sqrt{\frac{c_{\text{PUraw}}}{c_{\ln(D)U_{\text{raw}}}}} \quad (4)$$

Corrected wave speed calculated via the PU loop is then,

$$c_{\text{PUmean}} = \frac{1}{\rho} \frac{dP}{\alpha dU_{\text{raw}}} \quad (5)$$

If α given by Eq. (3) is substituted into Eq. (5), we obtain an expression that involves only pressure and diameter, and is therefore termed $\ln(D)P$ loop wave speed,

$$c_{\ln(D)P} = \sqrt{\frac{1}{2\rho} \frac{dP}{d \ln D}} \quad (6)$$

Importantly, since this wave speed does not involve velocity at all, it is insensitive to velocity acquisition errors. In fact, it can be shown that $c_{\ln(D)P}$ is equivalent to the classical Bramwell-Hill equation,

$$c = \sqrt{\frac{A}{\rho} \frac{dP}{dA}} = \sqrt{\frac{D}{2\rho} \frac{dP}{dD}} = \sqrt{\frac{1}{2\rho} \frac{dP}{d \ln D}} \quad (7)$$

Importantly, the Bramwell-Hill equation does not require unidirectional wave travel. Hence, unlike the velocity-based loop methods, Eq. (6) is also accurate even in the presence of early systolic wave reflection. Note that, in practice, Bramwell-Hill wave speed is usually

approximated via the distensibility coefficient (DC) (Segers *et al.*, 2014), i.e. using maximum (P_{\max} , A_{\max}) and minimum (P_{\min} , A_{\min}) values of P and A as follows,

$$c_{DC} = \sqrt{\frac{1}{\rho} \frac{1}{DC}} = \sqrt{\frac{A_{\min}}{\rho} \frac{P_{\max} - P_{\min}}{A_{\max} - A_{\min}}} \quad (8)$$

Use of maximum and minimum pressures and areas in this equation may lead to a slightly different value to that calculated with a regression line over the early systolic phase of the $\ln(D)P$ loop (i.e. to apply Eq. (6)) (Spronck *et al.*, 2017). Aside from this small distinction, correcting for a potentially inaccurate velocity signal in the PU and $\ln(D)U$ loop methods leads to the standard Bramwell-Hill equation, whose accuracy is determined by errors in acquired diameter and pressure, but not velocity.

Mean Velocity

An important byproduct of the wave speed correction is that an estimate of U_{mean} may be obtained from U_{raw} via the simple relation,

$$U_{\text{mean},\alpha} = \alpha U_{\text{raw}} \quad (9)$$

which we refer to as the α -correction of velocity, $U_{\text{mean},\alpha}$. However, this correction is dependent on the same assumptions that are required for the PU and $\ln(D)U$ loop methods, namely, the absence of reflected waves due to an assumption in Eqs. (1) and (2) that $dP = dP_+$, $dU_{\text{mean}} = dU_{\text{mean}+}$ and $d\ln D = d\ln D_+$ during early systole (where the + subscript refers to a forward-running wave). Where reflected waves (i.e. backward components dP_- , $dU_{\text{mean}-}$ and $d\ln D_-$) are non-negligible, Eqs. (1) and (2) are no longer valid and hence Eq. (9) may not provide an accurate estimate of U_{mean} . To correct for wave reflection, we draw from the excellent work of Segers et al (Segers *et al.*, 2014) in which the effect of wave reflection on wave speed was quantified via the frequency-dependent coefficient β_k as follows

$$\beta_k = \sqrt{\frac{1}{\rho} \frac{P_k}{U_k} \frac{A_k}{Q_k}} \quad (10)$$

which has clear similarities to Eq. (3). Here, P_k , A_k , U_k and Q_k are the k -th sinusoidal harmonics of pressure, cross-sectional area, velocity and flow respectively (noting that $Q = AU$), and β_k is related to the frequency-dependent reflection coefficient (Γ_k) via

$$\beta_k = \frac{1 + \Gamma_k}{1 - \Gamma_k} \quad (11)$$

Although β_k is frequency-dependent, we take an average value over the first ten harmonics ($\text{mean}(\beta_{1-10}) \equiv \beta$) and exclude any harmonic values of β_k that can be reasonably deemed non-physiological, that is, values outside the range $0.3 < \beta_k < 4$ corresponding to the reflection coefficient range of $-0.54 < \Gamma_k < 0.6$.

In the presence of reflected waves (i.e. non-zero dP_- , $d \ln D_-$ and dU_-), the calculated value of α from Eq. (3) is

$$\alpha^2 = \frac{2 (dP_+ + dP_-)(d \ln D_+ + d \ln D_-)}{\rho (dU_{\text{raw}+} + dU_{\text{raw}-})^2} \quad (12)$$

Since $dP_- = \Gamma dP_+$, $d \ln D_- = \Gamma d \ln D_+$ and $dU_{\text{raw}-} = -\Gamma dU_{\text{raw}+}$,

$$\alpha^2 = \frac{2 dP_+ d \ln D_+}{\rho dU_{\text{raw}+}^2} \beta^2 \quad (13)$$

A hypothesized wave reflection-insensitive correction factor is therefore α/β , leading to an ‘ α/β -correction’ and a revised estimate of mean velocity,

$$U_{\text{mean},\alpha/\beta} = \frac{\alpha}{\beta} U_{\text{raw}} \quad (14)$$

This final α/β -corrected velocity ($U_{\text{mean},\alpha/\beta}$) accounts for scale errors in the acquired velocity signals (α), while compensating for the influence of reflected waves (β).

Figure 2 summarizes the procedure for correcting wave speed and velocity using the techniques described above, using an example from our patient MRI study described below.

Verification study using cardiac MRI

After approval from the Human Research Ethics Committee of the Royal Children's Hospital, forty-six patients undergoing routine clinical scans had PCMRI obtained from the ascending aorta at the level of the right pulmonary artery, taking care to ensure perpendicular alignment with the ascending aorta in two orthogonal planes. Patients with aortic stenosis were not included, as accurate cross-sectional flow assessment cannot be assured in this setting. Scans were performed on an Aera 1.5 Tesla MRI machine (Siemens, Erlangen, Germany) using a segmented 2D phase contrast gradient echo sequence, with a 320 mm field of view, 6 mm slice thickness, 3.38 ms echo time, flip angle of 20 degrees and a repetition time of 22.8 ms. Two segments were acquired per heart beat, with interleaved sampling giving a calculated temporal resolution of 128 phases per cardiac cycle. Right brachial blood pressure was recorded in triplicate with an MRI-compatible digital oscillometric monitor (HEM 705-CP, OMRON, Japan) using a cuff width that was greater than 40% of the upper arm circumference. Using in-house software, magnitude images were semi-automatically segmented to produce a cross-sectional area waveform. An effective diameter waveform was then calculated, along with maximum and mean velocity waveforms from the spatially integrated flow. Typical PCMRI-derived U and D waveforms are shown in Figure 2.

Central aortic systolic pressure was estimated by assuming that diameter and pressure waveforms have the same shape, with a linear two-point calibration of the aortic effective diameter waveform to mean and end-diastolic brachial pressures. This was based on the well-established principle that mean and end-diastolic pressures are relatively constant throughout the network of large arteries (Quail *et al.*, 2014; Pauca *et al.*, 2001; Van Bortel *et al.*, 2001); we also tested the impact of this assumption in the present study using the virtual cohort, as explained below. This pressure was then used to calculate wave speed via the PU and $\ln(D)P$ methods. The time period used for the linear regressions was manually selected as the most linear portion of the early-systolic relation. Wave speed was calculated with the PU and

ln(D)U loop methods using mean velocity ($c_{PU_{mean}}$ and $c_{ln(D)U_{mean}}$) and maximum velocity ($c_{PU_{raw}}$ and $c_{ln(D)U_{raw}}$). Subsequently, α and β were calculated from maximum velocity, pressure and diameter waveforms. Corrected wave speed ($c_{PU_{mean}} = c_{ln(D)P}$) was then calculated via α according to Eq. (5). The distensibility coefficient wave speed (c_{DC}) was also calculated with estimated central pulse pressure via Eq. (8). The maximum velocity waveform was scaled by α alone and also α/β and compared with the true mean velocity measured from PCMRI.

Verification study in a virtual cohort

A database of 3,325 virtual subjects has been recently created from a one-dimensional model of 55 major systemic arteries (Willemet *et al.*, 2015; Willemet *et al.*, 2016), with geometry based on the study of Stergiopoulos *et al* (1992). Details of the methodology and results have been published by Willemet *et al* (2015). Briefly, the virtual cohort was generated from a reference model by introducing variations in cardiac and arterial parameters within healthy ranges. This led to a diverse set of virtual subjects representing the normal spectrum of haemodynamic, structural and geometric arterial characteristics. For each virtual subject, blood pressure, flow, velocity and luminal area waveforms were calculated using the standard one-dimensional governing equations and an elastic pressure-area relation. This enabled comparison of true wave speed (see Equation 15 below) with the various estimation techniques described above, as in Willemet *et al* (2016). The start and end of the early systolic period were defined as 5% and 60% of the velocity upstroke for both the PU and ln(D)U loop methods. Reference wave speed (c_{ref}) was calculated from the prescribed arterial wall properties using the Moens-Korteweg equation,

$$c_{ref} = A_m^{1/4} \sqrt{\beta_w / (2\rho A_d)} \quad (15)$$

where A_m and A_d are the luminal cross-sectional areas at mean and diastolic pressure, respectively, and $\beta_w = 4/3 \sqrt{\pi E h}$ is a constant that accounts for the Young's modulus (E) and thickness (h) of the wall. The adopted elastic wall law neglects wall viscosity, hence wave speed is not frequency-dependent in this virtual cohort.

The virtual cohort was used to investigate the following questions related to wave speed estimation. First, even if mean velocity were measured perfectly, to what extent does wave reflection introduce error into $c_{PU_{mean}}$ and $c_{\ln(D)U_{mean}}$ at key vascular sites (ascending aorta and common carotid, brachial and femoral arteries)? Second, how are these errors affected when random scaling errors in the range -50% and $+150\%$ are introduced to velocity (which corresponds to the range of errors expected with Doppler ultrasound and/or use of maximum velocity)? Third, how robust is corrected wave speed (i.e. the $\ln(D)P$ method) to errors in pressure and diameter; in particular, what is the effect of (i) estimating pressure from local diameter via a linear two-point calibration to brachial mean and diastolic pressures and (ii) up to $\pm 20\%$ offset errors (i.e. constant biases) in diameter measurements? Note that any constant scale error (ϵ), i.e. error of diameter waveform amplitude, has no impact on $\ln(D)U$ or $\ln(D)P$ wave speed, since,

$$d \ln(\epsilon D) = \frac{1}{\epsilon D} d(\epsilon D) = \frac{1}{D} dD = d \ln D \quad (16)$$

Similar questions were then posed in relation to estimating mean velocity, namely (1) what is the effect of wave reflection on α -corrected velocity; (2) how accurately can U_{mean} be estimated from U_{raw} using the α and α/β corrections, where U_{raw} is a randomly scaled (-50% to $+150\%$) version of U_{mean} ; and (3) how much error is likely to be introduced to estimated U_{mean} when applying these techniques in practice, i.e. in the presence of diameter errors and when using of non-local (brachial) mean/diastolic blood pressure to estimate local pressure.

Statistical Analysis

Data were analyzed with repeated measures one-way analysis of variance using SPSS (version 20, IBM Inc.), with Levene's test to assess normality. The Pearson correlation coefficient (R) was used to compare wave speed from the loop methods with c_{DC} . Differences between wave speeds and velocities were assessed with paired t-tests when normally distributed, or Wilcoxon signed rank test for non-normal data where indicated. Results are reported as mean \pm SD, with significance taken at $P < 0.05$.

Results

Verification study using cardiac MRI

Of the 46 patients, 12 were excluded due to poor image contrast during the early systolic period, which precluded accurate segmentation. Of the remaining 34 patients, 21 (62%) were male and the mean age was 17.3 ± 5.1 years. Ten patients were normal and the remainder represented different patient groups (12 post-coarctation repair, 4 Turner syndrome, 3 Marfan syndrome, 3 post-Tetralogy of Fallot repair and 2 post-arterial switch).

When wave speed was assessed with measured U_{mean} , average $c_{PU_{mean}}$ and c_{DC} were not statistically different ($P = 0.5$), while $c_{ln(D)U_{mean}}$ overestimated c_{DC} by 0.78 ± 1.44 m/s ($P = 0.004$). When using maximum velocity waveforms, $c_{PU_{raw}}$ was $26\% \pm 16\%$ lower and $c_{ln(D)U_{raw}}$ was $67\% \pm 43\%$ higher than c_{DC} (both $P < 0.001$, Table 1 and Figure 3A), leading to an α correction factor of 0.68 ± 0.14 . Corrected wave speed (i.e. $c_{ln(D)P}$) was $8\% \pm 3\%$ greater than c_{DC} (2.64 ± 0.64 vs 2.45 ± 0.64 m/s, $P < 0.001$) and displayed the highest correlation coefficient with c_{DC} amongst the various methods ($R = 0.997$, Table 1).

The value of α/β was not different to the ratio of PCMRI mean and maximum velocities (0.63 ± 0.15 vs 0.61 ± 0.10 , $P = 0.46$). Aortic peak U_{raw} was 55.3 ± 20.9 cm/s higher than the peak U_{mean} ($P < 0.001$). This error was substantially reduced with α -correction

(10.0 ± 21.0 cm/s) and was further reduced ($P < 0.001$) with α/β -correction (2.9 ± 21.8 cm/s; Table 2 and Figure 3B).

Virtual cohort

Table 3 and Figure 4 display the relationship of wave speed calculated with the various methods to c_{ref} (Moens-Korteweg) at four arterial locations in the virtual cohort. c_{ref} differed from c_{DC} by less than 5% in all locations. When calculated from true U_{mean} , P and D (Figure 4, top), PU and $\ln(D)U$ loop methods correlated well with c_{ref} in the aortic root, although c_{PU} underestimated and $c_{\ln(D)U}$ overestimated c_{ref} . In more distal vessels, wave reflection caused c_{PU} to overestimate and $c_{\ln(D)U}$ method to underestimate c_{ref} by up to $54.8\% \pm 18.0\%$ and $-36.9\% \pm 6.7\%$ respectively (carotid artery). When a random velocity scaling error was introduced, a large spread of errors was evident for c_{PU} and $c_{\ln(D)U}$, whereas $c_{\ln(D)P}$ was unaffected (Figure 4, middle). Additionally introducing a random offset error in diameter (up to $\pm 20\%$) and estimating local pressure from the diameter waveform and brachial mean/diastolic pressures introduced only minor errors to $c_{\ln(D)P}$ (Table 3 and Figure 4, bottom).

Figure 5 and Table 4 outline the relationships between true and estimated peak U_{mean} in the virtual cohort. When true velocity, local pressure and diameter were used (i.e. no errors present in the raw data), applying α -correction or α/β -correction introduced some scatter and/or bias but maintained a good correlation with the reference velocity (all $R \geq 0.9$). Although the α -correction introduced substantial error to carotid velocity ($54.8\% \pm 18.0\%$), this was rectified with α/β -correction ($-1.8\% \pm 10.3\%$). A similar pattern also held true when random velocity scale errors were introduced (Figure 5, middle row), and when diameter offset errors were introduced and local pressure was estimated from local diameter and brachial mean/diastolic pressures (bottom row), with particular benefit of α/β -correction evident in the carotid and brachial arteries.

Discussion

The major findings of this study are that 1) use of maximum velocity or error-prone estimates of mean velocity, along with early-systolic wave reflection and errors in velocity acquisition common to routine vascular ultrasound, are likely to cause substantial errors in wave speed estimation via the PU or $\ln(D)U$ loop methods; 2) combining PU and $\ln(D)U$ loop wave speed expressions leads to the $\ln(D)P$ method that is analytically identical to the Bramwell-Hill equation and is unaffected by wave reflection and velocity errors; and 3) it is feasible to estimate a mean velocity waveform from a maximum velocity waveform (or indeed, any inaccurately scaled waveform) using diameter and pressure information, with scaling errors corrected by the α factor, and errors introduced by wave reflection corrected by the β factor. The proposed wave speed and mean velocity estimation techniques require a pressure waveform, but direct, non-invasive measurements of local pressure (e.g. in the aorta) may be difficult to obtain in practice. However, a key finding was that estimation of this waveform from a local diameter waveform calibrated to brachial cuff mean and diastolic pressures is a feasible, robust and relatively accurate alternative.

Wave speed calculation

'Single location' methods provide a local measure of arterial wave speed that is crucial for accurate assessment of wave reflection via wave separation analysis (Parker, 2009; Westerhof *et al.*, 1972). The PU and $\ln(D)U$ loop methods are commonly employed for such purposes, with U often derived from volumetric flow via cross-sectional area in experimental studies (Penny *et al.*, 2008; Hollander *et al.*, 2001; Feng and Khir, 2010). When seeking to apply these methods in humans, however, it is important to recognise that a mean velocity is required, whereas maximum velocity is routinely and most conveniently obtained from the Doppler spectral envelope. While maximum velocity has been used to calculate wave speed

in various arteries (Curtis *et al.*, 2007; Zambanini *et al.*, 2005), our data suggests this may lead to ~30% underestimation with the PU loop and ~70% overestimation with ln(D)U loop in the ascending aorta (Figure 3A). In theory, errors as great as 50% underestimation (PU loop) and 100% overestimation (ln(D)U loop) would be expected in the case of a parabolic velocity profile.

Another important source of error in single location wave speed calculations is wave reflection. In both fluid-structure interaction simulations of the carotid artery and patient measurements, Swillens *et al* (2013) found that the arrival of reflected waves in early systole leads to substantial overestimation of wave speed by the PU loop (8-9 m/s) and underestimation by the ln(D)U loop (3-4 m/s), compared with the reference value (~6 m/s), consistent with our findings in the virtual cohort (see Figure 4). This phenomenon was also predicted in other arteries by Alastruey (Alastruey, 2011) using a 1D model of the major systemic arteries, with the errors being eliminated in a well-matched arterial network. Even in a network with well-matched junctions, arterial tapering may also contribute to wave reflection and wave speed errors (Willemet *et al.*, 2016). Borlotti *et al* (Borlotti *et al.*, 2014) also showed that negative wave reflection causes opposite errors (underestimation for PU loop, overestimation for ln(D)U loop) to positive wave reflection. Importantly, a confounding effect of wave reflection may affect these single location methods even when a linear relation exists during early systole (Segers *et al.*, 2014; Swillens *et al.*, 2013; Mynard *et al.*, 2011).

Several methods have been proposed to improve the accuracy of single location wave speed estimates in the presence of wave reflection. Averaging values from the PU and ln(D)U loop method reduced, but did not eliminate, the error (Alastruey, 2011; Segers *et al.*, 2014). Segers *et al* (Segers *et al.*, 2014) overcame the effects of wave reflection by combining information from Fourier harmonic PU and QA loops, but noted that the requirement to measure pressure, velocity, flow and area was a limiting factor from a practical point of view.

We have shown for the first time that combining PU and ln(D)U loop equations leads to an expression of the well-known equation developed by Bramwell and Hill (Bramwell and Hill, 1922); the resulting ln(D)P loop method is insensitive to wave reflection and is velocity-independent. Note that Alastruey (Alastruey, 2011) also proposed a pressure-diameter based method (D²P), with wave speed calculated from the slope of pressure and the square of diameter during late diastole according to

$$c_{D^2P} = D_0 \sqrt{\frac{1}{\rho} \frac{dP}{dD^2}} \quad (17)$$

where D_0 is the mean arterial diameter. This is also an expression of the Bramwell-Hill equation and shares the same advantages as the ln(D)P method.

An important finding of this study is that, although calculation of wave speed via the Bramwell-Hill equation (whether in the form of $c_{\ln(D)P}$, c_{DC} or c_{D^2P}) requires measurement of pressure and diameter, acceptable errors are obtained in the aorta, carotid and femoral arteries even when (i) $\pm 20\%$ errors in diameter offset are present (while diameter scaling errors have no effect whatsoever, see Eq. (16)), and (ii) local pressure is estimated by calibrating the measured local diameter to brachial mean and diastolic pressures (Figure 4, bottom panels). The associated errors appear to be small compared with those likely to be caused by wave reflection and mean velocity error for the PU and ln(D)U loop methods.

The PU and ln(D)U loop methods are a popular choice for studies applying wave separation analysis and while the mathematical formulations of these methods are sound, they do rely on several key assumptions being satisfied, namely the use of mean velocity and the absence of reflected waves. These assumptions are not required for the Bramwell-Hill equation. Further work is needed to establish whether the use of Bramwell-Hill wave speed leads to more reliable assessment of arterial wave dynamics.

Mean velocity estimation

Non-invasive measurement of instantaneous mean velocity is challenging. Although sometimes calculated as flow divided by cross-sectional area with PCMRI, this modality is relatively expensive and is not used in all settings. Ultrasound-based methods have been reviewed elsewhere (Evans, 1985; Gill, 1985; Hoskins, 2011). Averaging the Doppler frequency shift in a large sample volume is subject to errors arising from non-uniform beam insonation, velocity profile dependence and beam misalignment (Hoskins, 2011); averaging inner and outer Doppler envelopes (Borlotti *et al.*, 2012) may also be subject to such errors and does not account for the distribution of velocities in the Doppler spectrum. Estimating mean velocity from maximum velocity and an assumed velocity profile (e.g. parabolic) may be inaccurate if the velocity profile differs from the assumed shape (Mynard and Steinman, 2013) and inherits substantial errors involved in estimating maximum velocity due to geometric spectral broadening (Hoskins, 2011; Hoskins, 1999) and operator dependence (Mikkonen *et al.*, 1996; Corriveau and Johnston, 2004).

A number of contemporary studies have acquired mean velocity from range-gated colour Doppler using the Aloka Prosound $\alpha 10$ system (Niki *et al.*, 2002; Harada *et al.*, 2002; Ohte *et al.*, 2003; Bleasdale *et al.*, 2003; Feng and Khir, 2010), but quantitative analysis of colour Doppler is not available on many commercial systems used in routine clinical practice. Although colour Doppler is a multi-gate approach that indicates the velocity profile on a 2D slice of the vessel, accuracy of the obtained mean velocity may be influenced by velocity profile skewing (Mynard and Steinman, 2013), finite sample volume size (Evans *et al.*, 1989), user dependence and/or incomplete coverage of the vessel diameter. For example, some investigators have sampled from approximately one half to two thirds of the vessel diameter (Ohte *et al.*, 2003; Liu *et al.*, 2010; Li and Guo, 2013), while others have used a range gate that is ‘as wide as possible’ but still neglects a substantial near-wall region (Niki *et*

al., 2002; Niki *et al.*, 2005; Takaya *et al.*, 2013); these approaches will overestimate mean velocity as lower velocities at the edge of vessels are ignored (Hoskins, 1999).

We have proposed a novel method that can be used to estimate mean velocity (or volumetric flow, by multiplication of cross-sectional area) from an acquired signal that contains an arbitrarily large scaling error. This method makes use of pressure and diameter information and may be used to convert from a maximum velocity to a mean velocity via the factor α/β . The correction factor α , derived from the PU and $\ln(D)U$ loop wave speed equations, eliminates scaling errors in estimated U_{mean} , which may arise from acquisition of maximum velocity and/or common sources of measurement error (Mynard and Steinman, 2013; Winkler *et al.*, 1995; Hoskins, 2011; Corriveau and Johnston, 2004; Mikkonen *et al.*, 1996; Cobbold, 2006). The second correction factor β , introduced to counteract the effect of proximal wave reflections, was based on recent work by Segers *et al.* (Segers *et al.*, 2014) that made use of Fourier decomposition to correct loop-based wave speed estimates for wave reflection; our work extended this theory to estimation of mean velocity.

In our clinical data, the use of α -correction alone in the ascending aorta reduced the error in measured velocity to near-acceptable levels (from 71% to 15%), suggesting only a small influence of wave reflection. Nevertheless, α/β -correction led to a statistically significant additional reduction of the error (15% to 5%). However, the inclusion of β resulted in more substantial improvements in the carotid and brachial arteries of the virtual cohort, where proximal wave reflections were more prevalent (see Figure 5 and Table 3).

The velocity correction methods described have some limitations. Scaling of a peak velocity waveform to yield a mean velocity waveform assumes that these waveforms have the same shape. Although a reasonable approximation under many circumstances, particularly during the systolic flow upstroke, this assumption may be less accurate if extreme velocity profile skewing is present, as may occur in highly curved vessels or in some

disease conditions (e.g. aortic stenosis) (Mynard and Steinman, 2013). Correction of velocity also requires measurement of a diameter waveform, and as such poor-quality imaging of the vessel wall or imaging of very stiff vessels may limit the accuracy of this method. While the gold-standard ultrasound-based method for this purpose is radio-frequency echo-tracking (Hoeks *et al.*, 1990), this technique is not widely available in commercial systems. The accuracy of other more accessible methods (e.g. based on M-mode or B-mode imaging) requires further investigation. Finally, the Bramwell-Hill equation does not account for viscoelastic effects, which lead to a frequency-dependent wave speed. Future studies should investigate the impact of viscoelastic effects, as well as the pressure-dependence of arterial stiffness.

Conclusion

Assessment of local wave speed non-invasively with PU and ln(D)U loop methods is challenging due to the need for accurate acquisition of the mean velocity waveform and an absence of wave reflection during early systole. While maximum velocity from the Doppler spectral envelope is easily obtainable with commercial ultrasound systems, this should not be used to calculate wave speed with the loop methods. Instead, ln(D)P (i.e. Bramwell-Hill equation) is substantially more accurate and robust, being insensitive to velocity errors and wave reflection. Although a local measurement of pressure is preferred, estimation of local pressure from the local diameter calibrated to brachial mean/diastolic pressures results in acceptable errors, thus enabling a fully non-invasive investigation. Finally, a mean velocity waveform can be estimated from a velocity signal that contains any form of scaling error, as may arise from use of maximum velocity and/or from various measurement errors, via two correction factors (α and β) derived from pressure and diameter information. Volumetric flow may also be estimated once mean velocity and diameter are known. These findings constitute an important advancement towards robust and practical application of state-of-the-art

haemodynamic analysis techniques (e.g. wave separation and wave intensity analysis) with widely-available clinical equipment.

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Disclosures

None.

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Figure Captions

Figure 1. Typical velocity spectrum obtained from Doppler ultrasound. In this paper, ‘mean’ velocity (U_{mean}) refers to the cross-sectionally averaged velocity waveform, ‘maximum’ velocity (U_{raw}) refers to the instantaneous maximum velocity within the vessel lumen (which may be subject to measurement errors) and ‘peak’ velocity refers to the highest (mean or maximum) velocity value during the cardiac cycle.

Figure 2. General schema for calculating wave speed and mean velocity, with an example taken from ascending aortic MRI. When a measured velocity waveform (U_{raw}) contains a scale error, associated errors are introduced to wave speed calculated via the pressure-velocity (c_{PUraw}) and diameter-velocity ($c_{\text{ln(D)Uraw}}$) loop methods; corrected wave speed ($c_{\text{ln(D)P}}$) is insensitive to velocity errors and wave reflection. Calculation of α via the inaccurate c_{PUraw} and $c_{\text{ln(D)Uraw}}$ as well as the β factor, enables an estimate of mean velocity ($U_{\text{mean},\alpha/\beta}$) to be derived from U_{raw} . True mean velocity (U_{mean}) is shown for reference. Local pressure (P) may be measured or estimated non-invasively from diameter calibrated to brachial mean and diastolic pressures.

Figure 3. (A) (A) Mean (SD) percentage errors in wave speed calculated from maximum velocity with the PU and ln(D)U loop methods and via the velocity-independent ln(D)P method, where errors are with respect to wave speed calculated via the distensibility coefficient (c_{DC}). (B) Errors in peak maximum velocity (peak U_{raw}), α -corrected velocity and α/β -corrected velocity, compared with measured peak U_{mean} . (C,D) Corresponding Bland-Altman plots showing individual data points, mean values as horizontal lines and standard deviation as vertical bars. ** Maximum velocity was greater than both α and α/β -corrected velocity ($P < 0.001$).

Figure 4. Errors in wave speed estimated from the PU, ln(D)U and ln(D)P methods at four arterial locations in the virtual cohort. In the top row, wave speed was calculated using the true local mean velocity, pressure and/or diameter. In the middle row, a random velocity scale error (between -50% and $+150\%$) was introduced. In the bottom row, a random offset error (up to $\pm 20\%$) in diameter was also introduced and local blood pressure was estimated from the local diameter waveform calibrated to brachial systolic and diastole pressure. Dashed lines are lines of unity. Reference wave speed (c_{ref}) is calculated from the Moens-Korteweg equation via the known local area, Young's modulus and wall thickness of the vessel (see Equation (15)). Horizontal and vertical lines indicate the mean and standard deviation of the error respectively.

Figure 5. Estimated peak mean velocity (peak $U_{mean,est}$) versus the reference (i.e. true) values (peak U_{mean}) in the virtual cohort. Blue dots correspond to uncorrected velocities, orange dots to velocities corrected via the α factor (correction of velocity errors), and black dots to velocities further corrected via the β factor (correction for wave reflection). Top, middle and bottom rows are as in Fig. 4. Note that, in the top row, perfectly accurate recordings of mean velocity are assumed, hence 'uncorrected' velocities are equal to the true velocities. Horizontal and vertical lines indicate the mean and standard deviation of the error respectively. Note that X-axis scales differ with location.

Table 1. Comparison of aortic wave speed methods with Bramwell-Hill (MRI data, n = 34)

	Wave speed (c), m/s	Error, m/s	Regression Equation (R)
Bramwell-Hill (c_{DC})	2.45±0.64	-	-
PU_{mean}	2.35±0.81	-0.10±0.69	0.72x + 0.58 (0.57) [#]
$\ln(D)U_{mean}$	3.23±1.81	0.78±1.44 [*]	1.96x - 1.57 (0.70) [#]
PU_{raw}	1.81±0.62	-0.64±0.49 [*]	0.68x + 0.14 (0.70) [#]
$\ln(D)U_{raw}$	4.08±1.60	1.63±1.26 ^{*†}	1.71x - 0.12 (0.69) [#]
$\ln(D)P$	2.64±0.64	0.19±0.05 [*]	0.99x + 0.2 (0.99) [#]

Data are mean±SD. ^{*} $P < 0.01$ for difference with c_{DC} , [#] $P < 0.001$ for linear relationship c_{DC} . [†] Tested with

Wilcoxon signed rank test due to non-normal distribution. Data presented as mean ± standard deviation.

DC = distensibility coefficient; D = diameter; P = pressure; U_{mean} = mean velocity; U_{raw} = maximum velocity

Table 2. Comparison of velocity scaling methods with human aortic mean velocity MRI data (n=34)

	Peak Velocity, cm/s	Error, cm/s	Regression Equation (R)
U_{mean}	85.3±24.0	-	-
U_{raw}	140.6±31.3	55.3±20.9*	0.97x + 58 (0.74) [#]
$U_{\text{mean},\alpha}$	95.3±27.5	10.0±20.4*	0.79x + 27.5 (0.69) [#]
$U_{\text{mean},\alpha/\beta}$	88.2±30.1	2.9±21.8	0.87x + 13.7 (0.70) [#]

Data are mean±SD. * $P < 0.01$ for difference compared with U_{mean} ; [#] $P < 0.001$ for linear relationship U_{mean} ; U_{mean} = mean velocity; U_{raw} = maximum velocity; $U_{\text{mean},\alpha}$ = α -corrected velocity; $U_{\text{mean},\alpha/\beta}$ = α/β -corrected. Data presented as mean ± standard deviation.

Table 3. Wave speed estimation in the virtual cohort ($n=3325$)

	Aortic Root	Carotid Artery	Brachial Artery	Femoral Artery
c_{ref} (m/s)	5.70 ± 2.12	7.76 ± 1.36	8.82 ± 1.54	12.37 ± 2.15
<i>Wave speed errors (cm/s) when using true U, P, D</i>				
c_{DC}	$-0.27 \pm 0.08^*$	$-0.23 \pm 0.07^*$	$-0.22 \pm 0.06^*$	$-0.19 \pm 0.04^*$
PU loop	$-0.88 \pm 0.52^*$	$4.48 \pm 2.2^*$	$1.30 \pm 0.61^*$	$2.02 \pm 0.62^*$
ln(D)U loop	$0.76 \pm 0.67^*$	$-2.9 \pm 1.02^*$	$-1.31 \pm 0.49^*$	$-1.90 \pm 0.50^*$
ln(D)P loop	$-0.14 \pm 0.03^*$	$-0.13 \pm 0.03^*$	$-0.11 \pm 0.02^*$	$-0.10 \pm 0.01^*$
<i>Wave speed errors (cm/s) after U scale error applied (-50% to 150%)</i>				
c_{DC}	$-0.27 \pm 0.08^*$	$-0.23 \pm 0.07^*$	$-0.22 \pm 0.06^*$	$-0.19 \pm 0.04^*$
PU loop	$-2.05 \pm 2.43^*$	$2.11 \pm 5.21^*$	$-0.61 \pm 4.11^*$	$-0.70 \pm 5.90^*$
ln(D)U loop	$4.52 \pm 4.77^*$	$-0.56 \pm 2.92^*$	$2.39 \pm 4.39^*$	$3.33 \pm 6.25^*$
ln(D)P loop	$-0.14 \pm 0.03^*$	$-0.13 \pm 0.03^*$	$-11 \pm 0.02^*$	$-0.10 \pm 0.01^*$
<i>Wave speed errors (cm/s) after U scale error (-50% to 150%) and D offset error (-20% to +20%) applied, and P estimated from calibrated diameter</i>				
c_{DC}	-0.00 ± 0.16	$-0.09 \pm 0.11^*$	$-0.22 \pm 0.06^*$	$-0.57 \pm 0.20^*$
PU loop	$-1.59 \pm 2.59^*$	$2.60 \pm 5.50^*$	$-0.61 \pm 4.06^*$	$-1.27 \pm 5.7^*$
ln(D)U loop	$4.36 \pm 4.68^*$	$-0.61 \pm 2.96^*$	$2.42 \pm 4.55^*$	$3.23 \pm 6.43^*$
ln(D)P loop	$0.14 \pm 0.11^*$	$0.01 \pm 0.07^*$	$-0.11 \pm 0.02^*$	$-0.49 \pm 0.22^*$

* $P < 0.001$ for difference compared with c_{ref} . All errors are with respect to reference wave speed (c_{ref}), as defined in the Methods section. Data presented as mean \pm standard deviation. c_{DC} is wave speed calculated via the distensibility coefficient using Equation (8).

Table 4. Estimation of peak U_{mean} in the virtual cohort ($n=3325$)

	Aortic Root	Carotid Artery	Brachial Artery	Femoral Artery
Peak U_{mean} (cm/s)	49.5 ± 16.1	23.4 ± 6.6	47.2 ± 12.2	42.6 ± 9.1
<i>Peak U_{mean} errors (cm/s) when using true U, P, D</i>				
α	-6.4 ± 4.0*	12.9 ± 3.9*	7.2 ± 2.3*	7.3 ± 2.2*
α/β -corrected	-10.0 ± 3.8*	-0.6 ± 2.5*	0.3 ± 1.7*	3.8 ± 3.9*
<i>Peak U_{mean} errors (cm/s) after U scale error applied (-50% to 150%)</i>				
Uncorrected	25.3 ± 30.8*	11.5 ± 14.3*	23.2 ± 29.1*	21.2 ± 25.8*
α -corrected	-6.4 ± 4.0*	12.9 ± 3.9*	7.2 ± 2.3*	7.3 ± 2.2*
α/β -corrected	-10.0 ± 3.8*	-0.6 ± 2.5*	0.3 ± 1.7*	3.8 ± 3.9*
<i>Peak U_{mean} errors (cm/s) after U scale error (-50% to 150%) and D offset error (-20% to +20%) applied, and P estimated from calibrated diameter</i>				
Uncorrected	24.8 ± 31.0*	11.2 ± 14.3*	23.2 ± 29.3*	20.6 ± 26.0*
α -corrected	-4.2 ± 4.2*	13.8 ± 4.4*	7.4 ± 4.0*	6.0 ± 3.9*
α/β -corrected	-8.0 ± 4.8*	0.0 ± 2.9	0.5 ± 3.5*	2.6 ± 4.8*

* $P < 0.001$ difference compared with true peak U_{mean} . Data presented as mean ± standard deviation.

Corresponding scatter plots are shown in Figure 5.

Figure 1. Typical velocity spectrum obtained from Doppler ultrasound. In this paper, ‘mean’ velocity (U_{mean}) refers to the cross-sectionally averaged velocity waveform, ‘maximum’ velocity (U_{raw}) refers to the instantaneous maximum velocity within the vessel lumen (which may be subject to measurement errors) and ‘peak’ velocity refers to the highest (mean or maximum) velocity value during the cardiac cycle.

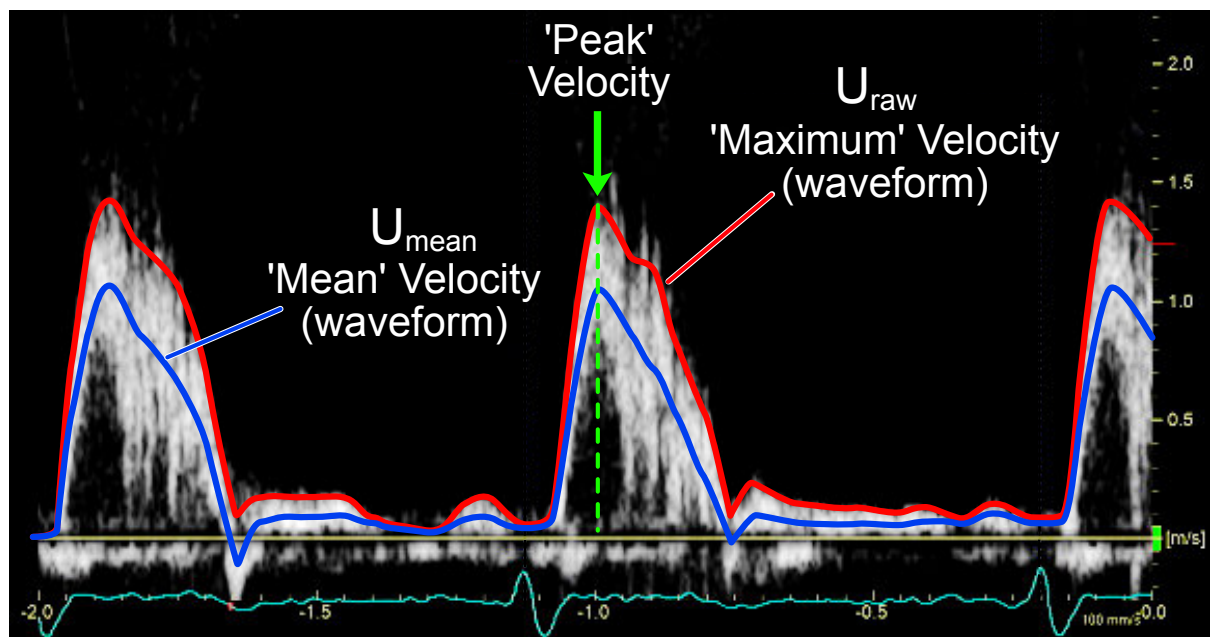


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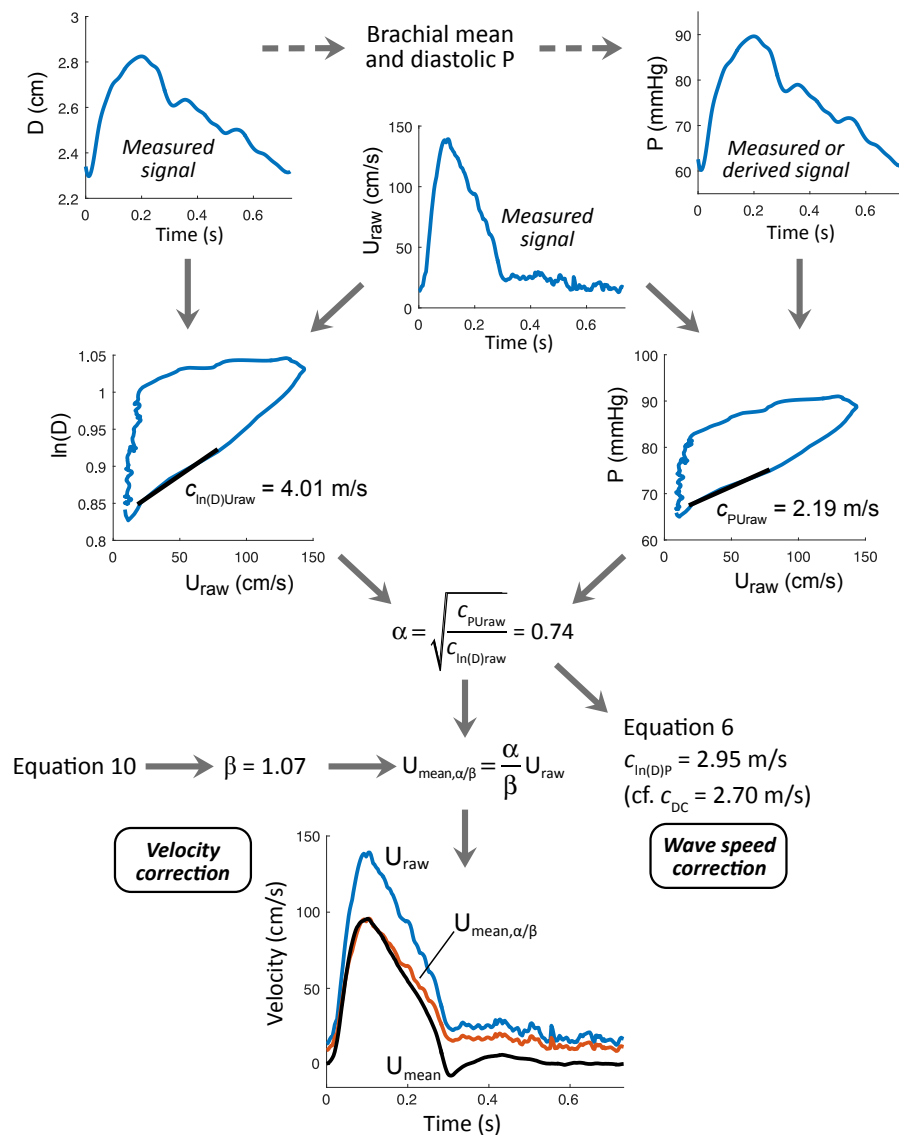


Figure 3. (A) Mean (SD) percentage errors in wave speed calculated from maximum velocity with the PU_{raw} and $\ln(D)U_{raw}$ methods and via the velocity-independent $\ln(D)P$ method, where errors are with respect to wave speed calculated via the distensibility coefficient (c_{DC}). (B) Errors in peak maximum velocity (peak U_{raw}), α -corrected velocity and α/β -corrected velocity, compared with measured peak U_{mean} . (C,D) Corresponding Bland-Altman plots showing individual data points, mean values as horizontal lines and standard deviation as vertical bars. ** Maximum velocity was greater than both α and α/β -corrected velocity ($P < 0.001$).

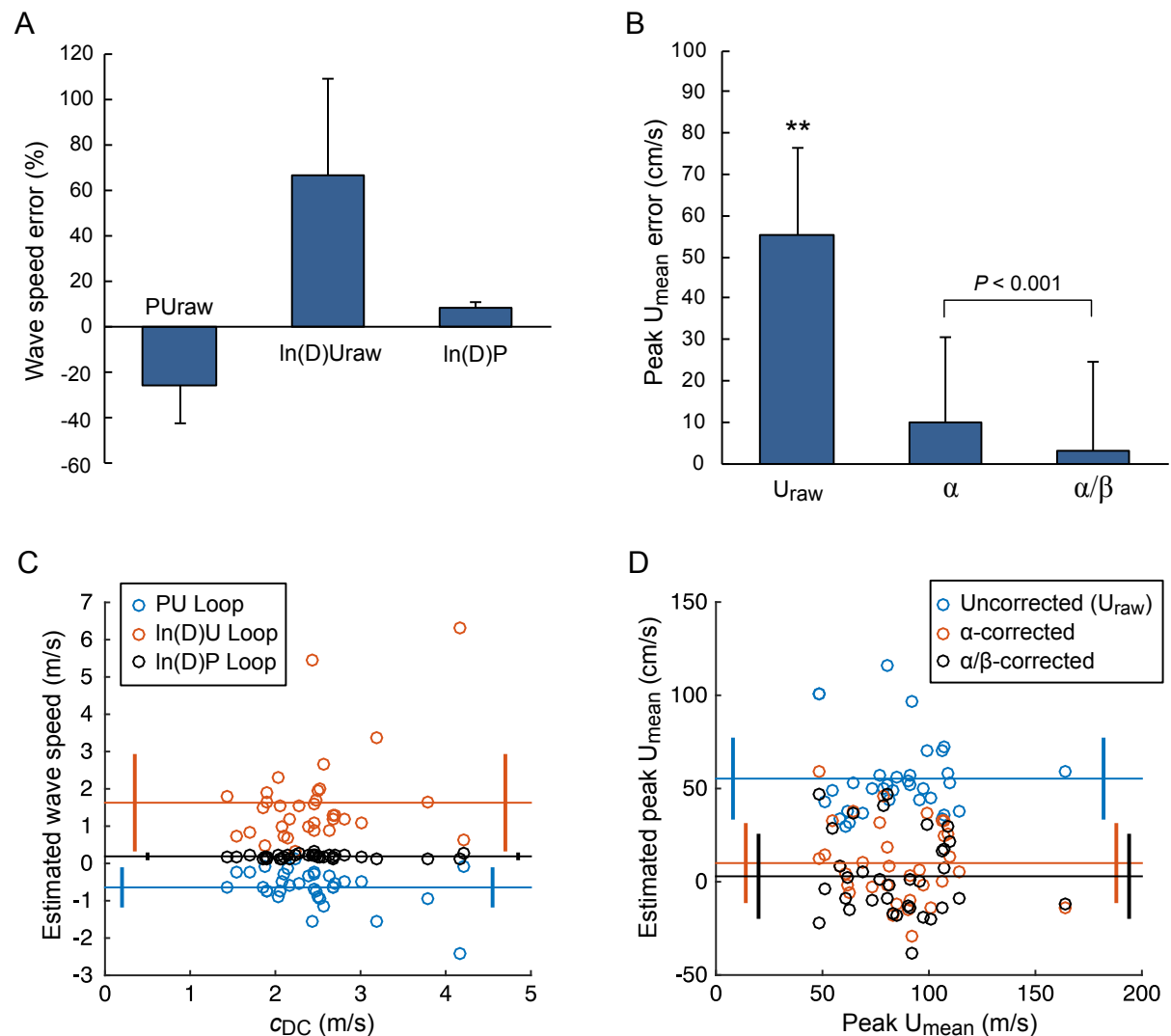


Figure 4. Errors in wave speed estimated from the PU, ln(D)U and ln(D)P methods at four arterial locations in the virtual cohort. In the top row, wave speed was calculated using the true local mean velocity, pressure and/or diameter. In the middle row, a random velocity scale error (between -50% and $+150\%$) was introduced. In the bottom row, a random offset error (up to $\pm 20\%$) in diameter was also introduced and local blood pressure was estimated from the local diameter waveform calibrated to brachial systolic and diastole pressure. Dashed lines are lines of unity. Reference wave speed (c_{ref}) is calculated from the Moens-Korteweg equation via the known local area, Young's modulus and wall thickness of the vessel (see Equation (15)). Horizontal and vertical lines indicate the mean and standard deviation of the error respectively.

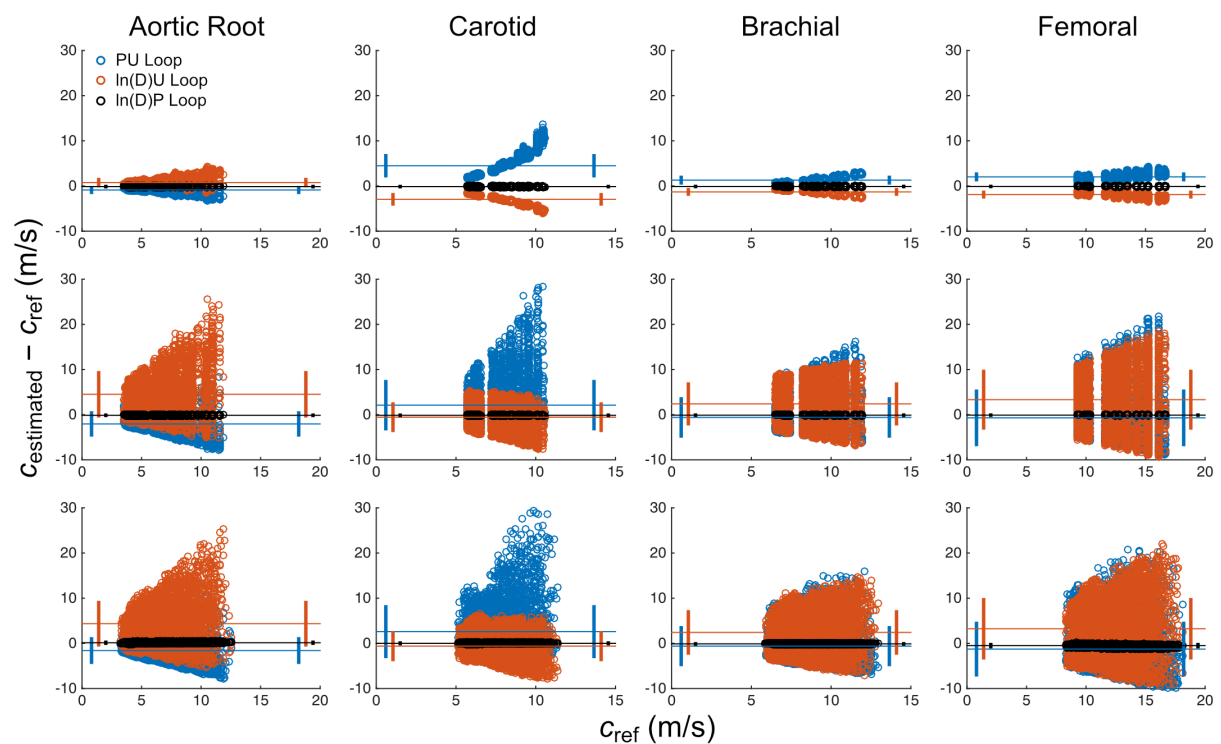


Figure 5. Estimated peak mean velocity (peak $U_{\text{mean,est}}$) versus the reference (i.e. true) values (peak U_{mean}) in the virtual cohort. Blue dots correspond to uncorrected velocities, orange dots to velocities corrected via the α factor (correction of velocity errors), and black dots to velocities further corrected via the β factor (correction for wave reflection). Top, middle and bottom rows are as in Fig. 4. Note that, in the top row, perfectly accurate recordings of mean velocity are assumed, hence ‘uncorrected’ velocities are equal to the true velocities. Horizontal and vertical lines indicate the mean and standard deviation of the error respectively. Note that X-axis scales differ with location.

