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1 Reproducibility of Atrial Fibrosis Assessment using Cardiac Magnetic 2 Resonance Imaging and an Open Source Platform

3 **Sim et al.** Atrial Late Gadolinium Enhancement Reproducibility

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5 Iain Sim^a, Orod Razeghi^a, Rashed Karim^a, Henry Chubb^a, John Whitaker^a, Louisa O’Neill^a, Rahul K
6 Mukherjee^a, Caroline H Roney^a, Henry Chubb, Reza Razavi^a, Matthew Wright^b, Mark O’Neill^{a,b}, Steven
7 Niederer^a and Steven E. Williams^a

8
9 ^a Division of Imaging Sciences and Biomedical Engineering, King’s College London, United Kingdom

10 ^b Cardiology Department, St. Thomas’ Hospital, London, United Kingdom

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14 **Address for correspondence:** Dr. S E Williams, Division of Imaging Sciences and Biomedical Engineering,
15 King's College London, 4th Floor North Wing, St. Thomas’ Hospital, 249 Westminster Bridge Road,
16 London, SE1 7EH; steven.e.williams@kcl.ac.uk; telephone 020 7188 7188; fax 020 7188 5442

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1 Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) imaging is the only available
2 tool for non-invasive assessment of atrial fibrosis, a key component of structural remodelling in atrial
3 fibrillation. LGE imaging can be used to refine the selection of patients for catheter ablation of AF and
4 to predict the likelihood of recurrence of atrial fibrillation following intervention. However, clinical
5 implementation of atrial LGE imaging has not become widespread, in part due to a lack of
6 standardisation of image processing techniques and varying reports of reproducibility(1,2).

7 We have created and tested semi-automatic software for the assessment of atrial fibrosis using LGE
8 CMR imaging. The CEMRG (Cardiac Electro-Mechanics Research Group) application uses the MIRTk
9 toolkit and is published online at www.cemrg.com. It is free to download, includes an operating
10 protocol for image segmentation and a troubleshooting manual; providing a toolkit for other centres
11 to be able to reproduce our methods.

12 The reproducibility of this software was evaluated in 3 groups of patients, 20 non-AF controls, 20 pre-
13 ablation AF patients and 20 post-ablation AF patients. CMR imaging was performed on 1.5T scanners
14 (Ingenia, Philips Healthcare, Netherlands and Magnetom Aera, Siemens, Germany). The full scanning
15 parameters have been previously published(3). Initially, each scan was analysed by two observers, and
16 categorised into groups of “severe”, “moderate”, “mild” and “none” based on a visual assessment of
17 atrial fibrosis. Then, each scan was analysed independently by two trained operators to calculate inter-
18 observer reproducibility. One operator repeated the analysis, to test intra-observer reproducibility.

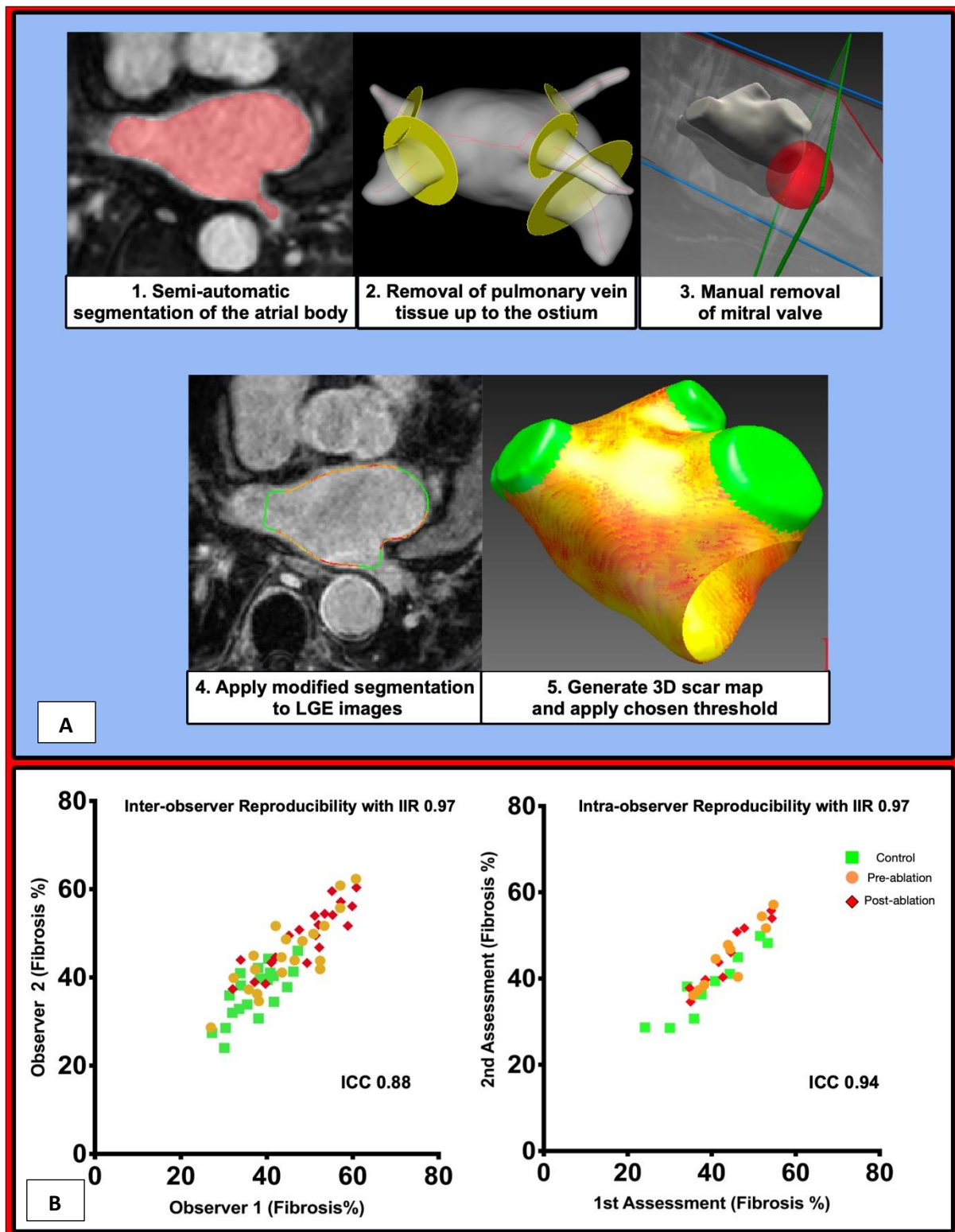
19 Global fibrosis burdens were calculated using predetermined and previously-published thresholds:
20 image intensity ratio (IIR) of 0.97, IIR 1.61 and mean blood pool signal +3.3SD. Intraclass correlation
21 coefficients (ICC) for interobserver reproducibility for each of these thresholds was excellent (ICC= 0.88,
22 0.99, 0.96, respectively), as was the intra-observer reproducibility (ICC=0.93, 0.90, 0.82 respectively)
23 (Figure 1B). The visual assessment showed limited interobserver reproducibility ($r=0.3$), though the
24 correlation between consensus visual assessment and global burden fibrosis was good ($r=0.72$).

25 Using the IIR 0.97 threshold, fibrosis burdens of pre-ablation (mean $45.1\pm 8.4\%$) and post-ablation
26 (mean $49.0\pm 7.5\%$) patients were significantly greater than control patients (mean $36.9\pm 5.3\%$, $P=0.02$
27 and $P<0.01$, respectively). In contrast, the IIR 1.61 threshold showed significant differences between
28 post-ablation and control patients ($P<0.05$); but no significant difference between pre-ablation and
29 control patients ($P>0.9$).

30 We aimed to improve the transparency and reproducibility of left atrial CMR LGE image analysis.
31 However, important limitations should be noted. Firstly, the software does not negate the need for

1 high-quality imaging and care must be taken to minimise motion and respiratory navigator artefacts.
2 Secondly, although the thresholds used here have previously been correlated with invasive
3 measurements of atrial fibrosis and arrhythmia recurrence(4), the use of an IIR threshold <1 with this
4 workflow may explain the high fibrosis burdens noted within the control group. Finally, although
5 automation of image processing improves reproducibility, it may limit accuracy, and quality control
6 steps will be essential in any processes implementing this software.

7 The quantification of atrial fibrosis with LGE CMR imaging, using this open-source software together
8 with specific analysis methods and objective thresholds is highly reproducible. This reproducibility holds
9 both between separate observers, and by the same observer on two occasions; and is greater than the
10 reproducibility of visual assessment of CMR-defined fibrosis. It is only by first showing reproducibility,
11 that the accuracy and utility of LGE CMR imaging can be proven and clinician confidence in the results
12 improved. The low number of centres using atrial CMR imaging is a significant limitation for research in
13 this area and, in allowing other centres to use and contribute to further development of this software,
14 a substantial barrier to entry into atrial fibrosis imaging is removed.



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2 Figure 1. **A**. Steps for image segmentation of fibrosis, a detailed protocol can be found online at
 3 www.cemrg.com. **B** Scatter plots for inter and intra-observer reproducibility are shown when using the
 4 IIR 0.97 threshold. Intraclass correlation coefficients are shown in the bottom right of each box.

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