54.8% of first time ICD recipients were candidates for S-ICD.¹

REFERENCE
Cardiac CT assessment of tissue thickness at the ostium of the left atrial appendage predicts acute success of radiofrequency ablation

Short title: Whitaker, LAA tissue thickness from CT

Authors:

John Whitaker* MB BCh MRCP, Sandeep Panikker* MBBS MRCP, Thomas Fastl* MSc, Cesare Corrado* PhD, Renu Virmani† MD, Robert Kutys‡ MS PA, Eric Lim† MBBS MRCP, Mark O’Neill* DPHIL FRCP FHRS, Ed Nicol* MD MBA FRCP, Steven Niederer* PhD and Tom Wong* MD FRCP FHRS.

John Whitaker and Sandeep Panikker contributed equally to the preparation of this manuscript

Affiliations:

* Division of Imaging Sciences and Biomedical Engineering King’s College London, St Thomas’ Hospital, London, United Kingdom
+ Heart Rhythm Centre, National Institute for Health Research (NIHR) Cardiovascular Research Unit, Imperial College, Royal Brompton and Harefield Hospitals, London, United Kingdom
† CV Path Institute, Gaithersburg, MD, United States of America
§ Department of Cardiology, National Heart Centre Singapore, Singapore

Correspondence to Tom Wong, MD, Heart Rhythm Centre, Royal Brompton and Harefield Hospitals, Sydney St, London SW3 6NP, United Kingdom. E-mail tom.wong@imperial.ac.uk

Phone: +44 20 7351 8619
Fax: +44 20 7351 8629

Funding Sources:

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pace.13203.

This article is protected by copyright. All rights reserved.
John Whitaker is a Medical Research Council Clinical Research Training Fellow (grant code MR/N001877/1).

This study was funded by the Boston Scientific Investigator Sponsored Research Study Program and supported by the NIHR Cardiovascular Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, the Medical Research Council (MRC) (UK) and the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the MRC, the NIHR or the Department of Health.

Seg3D is an Open Source software project that is principally funded through the SCI Institute’s NIH/NIGMS CIBC Center.

This project was supported by the National Institute of General Medical Sciences of the National Institutes of Health under grant number P41 GM103545-18.

Financial Disclosures: Dr Panikker has received a research grant from Boston Scientific. Dr Virmani is a consultant for Abbott Vascular, Medtronic, 480 Biomedical and W.L. Gore; has speaking engagements with Merck and receives honoraria from Abbott Vascular, Boston Scientific, C.R. Bard, Medtronic, Micropor Medical, OrbusNeich Medical, 480 Biomedical, and Terumo Corporation. The other authors report no conflicts.

Word count: 4792 words
ABSTRACT

**Background:** Tissue thickness at the site of ablation is a determinant of lesion transmurality. We reported the feasibility, safety and efficacy of long-standing persistent atrial fibrillation (PsAF) ablation, incorporating deliberate LAA isolation and occlusion and identified systematic differences in ostial LAA tissue thickness in a matched cohort of cadaveric specimens.

**Methods:** Pre-procedural CCT scans were acquired from 22 patients undergoing LAA isolation and subsequent occlusion. Using a novel CCT wall thickness algorithm, LAA ostial wall thickness was assessed *in vivo*, compared with measurements from the cadaveric specimens and analysed for differences between regions that demonstrated acute electrical reconnection and those that did not.

**Results:** Mean tissue thickness calculated for each LAA ostial quadrant was 2.1(+/-0.6)mm (anterior quadrant), 1.9(+/-0.4)mm (superior quadrant), 1.5(+/-0.4)mm (posterior quadrant) and 1.8(+/-0.7)mm (inferior quadrant). Tissue was significantly thicker in the anterior (p=0.004) and superior quadrants (p=0.014) than the posterior quadrant. Higher thickness measurements were recorded from quadrants demonstrated to be thicker from histology. Tissue was significantly thicker in regions that demonstrated acute electrical reconnection (1.9(+/-0.6)mm) when compared with those that did not (1.6(+/-0.5)mm) (p=0.008).

**Conclusions:** CCT imaging may be used to detect differences in wall thickness at different atrial locations and success of LAA ablation may be affected by local tissue thickness. Atrial wall thickness may need to be considered as a metric to guide titration of radiofrequency (RF) energy for safe and successful ablation.

**Clinical trial registration:** URL: https://clinicaltrials.gov. Unique identifier: NCT02028130
Key words: Atrial wall thickness, cardiac computed tomography (CCT), catheter ablation, left atrial appendage
INTRODUCTION

Catheter ablation is an effective treatment for symptomatic drug refractory paroxysmal and persistent atrial fibrillation (AF) and in certain circumstances may be offered as a first line treatment. Pre-ablation imaging is increasingly used, however attempts to validate imaging results using direct comparison with tissue measurements have rarely been made. One reason for AF recurrence is a failure to achieve durable isolation of regions targeted at the time of intervention, which may be related to tissue thickness at the ablation site.

The feasibility, safety and efficacy of long-standing PsAF ablation, incorporating deliberate left atrial appendage (LAA) isolation and occlusion has recently been demonstrated. In this study we assessed atrial wall thickness from pre-procedural cardiac computed tomography (CCT) and compared it with direct measurement of wall thickness from a matched sample of cadaveric specimens. Using these wall thickness measurements, we investigated whether LAA tissue thickness contributed to acute electrical reconnection of the LAA following its ostial isolation by radiofrequency (RF) ablation.

Methods

Clinical: The research study protocol was approved by the regional ethics committee and conformed to the Declaration of Helsinki. This study enrolled 22 patients with long-standing PsAF planned for ablation. All procedures were performed after obtaining written informed consent. Prior to ablation patients underwent contrast-enhanced CCT to assess left atrial appendage anatomy and exclude thrombus. Patients subsequently underwent wide area circumferential pulmonary vein isolation and linear ablation at the left atrial roof, lateral mitral valve isthmus (MVI) and cavitricuspid isthmus (CTI) under general anaesthetic following transesophageal echocardiography (TEE). LAA electrical isolation was also performed with ablation confined to the atrial side of the LAA ostium. In addition ablation was performed at the left superior pulmonary vein (LSPV)-LAA ridge on both the pulmonary venous and LAA sides. Catheter ablation procedures were guided by a 20-pole circular mapping catheter (Lasso, Biosense Webster, Diamond bar, CA), 3-dimensional electro-anatomical mapping system.
(EAMS) (CARTO 3, Biosense Webster) and standard electrophysiological recording (LabSystem Pro, Bard, Lowell, MA) systems. Ablation was performed with an open-irrigated 3.5mm tip ablation catheter (SmartTouch Thermocool, Biosense Webster). Target contact force was 15 to 20 grams (g) with power limited to 35W for the atrial side of the LAA ostium. Following electrical isolation, confirmed by demonstration of entrance and exit block using a circumferential mapping catheter within the LAA, a 60 minute waiting period was observed following which electrical isolation was reassessed with adenosine provocation. In the case of left atrium (LA)-to-LAA reconnection, the site of conduction recovery was defined according to the earliest electrogram observed on the circumferential mapping catheter and further ablation performed until it was re-isolated. Following completion of ablation the LAA was occluded using a Watchman percutaneous occlusion device.

**Cardiac Computed Tomography:** All patients were scanned using a Siemens Somatom Definition Flash Dual Source CT (Siemens, Forchheim, Germany). A high-pitch helical prospective acquisition was performed starting 1cm above the carina and extending to the apex of the heart. Acquisition started from approximately 60% of the R-R interval and continued until the end of the scan length, with breath held in expiration. The standard scan was performed using a test bolus technique for scan timing. A delayed scan was performed 60s following the beginning of the standard scan to allow contrast equilibration within the blood pool and involved a further acquisition from 1cm above carina and extending 40mm to cover the LAA. Exposure parameters were adjusted according to patient size. Scans were performed at 80kV and 400 quality referenced mAs (body mass index (BMI) < 20kg/m²), 100kV (300mAs) or 120kV (200mAs) (BMI > 30kg/m²). Images were reconstructed using filtered back-projection at 0.75mm slice width, 0.5mm slice increment. A total of 95mls of contrast was administered at 5/6 millilitres per second (ml/s) for 20g/18g cannula respectively, and according to the following protocol: 15ml contrast (test bolus; 5-6ml/s); 40mls saline (5-6ml/s); pause; 50mls contrast (5-6ml/s); 50mls contrast & saline (mixed at a ratio of 1:1; 5-6ml/s); 25ml saline (5ml/s). The overall median (range) radiation dose for this protocol is 3.5mSv (2.1 – 5.2mSv),
with a dose-length product of 251 mGycm (150 – 374 mGycm).

**Cardiac Computed Tomography analysis:** All CCT analysis was performed by a single reader blinded to the electrophysiology procedural data. Using a previously validated technique, CCT scans were processed to generate three-dimensional maps of tissue thickness across the LA. The process generated a segmentation of the atrial wall, which was then processed to calculate wall thickness (see figure 1 and data supplement). The segmentation of the atrial wall was reviewed to identify areas with potential errors (see results).

The thickness of the tissue at the LA-LAA junction was calculated by manually isolating the LAA from the wall thickness map (figure 2B/C). An automated algorithm within MATLAB (Mathworks, Natick, MA, USA) interrogated the lower portion of the cropped LAA to identify the continuous path with the lowest mean thickness, reflecting the LA-LAA junction identified histologically. The junction was automatically separated into 4 quadrants, according to position relative to the LSPV, and mean thickness within each quadrant calculated (figure 3) (for further details see data supplement).

**Histology:** Ten ex vivo human hearts were assessed from patients matched for the duration of continuous AF and left atrial size. No ablation had been performed in these patients. As previously reported, tissue thickness at the LAA ostium was assessed. Briefly, the hearts were incised laterally through the LA and ventricle to expose the LAA ostium. The tissue was divided into blocks corresponding to four quadrants (superior, inferior, anterior and posterior) (figure 3E). The posterior quadrant was defined as that adjacent to the LSPV and the anterior quadrant as adjacent to the mitral valve (MV). Tissue blocks were dehydrated, infiltrated and embedded in paraffin. Sections of thickness 4 to 6 µm were stained with Movat pentachrome. Slides were scanned using the ZEISS Axio Scan.Z1 (Carl Zeiss Microimaging, Inc, Jena, Germany). Morphometric analysis was performed using Zen 2012 Blue Edition (Carl Zeiss Microimaging, Inc), and measurements taken at the junction of the LA and the LAA (figure 4).
Statistics: All statistical calculations were carried out in SPSS Statistics (IBM Corporation, New York). Continuous variables are expressed as mean±/standard deviation. Means were compared using one-way analysis of variance (ANOVA) or two tailed, independent samples student’s t-test. A result was considered statistically significant at the 5% significance level (p<0.05).

Results
Clinical: Detailed outcome data and follow up for the study cohort has previously been reported\(^2\). The focus of this report is the regional distribution of acute LAA electrical reconnection following electrical isolation and its relation to ostial LAA tissue thickness. Of the 22 patients enrolled, acute electrical isolation was achieved in 20 patients (91%). Acute electrical reconnection of the LAA occurred in 17 of these 20 patients. In each case reconnection occurred spontaneously during the waiting period. 37 episodes of acute electrical reconnection occurred in a total of 21 individual quadrants (2.2±1.2 per case). These occurred in the anterior quadrant in 21 cases (57%), superior quadrant in 13 cases (35%), inferior quadrant in 2 cases (5%) and posterior quadrant in 1 case (3%). In 2 cases successful LAA isolation was never achieved. The average RF time to achieve complete LAA isolation (including the ablation of any acute reconnection(s) after initial LAA isolation) was 33.5 ±27.7 minutes and was performed using a continuous (‘drag’) ablation technique.

Cardiac Computed Tomography: Mean wall thickness of each section (posterior, inferior, anterior and superior) of the base of the LAA was calculated from each CCT (see data supplement, figure 5). In 7 of the 22 segmentations, the epicardial surface of the LAA fused with the LSPV, which has a similar HU intensity to the tissue of the LAA wall. In these areas, a clear boundary between the tissue comprising the LAA and the LSPV cannot be distinguished on the segmentation, as demonstrated in figure 6A. Measurement of ostial LAA tissue thickness in the posterior section of LA-LAA junction was considered unreliable in these scans and excluded from subsequent analysis. This phenomenon was not observed in any other region and was
readily identifiable by inspection of a volume rendered image of the atrial myocardial mask (figure 6 panel A5), which was performed routinely during image analysis. The mean wall thickness measurement in each section was as follows: anterior: 2.1+/−0.6mm; superior: 1.9+/−0.4mm; posterior: 1.5+/−0.5mm; inferior: 1.8+/−0.7mm (figure 3E). One way ANOVA test demonstrated a significant difference between the group means (p=0.027). Student’s t-test demonstrated a significant difference between the anterior and posterior segments (p=0.004) and the superior and posterior segments (p=0.014).

**Histology:** As previously reported\(^2\), in the 10 human hearts that were examined from patients matched to the study population according to duration of AF and LA diameter, tissue in the anterior (2.5±0.8mm, range 1.4-4.0mm) and superior (2.4±1.2mm, range 1.1-4.8mm) quadrants was significantly thicker than the inferior (1.6±0.8mm, range 0.6-3.6mm) and posterior 1.6±0.8mm, range 0.8-2.9mm) quadrants.

**Lesion efficacy and Wall Thickness:** In patients in whom complete LAA isolation was achieved, 74 quadrants had CCT permitting calculation of mean tissue thickness and underwent RF ablation. Mean CCT derived thickness of tissue in regions that demonstrated acute electrical reconnection (n=20) was higher (1.9+/−0.6mm (range 1.0-2.9mm)) than mean thickness in those that did not (1.5+/−0.5mm (range 0.5-2.5mm), (p=0.009)). No cases of electrical reconnection occurred in segments in which thickness could not be analysed.

Some regions demonstrated multiple episodes of electrical reconnection and required repeated RF delivery to achieve durable electrical isolation. We considered whether tissue thickness was a factor in the likelihood of recurrent reconnection. One-way ANOVA demonstrated a significant difference (p=0.032) between the mean wall thicknesses for areas with 0 (mean thickness = 1.5+/−0.5mm, n=57), 1 (mean thickness = 1.9+/−0.7mm, n=11) and >1 (mean thickness = 2.0+/−0.5mm, n=7) acute reconnections. Tissue thickness was significantly lower in segments with 0 vs 1 acute reconnection (p=0.048) and segments with 0 vs >1 (p=0.036) while there was no significant difference between segments with 1 vs >1 acute reconnections (p=0.80).

This article is protected by copyright. All rights reserved.
Discussion
The major findings of this study are: 1) regional atrial wall thickness can be measured using CCT in humans; 2) differences in circumferential ostial LAA tissue thickness correspond with observations in AF-matched cadaveric samples and 3) local tissue thickness may influence effectiveness of catheter ablation during LAA isolation.

CCT is the optimal modality for assessing atrial wall thickness due to its high spatial resolution and clear identification of the endocardial surface. It is the most widely used modality for this indication\(^5\), but validation of CCT results against direct tissue measurements has been limited. Our study is the first to compare \textit{in vivo}, CCT derived wall thickness measurements at specific atrial locations with human tissue measurements from a matched cadaveric cohort. Previous studies have demonstrated significant variation in wall thickness at different atrial locations \(^6\text{–}^8\). We have previously demonstrated that tissue thickness is different at each of the four quadrants of the LA-LAA junction on pathological samples\(^2\). The identification of greater wall thickness in the anterior and superior segments of the LA-LAA junction on CCT imaging is consistent with results from direct tissue examination.

The absolute value of tissue thickness derived from CCT in this study are similar to those taken from the cadaveric cohort, however caution should be used when directly comparing these measurements. The measurements are taken from different atria, albeit matched as closely as possible for pathology. Tissue that has been processed for histological examination is subject to different forces than the \textit{in vivo} human atrium and the tissue geometry is likely to have changed as a result. The CCT result represents an averaged thickness across approximately a quarter of the LA-LAA junction, while the pathological measurements were taken from a single point. This averaging on the CCT measurements may account for the smaller differences in thickness between each of the regions in the CCT results. The strategy of solving the Laplace equation to generate wall thickness measurements from CCT represents a robust approach to assessing thickness in 3-dimensional space\(^9\). This strategy, while optimal for \textit{in vivo} imaging, could not be
taken for the tissue samples, in which a simple Euclidean distance in a single tissue plane was taken. These differences in tissue loading at the time of measurement, measurement methodology and patient groups mean the results are best interpreted as confirmation that regional differences in tissue thickness exist in-vivo throughout the atrium and that these may be satisfactorily detected using CT imaging.

Tissue thickness has previously been reported as a predictor of atrial ablation success\textsuperscript{10}. Under the hypothesis that transmural lesions may be more difficult to create in thicker tissue, we considered tissue thickness in regions with and without durable electrical isolation. We have demonstrated that tissue was thinner at locations where there was no recovery of electrical conduction following initial RF delivery (1.6mm) than those at which there was recovery (1.9mm). The results presented here demonstrate for the first time a relationship between local atrial tissue thickness and a defined electrical end point. Acute electrical isolation is an important end point in most clinical ablation strategies and considered an important determinant of long term lesion durability\textsuperscript{11}. The magnitude of difference in thickness between quadrants may be unlikely to be relevant to achieving a transmural lesion. However, an average thickness was calculated across the quadrant in order to confidently include the point of electrical reconnection. This averaging is likely to result in reduced absolute differences between calculated tissue thickness than if point measurements at the point of electrical reconnection were taken.

Power, temperature and contact force are routinely used to titrate RF delivery in order to improve the durability of atrial ablation\textsuperscript{11-13}. The accurate titration of RF delivery may be further facilitated by software tools that aggregate information from known determinants of lesion morphology into simple scales\textsuperscript{14,15}. These tools offer the prospect of further refinement in the titration of RF based on multiple parameters computed in real time. The use of such tools has previously depended largely on the assumption of a uniform tissue thickness. The evidence presented here, and emerging from other centres\textsuperscript{16}, is that this assumption is not valid. In the
future, tools to predict atrial lesion adequacy may facilitate titrated RF delivery based on local tissue thickness as well as ablation parameters. Importantly, from a safety perspective, knowledge of tissue thicknesses may help to reduce the risk of perforation from excessive RF energy delivery in areas of relatively thin tissue.

While the incorporation of tissue thickness alongside standard ablation parameters when titrating RF energy is a possibility for the future, the results presented here do not support its use in this way at present. While significant differences were identified between the thickness of tissue that demonstrated acute electrical reconnection and those that did not, there remained a large overlap in tissue thickness between each group. Tissue geometry, catheter features and tissue edema are all likely to be important factors determining ablation success, as well as standard ablation parameters. There was no attempt to control for these parameters in this study. We observed what the impact of tissue thickness was in the context of a standardised clinical ablation strategy with clear electrophysiological end points. These results demonstrate that tissue thickness is a determinant of acute ablation success but a controlled assessment of ablation titrated according to tissue thickness is required prior to its use in this way. The results presented here suggest a controlled assessment of RF titrated according to local tissue thickness would be valuable.

**Limitations**
The acquired CCT resolution did not adequately identify the boundary between LAA epicardium and LSPV in a proportion of CCTs. Affected CCTs were readily identifiable from the volume rendered segmentation of the atrial wall (figure 6) so this is unlikely to result in spurious measurements, however in these CCTs accurate prediction of tissue thickness was not possible. Better soft tissue contrast and higher resolution CCT may reduce the incidence of this issue in the future\(^\text{17}\). Using the current imaging and segmentation strategy, this technique for assessing local wall thickness can only be comprehensively applied in cases where adequate definition between the wall of the LAA and the LSPV exists.
In addition, the strategy for measuring wall thickness was different on CCT and pathological samples and the cohorts were different.

This was not a controlled study of the effect of tissue thickness on success of atrial ablation and there were differences in RF energy delivery at different sites. This means that no conclusions can be drawn about the titration of RF energy on the basis of tissue thickness. In addition, while there was a clear histological definition of the LA-LAA junction, this narrow portion of tissue was not identified on EAMS. While the RF was likely to have been delivered in the vicinity of this portion of tissue it may not have been localized precisely here in all cases. Additional factors will also influence likelihood of achieving acute electrical isolation including energy delivery, catheter stability and orientation. The thickest tissue was found in the anterior quadrant of the LAA ostium, which is also typically the most difficult position in which to achieve catheter stability and this may be an additional factor influencing likelihood of achieving acute electrical isolation.

**Conclusion**

Using CCT imaging, we have demonstrated clinically relevant measurements of local atrial wall thickness and variation of tissue thickness at different atrial locations. Furthermore, LAA isolation may be affected by local tissue thickness. Atrial wall thickness deserves further consideration as a determinant of lesion transmurality and thus safe and successful ablation.
References


**Figure legends:**
Figure 1: Voxel intensity based segmentation of atrial wall

Panel A: Histogram of voxel intensities comprising atrial wall (red) and blood pool (blue).

Panel B: Volume rendered segmentation of the atrial blood pool. Panel C: Stages of iterative growing algorithm showing blood pool (red) as starting point and subsequent steps as algorithm expands into region with predefined voxel intensity of atrial wall (blue). Large panel

This article is protected by copyright. All rights reserved.
shows volume rendered segmentation of atrial wall (blue) with mitral valve (green) and ends of pulmonary veins (orange) tagged.

Figure 2: Isolation of left atrial appendage

Panel A: Rendering of endocardial surface of left atrium (LA) Panel B: Manual cropping of LAA.
Panel C: Point cloud representation of left atrial appendage (LAA). Dots around the base indicate the algorithm identified LA-LAA junction colour coded according to quadrant.
**Figure 3:** Interrogation of the base of the cropped left atrial appendage (LAA) to identify the left atrium (LA)-LAA junction

**Panel A:** Schematic representing the base of the LAA separated into discrete portions. Dotted line represents plane fitted to select LA-LAA junction. **Panel B:** Separation of LAA base into quadrants. **Panel C:** Point cloud representation of the LAA. Vertical stacks indicate regions interrogated as potentially forming junction. Larger red dots indicate identified LA-LAA junction. **Panel D:** View through the LAA ostium oriented to reflect segments in panel B, which are superior (red), anterior (blue), inferior (white) and posterior (red). **Panel E:** Representative example of tissue orientated according to panel B and panel D with mean measurements from tissue at these sites.

**Figure 4:** Atrial wall thickness measurements taken from pathological samples.

**Panels A-D** show tissue from each quadrant of the left atrial appendage (LAA) ostium.

Magnified inserts identify position defined as histological left atrium(LA) to LAA junction and position/orientation chosen for measurement of tissue dimensions.
Figure 5: **Regional wall thickness and thickness in regions demonstrating electrical reconnection**

**Panel A:** Cardiac computed tomography (CCT) derived wall thickness by segment. **Panel B:** CCT derived wall thickness by segments separated according to incidence of acute electrical reconnection. **Panel C:** CCT derived wall thickness by segments separated according to acute electrical reconnection.

Figure 6: **Failure to resolve epicardium at left superior pulmonary vein**
**Figure 6:** LA: Left atrium; LAA: Left atrial appendage; LAA Os: Left atrial appendage ostium; LSPV: Left superior pulmonary vein; LIPV: Left inferior pulmonary vein. CCT: Cardiac computed tomography. Panel showing planar imaging and volume rendering demonstrating failure of accurate measurements at the posterior segment. **Panel A:** A1/A3: Sagittal image (A1) and axial image (A3) demonstrating LSPV lying proximal to base of LAA. A2/A4: Segmented atrial myocardium projected onto CCT demonstrating fusion of posterior wall of appendage with tissue (indicated by white arrow). A5: Volume rendered image of atrial myocardium demonstrating fusion of posterior segment of LAA base with LSPV (white arrow). **Panel B:** Same arrangement as panel A in case without fusion of posterior segment of LAA with LSPV. B1/B3: CCT images. B2/B4: Atrial myocardium. B5: Volume rendered image of atrial myocardium demonstrating clear gap between LAA and LSPV from the same CCT scan.