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Use of Computed Tomography to Identify Atrial Fibrillation Associated Differences in Left Atrial Wall Thickness and Density

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Abstract

Introduction—Left atrial (LA) tissue characteristics may play an important role in atrial fibrillation (AF) induction and perpetuation. Although frequently used in clinical practice, computed tomography (CT) has not been employed to describe differences in LA wall properties between AF patients and controls. We sought to noninvasively characterize AF associated differences in LA tissue using CT.

Methods—CT images of the LA were obtained in 98 consecutive patients undergoing AF ablation and in 89 controls. A custom software algorithm was used to measure wall thickness and density in four pre-specified regions of the LA.

Results—On average, LA walls were thinner (–15.5%, 95% confidence interval [CI] –23.2 to –7.8%, $p < 0.001$) and demonstrated significantly lower density (–19.7 Hounsfield Units [HU], 95% CI –27.0 to –12.5 HU, $p < 0.001$) in AF patients compared to controls. In linear mixed models adjusting for demographics, clinical variables, and other CT measurements, the average LA, interatrial septum, left atrial appendage, and anterior walls remained significantly thinner in AF patients. After adjusting for the same potential confounders, history of AF was associated with reduced density in the LA anterior wall and increased density below the right inferior pulmonary vein and in the left atrial appendage.

Conclusion—Application of an automated measurement algorithm to CT imaging of the atrium identified significant thinning of the LA wall and regional alterations in tissue density in patients with a history of AF. These findings suggest differences in LA tissue composition can be noninvasively identified and quantified using CT.

Keywords

atrial fibrillation; imaging; atrium; computed tomography

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Introduction

Although atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, its underlying pathogenesis remains incompletely understood. Alterations in left atrial (LA) geometry and tissue composition may play a critical role in arrhythmia induction and perpetuation. LA size is readily measured by common imaging modalities such as echocardiography, and the association between AF and LA enlargement has long been recognized.¹ Other atrial changes have also been correlated with AF, but these have previously been identified only by invasive procedures. Specifically, AF patients have been shown to have reduced LA wall thickness by autopsy, increased interstitial fibrosis determined from intra-operative cardiac biopsy, and alterations in endocardial voltage during catheter-based endocardial LA mapping when compared to controls.²⁻⁶ Such invasive methods limit the feasibility of extensive study in patient-oriented research.

CT is a widely available imaging modality that provides detailed assessment of cardiac anatomy. Despite the frequent use of chest CT prior to AF ablation, the potential of this common imaging modality to discern LA tissue characteristics in AF has not been fully realized. In addition to dimensional measurements, CT can also objectively quantify tissue density. Identification of density alterations within the atrium has the potential to noninvasively assess for atrial tissue pathology.

Digital data generated from CT scans are readily amenable to automated computerized analysis. A CT-based software algorithm has been developed and validated by members of our team (ET, MW) to characterize the histologic features of carotid artery plaque.⁷ This technology can be readily applied to other anatomical regions of interest, enabling assessment for LA structural abnormalities in patients with AF. The purpose of this study was to assess the ability of this custom software algorithm to compare regional measurements of atrial thickness and density among patients with AF to a control population without a history of arrhythmia.

Methods

Study Population

CT scans from ninety-eight consecutive patients without a history of left atrial ablation, congestive heart failure, coronary artery disease, cardiac surgery, congenital heart disease, or renal insufficiency undergoing AF ablation at the University of California, San Francisco were included in the study. All patients underwent cardiac CT imaging prior to their ablation procedure as part of a standardized protocol to define LA and pulmonary vein anatomy. Eighty-nine consecutive patients without significant cardiac disease or history of AF who underwent chest CT imaging to evaluate for the presence of pulmonary embolus at the same institution served as the comparator group. Individuals with incomplete contrast opacification of the LA were excluded. In addition, patients diagnosed with a pulmonary embolus or other cardiopulmonary pathology by CT were excluded from the control cohort. Demographic variables, medical history, and vital signs were collected from the medical record.

The baseline characteristics of the study population are described in Table 1. In comparison to the control group, the AF cohort was younger and had a greater proportion of male subjects. Patients in the control group were more likely to have a history of hypertension and had an increased average LV thickness, while patients with a history of AF had larger atrial and ventricular volumes. There was no difference in resting heart rate between the two groups.

The study was approved by the University of California, San Francisco Committee on Human Research.

CT Imaging

Contrast-enhanced CT images were obtained in the axial plane using a 16- section scanner with a slice thickness of 1.25 mm, 0.33 second gantry rotation time, 120 kilovolt tube voltage, and 850 milliamperere tube current. A total of 90 milliliters (mL) of non-ionic iodinated contrast (Omnipaque 300) was injected at 4 mL per second. Timing of image acquisition was determined by bolus tracking software; imaging was initiated when contrast reached the pulmonary artery in the control group and the left atrium in the AF group. Duration of image acquisition was the same between groups, although differences in body size resulted in different imaging duration between individual patients. Atrial measurements were made in a blinded fashion by a radiologist. The LA endocardial border was automatically delineated on every fourth axial slice. LA volume was then derived by summing the product of each measured area by a thickness of 5 mm (4 slices of 1.25 mm). An analogous method was applied to measure the LV volume.

Atrial wall thickness and density were measured in the axial plane using an automated program developed by the study authors (ET, MW). This computerized algorithm was previously validated for the assessment of carotid artery tissue composition through comparison of CT image data with histopathologic analyses.⁷ To assess atrial wall characteristics, the algorithm required borders of contrasting density (e.g., LA wall directly adjacent to the blood pool or aerated lung) to frame the myocardium of interest. We identified four regions of the LA reliably amenable to sampling using this automated method (Figure 1): the area immediately below the right inferior pulmonary vein, the interatrial septum, the left atrial appendage, and the anterior left atrial wall. Using the automated algorithm, the minimal wall thickness in a given region of interest was determined for each axial slice. After all slices from a given region were compared, the thinnest measurement was recorded. This technique minimized measurement error due to slices that were off-angle, as such assessments would tend to overestimate the true wall dimension. LV wall thickness was measured in a similar manner using the thinnest measurements recorded for the ventricular septum and the lateral wall of the ventricle. Finally, the same automated algorithm quantified average tissue density in Hounsfield Units (HU) for each slice from a given LA region. Densities obtained from every slice in each region were then averaged to determine the final reported density value.

Atrial measurements in the AF cohort were collected at a random point in the cardiac cycle. For control patients, image gating was used to acquire LA measurements immediately prior to atrial systole.

Statistical Analysis

Normally distributed continuous variables are presented as mean \pm SD and were compared using *t*-tests. Continuous variables that were not normally distributed are presented as medians and interquartile ranges (IQR) and were compared using the Wilcoxon ranksum test. Proportions were compared using the chi-squared test. Linear mixed models were used to determine whether history of AF was independently associated with LA thickness and density. In these models, random effect terms for patient were included to address the potential effects of within-patient clustering of the four atrial measurements (below the right inferior pulmonary vein, interatrial septum, left atrial appendage, and anterior wall). Heterogeneity in the regional LA thickness and density differences due to AF was assessed using a Wald test. Covariates known or suspected to be important to AF and atrial size, as well those significantly associated with both the predictor and outcome with *p* values < 0.1 ,

were included in the adjusted models. Restricted cubic splines were used to model non-linearities in the effects of age, body mass index (BMI), LA and LV volumes, and LV thickness. LA thickness outcomes were log-transformed to achieve normality, and regression results were back transformed to estimate percentage differences in measured thickness between patients with and without history of AF. All analyses were performed using Stata 11 (StataCorp, College Station, TX, USA). A two-sided $p < 0.05$ was considered significant.

Results

A total of 187 patients were included (98 in the AF cohort, 89 in the control group). Among participants in the arrhythmia cohort, 76 (77%) had paroxysmal AF while 23 (23%) had persistent AF. At the time of presentation for AF ablation, 56 (57%) participants were in sinus rhythm. CT imaging was performed a median of 1 day (IQR 1 to 9 days) prior to ablation.

On average, the LA wall was thinner in AF patients when compared to controls (0.7 mm AF versus 0.9 mm controls, $p < 0.0001$). Unadjusted and multivariate differences in overall and regional mean atrial thickness measurements between patients with AF and controls are described in Table 2. In linear mixed models adjusting for patient demographics (age, sex, and race), clinical variables (history of hypertension, BMI, and resting heart rate), other CT measurements (LA volume, LV volume, and LV thickness), and clustering by individual, overall LA wall, interatrial septum, left atrial appendage, and anterior wall measurements remained significantly thinner in patients with AF. In addition, the adjusted differences in atrial thickness between regions differed significantly more in the AF patients compared to controls (Wald test of heterogeneity $p = 0.008$).

Table 3 lists unadjusted and adjusted differences in overall and regional atrial densities. In the AF cohort, LA myocardium was overall less dense compared to controls. The interatrial septum and anterior wall showed significantly lower average HU when measured in AF patients, while the density of the left atrial appendage was greater. After adjusting for the same potential confounders described above and after taking clustering by individual into account, overall LA density was no longer significantly different, the lower density in the anterior wall persisted, the left atrial appendage density remained higher, and the density below the right inferior pulmonary vein was significantly increased in the AF cohort compared to controls. The adjusted differences in atrial density between regions differed significantly more in the AF patients compared to controls (Wald test of heterogeneity $p < 0.001$).

LA volume was not significantly correlated with LA wall thickness or density, either before or after adjustment for patient demographics, comorbidities, and left ventricular parameters. Atrial size was measured at end atrial diastole in the control cohort and at a random point during the cardiac cycle in the AF patients. To determine whether atrial measurements obtained at different times during the cardiac cycle contributed to our findings, repeat assessment was performed using average LA size (LA end diastolic volume + LA end systolic volume/2) in the control group. Atrial volumes remained significantly larger in the AF cohort compared to controls after this adjustment. After adjusting for average LA size, none of the results meaningfully changed. In order to determine if the presence of AF at the time of the imaging study may have affected our findings, we performed a sensitivity analysis restricted only to those patients in the AF group that presented for their ablation in sinus rhythm. Restricting the analysis in this way also did not meaningfully change our results.

Discussion

Using an automated software algorithm to analyze CT imaging of LA tissue, we identified significant differences in LA wall thickness and density among patients with AF. Both before and after adjusting for a variety of baseline historical, clinical, and radiographic variables, AF was associated with significant overall thinning of the atrium. This finding was primarily driven by reductions in wall thickness of the interatrial septum, left atrial appendage, and anterior left atrium. LA tissue in AF patients also exhibited overall decreased radiographic density. Both LA wall thickness and radiographic density measurements demonstrated significantly more heterogeneity between the four different LA walls in patients with AF compared to controls. From a clinical perspective, our findings indicate LA wall abnormalities can be noninvasively identified in patients with AF and suggest such wall changes do not impact the atrium in an anatomically uniform manner.

Differences in atrial thickness and density were identified using custom measurement software applied to contrast-enhanced CT images. This software algorithm was validated for the assessment of carotid artery disease by comparing CT analysis to pathology specimens obtained during carotid endarterectomy;⁷ its use in examination of the LA myocardium represents a new approach. The observed difference in LA wall thickness between patients with a history of AF and controls (on average 25% thinner in the AF cohort) is consistent with the magnitude of relative change in LA chamber diameter that has been shown to be important in predicting AF risk.¹ It is therefore interesting to speculate on the relative importance of wall thickness versus chamber dimensions in relation to AF risk, as the prior inability to non-invasively measure wall thickness previously prohibited a comparison of these two parameters in clinical cohorts. Computerized atrial assessment is especially compelling in the setting of the small measurements needed for left atrial wall thickness (compared to the larger LA diameter, for example), and an automated algorithm has the potential to reduce measurement error and minimize inter-observer variability. Due to the cross-sectional nature of our study design, it remains unknown whether a thinner LA wall is an independent risk factor for AF or whether AF causes reductions in LA wall thickness.

Increased LA size is a well described risk factor for the development of AF.¹ In the present study, LA volume was significantly increased among the AF cohort compared to controls. However, reductions in LA wall thickness persisted after adjustment for atrial volume. The correlation between AF and atrial thinning is in agreement with autopsy data describing a reduction in posterior LA wall thickness among patients with a history of AF.⁸ A single previous study using CT imaging demonstrated an association between AF and increased LA wall thickness.⁹ However, this prior investigation only used a single measurement of LA wall diameter in the anterior region of the atrium, did not adjust for potential cofounders, and did not employ an automated LA measurement protocol. These differences in methodology may explain our discordant finding of AF-associated anterior wall thinning. Longitudinal follow up in this prior study notably reported that a thinner anterior atrial wall was associated with clinical progression from paroxysmal to chronic AF, suggesting that atrial wall thinning may predict disease evolution.

In addition to atrial wall thickness, we also assessed changes in LA wall density using CT imaging. Prior histologic studies examining canine^{2,3} and human^{4,5} myocardium have demonstrated AF-associated differences in the LA substrate, predominately attributed to fibrosis. We hypothesized that CT could noninvasively identify these LA tissue differences through measurement of changes in atrial wall density. CT quantifies tissue density in terms of HU, a standard radiographic scale that normalizes the densities of imaged structures to that of water and air. Muscle and bone have progressively more positive HU values, while the HU for fat and air are correspondingly more negative. The expected variation in HU

between normal and fibrotic atria is not known, and conclusions regarding the histologic changes driving these radiographic differences would be premature and speculative. Nevertheless, the current study demonstrates the feasibility of atrial density measurement using chest CT and indicates that such density significantly differs between patients with and without AF. Future studies are needed to correlate myocardial histology with CT density measurements. The significant heterogeneity in both our thickness and density data suggests the structural changes associated with AF are not uniformly distributed throughout the atrium. This observation supports prior research that has identified regional variation in LA voltage using endocardial electroanatomic mapping.⁶

Recent data utilizing delayed enhancement MRI of the LA indicates such a technique may be useful to noninvasively detect atrial fibrosis.¹⁰ CT has several clinical advantages over MRI, including widespread availability, lower cost, enhanced spatial resolution, and faster image acquisition. The software algorithm used in the current study does not require a specialized imaging protocol and can therefore be applied both prospectively and retrospectively to any chest CT performed with intravenous contrast. In addition, because CT measurements are made in the axial plane, this technique is not specific to axial slice thickness. LA ablation procedures for AF are growing in popularity, although the success of the procedure remains less than 70%.¹¹ CT images are frequently obtained prior to these procedures to aid in intraprocedural LA mapping. LA morphology characteristics identified using our algorithm may eventually be employed to define appropriate procedural candidates and to determine anatomic ablation targets. In addition, detection of particularly thin regions of the LA through CT analysis could help identify areas most prone to esophageal injury during ablation, thereby preventing the often lethal formation of an atria-esophageal fistula.¹²

Over three million Americans are presently living with AF, and this number is expected to grow substantially in future years.¹³ The significant increases in morbidity and mortality associated with AF¹⁴ underscore the appeal of primary prevention strategies to treat those at high risk for arrhythmia development.¹⁵ The formation and assessment of such preventive interventions will require accurate prediction models to identify and follow at-risk patients. Current prediction tools primarily rely upon clinical variables to gauge AF risk.¹⁶ CT imaging identified distinct atrial changes that remained significantly associated with AF after adjusting for other clinical risk factors (including age, sex, hypertension, and BMI), suggesting that CT parameters might add useful information to prediction models. Future prospective studies are needed to define the cause and effect relationship between AF and LA changes. The frequent clinical use of CT scans, coupled with the feasibility of retrospectively analyzing any contrast enhanced chest CT image with the presently described algorithm, suggests the atrial parameters measured in this study may ultimately have broad applicability.

Limitations

Potential limitations of this study should be recognized. Gated data acquisition was utilized for controls, while data was obtained at a random point in the cardiac cycle for AF patients regardless of their rhythm at the time of imaging. However, LA wall measurements were assessed at the end of atrial diastole for control patients, corresponding to the portion of the cardiac cycle with the expected thinnest atrial dimension. This limitation in image gating would therefore tend to *minimize* the significant differences observed in atrial thickness between cohorts and should not explain our positive findings. Similarly, data was acquired during atrial systole in an unknowable portion of the AF cohort in sinus rhythm at the time of imaging and could have resulted in increased atrial density measurement. While differences in acquisition timing might explain the increased density observed in some LA regions among the AF cohort, it would unlikely be responsible for the decreased density

observed in the anterior wall of AF patients. Limitations in methodology did not allow for precise rhythm determination among the AF cohort at the time of CT image acquisition. However, the median time difference between imaging and ablation was only one day, and more than half of the arrhythmia cohort was in sinus rhythm upon presentation for ablation. In addition, repeat analyses performed after excluding those patients in AF at the time of ablation did not yield meaningfully different results, suggesting the observed CT findings were not due to the presence of AF at the time of CT acquisition. Finally, slight differences in the relative timing of contrast administration and image acquisition between the AF and control groups could have biased atrial density measurements. However, such bias would likely systematically raise or lower density measurements in all parts of the atrium. Because wall density among AF patients was increased in certain regions while reduced in others, we do not believe differences in image timing relative to contrast administration would entirely account for our results.

Conclusion

In conclusion, we report the use of a CT-based automated software algorithm to quantify differences in LA wall thickness and density between patients with and without a history of AF. A history of AF was associated with significant LA tissue thinning, overall decreased density, and increased heterogeneity in both measurements between LA walls, demonstrating that distinctive LA tissue characteristics can be noninvasively assessed by this commonly employed imaging modality. Future use of this automated algorithm to quantify LA wall parameters has the potential to enhance understanding of arrhythmia pathogenesis, improve AF prediction models, and refine patient selection for invasive ablation procedures.

Acknowledgments

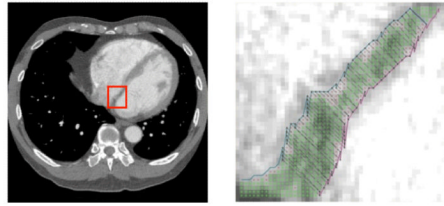
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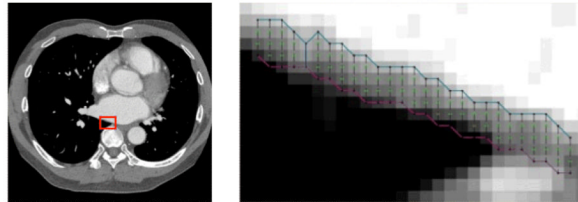
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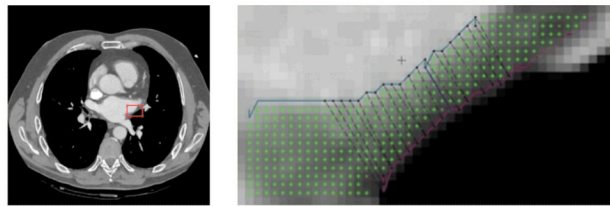
A. Interatrial septum



B. Below Right Inferior Pulmonary Vein



C. Left Atrial Appendage



D. Anterior Left Atrial Wall

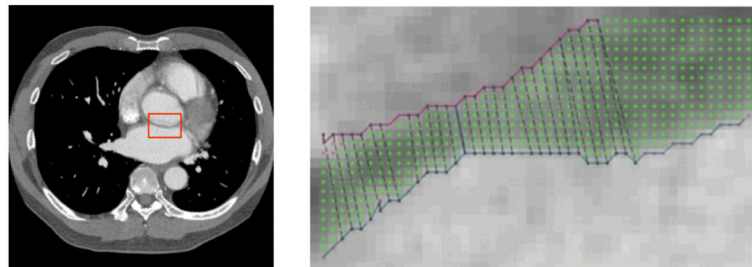


Figure 1. Illustration of the automated, computer-based segmentation of the left atrial (LA) wall
 In order to perform wall segmentation, the computer algorithm requires borders of contrasting density (e.g., LA wall directly adjacent to the blood pool or aerated lung) to frame the myocardium of interest. Each of the four regions of interest is shown in panels A-D (with magnified view shown on the right for each). Once the algorithm automatically delineates the inner and outer borders of the atrial wall, the average density of the assessed portion of the LA wall and its minimal thickness are quantified by the software.

Table 1

Baseline Characteristics

	AF (n = 98)	Controls (n = 89)	P value
Age (years)	55 ± 9	68 ± 13	<0.001
Male	83 (85%)	47 (53%)	<0.001
Race			0.005
White	81 (83%)	52 (58%)	
Black	1 (1%)	7 (8%)	
Asian	8 (8%)	17 (19%)	
Latino	4 (4%)	9 (10%)	
Native American	0	1 (1%)	
Other	4 (4%)	3 (3%)	
Hypertension	36 (37%)	74 (83%)	<0.001
BMI (kg/m²)	29 ± 5	27 ± 5	0.001
Heart Rate (beats/min)	69 ± 17	72 ± 13	0.25
LA Volume (ml)	107 ± 30	97 ± 29	0.028
LV Volume (ml)	178 ± 49	105 ± 34	<0.001
LV Thickness (mm)	3 ± 1	4 ± 1	<0.001

AF, atrial fibrillation; BMI, body mass index; LA, left atrium; 390 LV, left ventricle.

Table 2
Unadjusted and Adjusted* Percent Differences in LA Thickness Among Patients with AF Compared to Controls

LA Region	Unadjusted Difference (%)	95% CI	P value	Adjusted* Difference (%)	95% CI	P value
Overall	-16	-23 to -8	<0.001	-25	-39 to -12	<0.001
Interatrial septum	-30	-41 to -20	<0.001	-38	-52 to -24	<0.001
Below right inferior pulmonary vein	-2	-17 to 13	0.81	-11	-31 to 9	0.30
Anterior wall	-16	-29 to -3	0.01	-28	-44 to -12	<0.01
Left atrial appendage	-12	-25 to -2	0.09	-22	-40 to -5	0.01

AF, atrial fibrillation; CI, confidence interval; LA, left atrium.

* Multivariate model included adjustment for age, race, body mass index, history of hypertension, heart rate, left atrial volume, left ventricular volume, and left ventricular thickness.

Table 3

Unadjusted and Adjusted* Differences in Mean LA Hounsfield Units (HU) Among Patients with AF Compared to Controls

LA Region	Unadjusted Difference (HU)	95% CI	P value	Adjusted* Difference (HU)	95% CI	P value
Overall	-20	-27 to -13	<0.001	-3	-18 to 12	0.68
Interatrial Septum	-29	-42 to -16	<0.001	-12	-31 to 7	0.22
Below right inferior pulmonary vein	9	-4 to 22	0.19	22	3 to 41	0.02
Anterior wall	-76	-89 to -63	<0.001	-59	-78 to -40	<0.001
Left atrial appendage	18	5 to 31	<0.01	36	17 to 55	<0.001

AF, atrial fibrillation; CI, confidence interval; HU, Hounsfield units; LA, left atrium.

*Multivariate model included adjustment for age, race, body mass index, history of hypertension, heart rate, left atrial volume, left ventricular volume, and left ventricular thickness.