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The Role of Atrial Structural Remodeling in Atrial Fibrillation Ablation:An Imaging Point of View For Predicting Recurrence.

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia and is associated with a significant morbidity and mortality. Invasive catheter ablation of AF has emerged as an effective therapy for patients with symptomatic AF. Atrial remodeling, particularly structural remodeling, is important not only for AF persistence but also for AF recurrence after ablation. Atrial dilation and fibrosis are two of the core processes involved in atrial structural remodeling. Increased automaticity and triggered activity occur in atrial structural remodeling, which may cause difficulty in maintaining sinus rhythm after ablation. Furthermore, an enlarged left atrium (LA) may increase the difficulty in achieving catheter stability and thereby require more energy to complete AF ablation. AF causes similar remodeling in both the left and right atria (RA), and myocardial changes in both atria influence AF recurrence. A non-invasive assessment of fibrotic structural remodeling helps predict the outcome of AF ablation. A variety of cardiac imaging modalities, such as two- or three-dimensional echocardiography or multi-detector row computed tomography, have been used to estimate the magnitude of atrial structural remodeling by measuring atrial volume or LA function. Furthermore, delayed enhanced cardiac magnetic resonance imaging has been used to detect not only atrial fibrosis but also the effect of the ablation point. Thus, atrial remodeling, particularly structural remodeling, plays an important role in AF recurrence. These non-invasive imaging modalities are significant tools for estimating atrial enlargement to improve patient selection for AF ablation at the point of paroxysmal AF, and for estimating atrial fibrosis to select the AF treatment including ablation strategy at the point of development to persistent or permanent AF.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the United States, Europe, Japan and other developed countries. AF is associated with a significant morbidity and mortality, including a 4- to 5-fold increased risk of stroke, a 2-fold risk of dementia, a 3-fold risk of heart failure, and a 40% to 90% increased risk of overall mortality. [1] The mechanism of AF is not fully understood, but following Coumel's triangle of arrhythmogenesis, some of the trigger factors, [2] the arrhythmogenic substrate, [3] and modulating factors [4] are understood. These factors include the autonomic nervous system,[5, 6] ischemia, [7] and hormones. [8] Invasive catheter ablation of AF has emerged as an effective therapy for patients with symptomatic AF. Atrial remodeling, particularly structural re-

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modeling, is important not only for AF persistence but also for AF recurrence after catheter ablation. Therefore, a non-invasive evaluation of the magnitude of atrial structural remodeling could be used to improve patient selection for AF ablation. We review the role of atrial remodeling in AF recurrence after catheter ablation from the perspective of using recent image modalities to estimate atrial structural remodeling.

Using Atrial Structural Remodeling to Predict AF Recurrence

AF results from continuous remodeling of the left atrium (LA), which involves electrical and structural transformations, altered metabolism, and autonomic changes. These changes are primarily associated with the arrhythmia, but they are also secondarily associated with aging, progression of underlying heart disease, and genetic and environmental factors. [4] During the first week of AF, the atrial substrate is modified by electrical remodeling, with shortening of the atrial refractoriness and slowing of the conduction velocity. Structural remodeling fascinates the maintenance of AF in the following months. Electrical remodeling is characterized by an AF-induced decrease in action potential duration and an increase in the risk of delayed after-depolarizations. In contrast, structural remodeling involves cell death, fibroblast proliferation, and excess extracellular matrix production leading to fibrosis. Fibrotic lesions can impede electric propagation to favor reentry.[9] Fibroblast-cardiomyocyte interactions promote reentry and ectopic impulse formation. Thus, the fibrosis causes AF to progress to permanent forms, and AF itself may promote structural remodeling, [10] creating a long-term positive feedback loop that contributes to the development of permanent forms of AF. Goette et al. [11] showed pathologically using the right atrial appendages from 259 patients undergoing open-heart surgery that increased atrial fibrosis is a direct cause of increased AF prevalence after surgery. Sanders et al. [12] demonstrated that patients with heart failure and no prior atrial arrhythmias have significant atrial structural remodeling characterized by anatomic and structural changes, including atrial enlargement, regions of low voltage, and scarring, abnormalities in conduction, including widespread conduction slowing and anatomically determined conduction delay and block, and increased refractoriness. Chronic atrial fibrosis and scarring alter intra-atrial conduction and increase atrial effective refractory periods. Altered conduction and barriers formed by the scar may form the critical circuits for intra-atrial reentry that promote AF persistence. Indeed, structural remodeling with atrial fibrosis may be more important than electrical remodeling in maintaining AF, which is consistent with animal studies.[13] Atrial dilation is closely associated with fibrosis[14], and atrial size has been shown to be an important risk factor for AF persistence. Thus, atrial dilation and fibrosis are two of the core processes involved in atrial structural remodeling.

Pulmonary vein (PV) ablation has become an important and increasingly effective treatment strategy for AF, particularly paroxysmal AF. Previous studies have reported that 65% to 85% of patients are free from recurrent AF after ablation, but 30% to 40% of patients require >1 procedure.[15-17] AF recurrence after catheter ablation depends on various factors, such as the left atrial diameter (LAD) or volume (LAV), [18, 19] left ventricular ejection fraction, [20] and LA scarring. [21] Pre-existing LA structural remodeling (scarring) is a strong independent predictor of AF recurrence after catheter ablation because the structural change of the LA myocardium has been identified as an arrhythmogenic substrate that contributes to AF relapse. [22, 23,24] Other important predictors have also identified the technical problems, such as the percentage of LA ablated [25] or vagal denervation, [26] and electrical block at linear lesions. [27] These factors, which influence AF recurrence, are all associated with a dilated LA, and the close relationship between dilated LA and AF recurrence has been understood on the basis of several concepts. First, the LA dilated by structural remodeling increases the automaticity and triggered activity in atrial fibers, [28, 29] which is likely to cause AF recurrence after ablation. [30] Second, based on the multiple reentrant wavelet hypothesis, AF can be more easily induced and maintained with a larger LA. [31, 32] Third, the enlarged LA may increase the difficulty of achieving catheter stability and thereby require more energy and longer lesions to complete AF ablation. The insufficient extent of ablation for the pre-existent LA scarring area concomitant with a dilated LA leads to re-connection between the LA and PVs after ablation[33]. Thus, AF recurrence is caused by more

extensive structural remodeling or less extensive ablation. Natale et al.[21] demonstrated that extensive LA structural remodeling with scar is likely to result in AF recurrence because of not procedural failure but an inability to achieve the end point of PV isolation. By identifying patients with extensive LA remodeling before ablation, operators can immediately predict a high chance of procedure failure. Based on this finding, it may be possible to alter therapy in this select group to maximize success. Patients with LA structural remodeling may require routine detailed mapping of the scar with ablation of all the potential isthmuses that could cause intra-atrial re-entry to minimize recurrence. A second procedure does not appreciably increase the cure rate, so perhaps repeat ablation should not be routinely offered. The goal of total freedom from antiarrhythmic therapy may also need to be revised in this group, and combination ablation with long-term drug therapy may be the most effective approach.

Is the right atrium (RA) a bystander in AF recurrence? RA structural remodeling has also been reported in patients with AF.[34-36] Sanders et al. [37] and John et al. [38] showed that both myocardial damage, as measured by voltage mapping, and an increase in atrial size were similar in magnitude between the LA and RA in patients with lone paroxysmal AF. These authors also showed a symmetrical change in electric remodeling between the LA and RA in patients with rheumatic mitral stenosis, suggesting a potential cause of AF. Using 64-multidetector computed tomography (MDCT) in a 6-month follow-up study in patients with paroxysmal AF, we reported that both LA and RA structural remodeling are independent predictors of AF recurrence. [39] Lo et al. [40] studied patients with combined paroxysmal and persistent AF who underwent three-dimensional (3-D) mapping and circumferential PV isolation (CPVI) and LA linear ablation, followed by LA and RA electrogram-based (complex fractionated atrial electrogram) (CFAE) ablation. Their results showed that a larger LAD and the presence of RA non-PV ectopy during the index procedure could predict a late recurrence during the long-term (13 ± 8 months) follow up. Although the PV is the major site of ectopic beats that initiate AF and isolation of the PVs and LA substrate modifications remain the keystones for AF ablation, 28 to 47% of patients had non-PV ectopy that initiated AF. [41-43] Among the non-PV ectopic sites initiating AF, the superior vena cava AF accounted for one-third of the population. Previously, atrial pacing or ablation in the high RA, interatrial septum, and Bachmann bundle had been used to prevent AF because multiple unstable reentrant circuits were observed in the RA. [3, 44, 45] Kalifa et al. [36] demonstrated that the sources of rapid atrial activation during stretch-related AF were located in the PV region, and their level of spatio-temporal organization correlated with pressure. High pressure in the PV junction and pulmonary hypertension may play an important role in AF recurrence. Furthermore, a previous study demonstrated that both RA and LA pressures were significantly and similarly increased in early and severe heart failure, and remodeling of both atria contributed to the development of atrial arrhythmia and pulmonary hypertension. [46] In addition, apart from the Bachman bundle, there are several muscular bridges that provide interatrial connections, such as the connections between the LA and the coronary sinus and those between the muscular sleeves of the right PVs and the RA. [47, 48] Those previous results indicate that the occurrence of AF causes similar structural and electrical remodeling in both atria, and as a result, the extent of LA and RA remodeling influences AF recurrence after ablation. [12]

Estimating Atrial Remodeling to Predict AF Recurrence

Atrial structural remodeling is estimated using atrial volume enlargement and myocardial fibrosis. As a common consequence of AF, LA enlargement caused by structural atrial remodeling has been proven to be associated with recurrent AF not only after ablation but also after spontaneous, chemical, or electrical cardioversion in the AFFIRM study. [49] Atrial fibrosis is also known to lead to the triggering and persistence of AF through structural changes in the LA substrate with electrical remodeling. A non-invasive assessment of fibrotic structural remodeling helps to predict the outcome of AF ablation. [50]

Echocardiography

Echocardiography is widely used to measure the LAD because it allows real-time imaging. In 2003,

Table 1 — Image Modality and Predictors of AF Recurrence

Modality UCG	AF type	Follow up (Blanking Period)	AF Recurrence	Predictors of AF Recurrence	Diagnostic Accuracy
Pappone et al.51) (2003) Italy	2D TEE	589 patients 69%(Paroxysmal) 31% (Permanent)	Median 861D (161-1491 D) (BP 0)	16% (1year) 21% (2years) 22% (3years) (Repeaed ab.)	LAD >45 mm (M-mode)	Adjusted HR 3.37 (95% CI, 2.19-5.19)
Berruezo et al.19) (2007) Spain	2D TEE	148 patients 60.8%(Paroxysmal) 23.6% (Persist) 15.5% (Permanent)	13.1 ± 8.4 M (>6 M) (BP 1 M)	26.40% (Repeated ab.)	LAD≤45 mm (M-mode) and no HT LAD >45 mm (M-mode) and HT	≤15% of Recurrence ≥50% of Recurrence
Miyazaki et al.52) (2011) Japan	2D TEE	474 (Paroxysmal)	29.9 ±13.4 M (BP 1 M)	32.90% (Initial ab.)	LAD<40mm (M-mode) 40< LAD ≤50 mm (M-mode) >50 mm (M-mode)	OR 1 Adjusted OR 1.303 (95% CI 1.058-1.594) Adjusted OR 2.141 (95% CI 1.278-3.325)
Parikh et al.54) (2012) USA	2D TEE or 2D TTE	88 patients 45.5% (Paroxysmal) 54.5% (Persistent)	12 M (BP 0)	12% (Paroxysmal) 48% (Persistent) (Repeated ab.)	Modified Simpson's rule LAV ≥99 mL (mean of 2 views) In the 2-, 3- and 4-chamber views LAD ≥49 mm (mean of 3 views by TEE) LAD ≥47 mm, (1 view by TEE) LAD ≥48 mm, (standard PLAX view by TTE) Biplane area-length methods from apical 4- and 2-chamber views	 OR 3.8 (95% CI 1.4-10.3) OR 6.5 (95% CI 2.3-18.6) OR 3.2 (95% CI 1.2-9.0) OR 5.0 (95% CI 1.8-13.7)
Shin et al.55) (2008) Korea	2D TEE	68 patients 58.8% (Paroxysmal) 41.2% (Persistent)	6 M (BP 0)	22% (Repeated ab.)	LAV >34 mL/m^2	Sens: 70%, Spec: 91%
Verma et al.63) (2004) USA	Intracardiac Doppler UC	102 patients (Persistent)	6 M (BP 1 M)	34% (Initial ab.)	19 cm/s of LA appendage peak emptying velocity 29 cm/s of LA appendage peak emptying velocity 36 cm/s of peak PV systolic wave velocity 46 cm/s of peak PV systolic wave velocity The time interval from the initiation of P-wave deflection (PA) to the peak of the mitral inflow A-wave (PDI)	AF Recurrence No AF Recurrence AF Recurrenc No AF Recurrence

Chao et al.64) (2011) British	Pulse Doppler UCG	132 patients (Paroxysmal)	23 ± 13 M (BP 2 M)	27% (Initial ab.)	>160 ms of PA-PDI interval	Sens: 80.6%, Spec: 70.8%
Hammerstingl et al.70) (2011) Germany	Global LA Strain UCG	103 patients 73.8% (Paroxysmal) 26.2% (Persistent)	6 M (BP 0)	29.10% (Initial ab.)	LA-radial and LA-longitudinal strain(Sr, Sl) 2-D speckle-tracking velocities derived from the apical 4- and 2-chamber views (4CV,2CV) 4CVSl <10.79% 4CVSr >– 16.65% 2CVSl<12.31% 2CVSr >–14.9%	 Sens: 85.7%, Spec: 90.5% Sens: 92.9%, Spec: 83.2% Sens: 89.3%, Spec: 88.3% Sens: 85.7%, Spec: 80.9%
Scintigraphy						
Arimoto et al.74) (2011) Japan	^{123}I- MIBG Scintigraphy	88 patients 54.5% (Paroxysmal) 45.5% (Persistent)	13.5 ± 2.2 M (BP 1 M)	28% (Initial ab.)	Cardiac washout rate of ^{123}I-MIBG (every 7.7% of increase) Washout rate of ^{123}I-MIBG >25.1%	 Adjusted HR 1.6 (95% CI 1.004-1.125) Sens: 64%, Spec: 80%
3D CT						
Abecasis et al.82) (2009) Portugal	64-MDCT	99 patients 78.8% (Paroxysmal) 14.1% (Persistent) 7.1% (Permanent)	16.7 ± 6.6 M (>6 M) (BP 3M)	38% (Initial ab.)	Semi-automatic software with atrium endocardial contour, automatic detection and operator correction. LAV >145 mL	 Sens: 78%, Spec: 74% Adjusted OR 8.7 (95% CI 2.7-27.6)
Helms et al.83) (2009) USA	16-MDCT	71.2% (Paroxysmal) 28.8% (Persistent)	12 M (BP 1 M)	34% (Repeated ab.)	Area of each slice by its thickness and summing all volumes for each slice (Simpson method) LAV >135 mL	 Sens: 36%, Spec: 96% Adjusted OR 7.6 (95% CI 1.1-53.0)
Parikh et al.54) (2010) USA	64-MDCT	88 patients 45.5% (Paroxysmal) 54.5% (Persistent)	12 M (BP 0)	12% (Paroxysmal) 48% (Persistent) (Repeated ab.)	Area of each slice by its thickness and summing all volumes for each slice (Simpson method) LAV ≥117 mL (upper quartile) LAV >130 mL	 Adjusted OR 4.8 (95% CI 1.4-16.4) Adjusted OR 22.0 (95% CI 2.5-191) ≥90% of AF Recurrence Ratio
Akutsu et al.39) (2011) Japan	64-MDCT	65 patients (Paroxysmal)	6 M (BP 1 M)	75.4% (Initial ab.)	OsiriX software for the MacOS X system RAV ≥87 mL LAV ≥99 mL Both	 Sens: 81.3%, Spec: 75.5% Sens: 81.3%, Spec: 69.4% Sens: 75%, Spec: 93.9%

Park et al.88) (2009) Korea	3D Spiral CT	70 patients 45.7% (Paroxysmal) 54.3% (Persistent)	21.7 ± 4.2 M (BP 0)	27.1% 18.8% (Paroxysmal) 31.6% (Persistent) (Initial ab.)	(Divided into 4 portions of LA: Venous LA, Posterior LA, Anterior LA, and LAA) Proportional Volume of Anterior LA (61.9±2.6%) (56.7 ± 6.9%) Proportional Volume of Anterior LA (Paroxysmal) (53.8 ± 18.3%) (75.6 ± 20.5%)	 AF Recurrence No Recurrence AF Recurrence No Recurrence
3D MRI						
Oakes et al.33) (2009) USA	1.5 T MRI TIM phased-array receiver coil or 32-channel cardiac coil	81 patients 50.6% (Paroxysmal) 49.4% (Persistent)	9.6 ± 3.7 M (6 to 19 M) (BP 3 M)	30.9% (Initial ab.)	3D visualization and segmentation of MRI using OsiriX software Mild Enhancement <15% of the LA wall Moderate Enhancement >15% and <35% Extensive Enhancement >35% Extent of Enhancement LAV <59.89 mL LAV >59.9 and <85.9 mL LAV >85.91 and >116.12 m LAV >116.13 mL	 14% of AF Recurrence 43.3% of AF Recurrence 75% of AF Recurrence Adjusted OR 4.88 (95% CI 1.73-13.74) Adjusted OR 1.02 (95% CI 1.01-1.04
Akoum et al.50) (2011) USA	1.5 T MRI TIM phased- array reciever coil	120 patients 50% (Paroxysmal) 70% (Persistent	283 ± 167 D (BP 3 M	31% (Initial ab.	3D visualization of MRI using custom made Utah Stage 1: <5% of LA wall Utah Stage 2: >5% and <20% Number of PVs encircled by scar after ablation LAV Utah Stage 3: >20% and <35% Overall LA scar of LA (%) after ablation Utah Stage 4: >35%	 0% of AF Recurrence 28% of AF Recurrence Adjusted HR 0.43 (95% CI 0.200.92) Adjusted HR 1.01 (95% CI 1.0-1.02) 35% of AF Recurrence Adjusted HR 0.63 (95% CI 0.42-0.94) 56% of AF Recurrence No predictor

Abbreviation: AF = Atrial Fibrillation, BP = Blanking Period, ab. = ablation, UCG = Ultrasound Cardiography, 2D TEE = 2 Dimensional Transoesophageal Echocardiography, TTE = Transthoracic Echocardiography, PLAX = parasternal long-axis, M = Month, D = Day, LAD = Left Atrial Dimension, HT = Hypertension, HR = Hazard Ratio, CI = Confidence Interval, LAV = Left Atrial Volume, Sens = Sensitivity, Spec = Specificity, OR = Odds Ratio, PA-PDI = The time interval from the initiation of P-w ave deflection (PA) to the peak of the mitral inflow A-wave (PDI), M = Month, Sr, Sl, 4CV, 2CV = LA-radial and LA-longitudinal strain (Sr, Sl) 2-Dimension speckle-tracking velocities derived from the apical 4- and 2-chamber views (4CV, 2CV), ^{123}I-MIBG = iodine-123-metaiodobenzylguanidine, 3-D CT = 3-Dimensional Computed Tomography, 64-MDCT = 64-Multidetector Computed Tomography, RAV = Right Atrial Volume, 3-D MRI = 3-Dimensional Magnetic Resonance Imaging.

Pappone et al. [51] reported a LAD >45 mm using M-mode transesophageal echocardiography (TEE) to be a predictor of AF recurrence for median 2.4 years after CPVI in 589 ablated patients with paroxysmal (69%) and chronic AF (31%) (Table 1). The success rate of 73.6% in ablated AF patients was defined as a result of repeated AF ablations. Berruezo et al.[19] also examined risk factors for AF recurrence in 148 combined AF patients (60.8% with paroxysmal, 23.6% with persistent, and 15.5% with permanent AF) undergoing CPVI with line ablation during 6 months and showed, using 2-D M-mode TEE, that a LAD >45 mm and a history of hypertension (HT) were independent predictors of AF recurrence. They used a one-month blanking period for AF recurrence during the follow up because late AF recurrence is distinguished from early recurrence after ablation. Using 2-D M-mode transthoracic echocardiography (TTE) in 474 Japanese patients with only paroxysmal AF, Miyazaki et al.[52] showed that the patients with moderate (40-50 mm) and severe LA dilation (>50 mm) had a 1.30-fold and 2.14-fold increase, respectively, in the probability of recurrent AF after pulmonary vein antrum isolation (PVAI) with line ablation, and/or elimination of all non-PV triggers of AF, during a mean follow up of 30 ± 13 months with a blanking period of 1 month compared to patients with a normal LA diameter (≤40 mm). The successful ratio of 67.1% was defined as a result of initial AF ablation. Those studies showed the significance of M-mode echocardiography in measuring LA size in patients with AF. However, in 2009, Hof et al.[53)] demonstrated that the LAD measured by M-mode TEE correlates poorly with the LA volume (LAV) measured by 3-D CT in patients with AF and that 2-D echocardiography is not useful for predicting AF recurrence. In contrast, in 2010, Parikh et al.[54] demonstrated that a LAD ≥49 mm using the 3-chamber view of TEE is a more powerful predictor of AF recurrence after repeated PVAI with line ablation, and/or CFAE ablation, during 12-month follow up compared to a LAV ≥99 mL in 88 combined AF patients using LAD in M-mode TTE, 2-, 3- and 4-chamber views of TEE, and LAV measured by modified Simpson's rule. It is controversial whether the LAD measured using 2-D echocardiography is accurate, but in the least, those studies showed that a LAD ≥50 mm by 2-D echocardiography is a risk factor of AF recurrence as shown in ACCF/AHA/HRS guideline [1] despite the type of AF (but mainly including paroxysmal AF), different body surface area by the race, different follow-up periods with different blanking periods, and different ablation procedures, including whether the ablation procedure was repeated during follow up. Shin et al. [55] evaluated the LAV as a predictor of AF recurrence after PVAI over a 6-month period without a blanking period. The LAV was measured using 2-D TEE but was assessed by biplane area-length methods from apical 4- and 2-chamber views in 68 combined AF patients (40 with paroxysmal and 28 with persistent AF). They showed that a LA volume >34 mL/m^2 (per body surface area) had a sensitivity of 70% and specificity of 91%, but the value of LAV for predicting AF recurrence was smaller compared to the 2-D TEE study by Parikh et al (LAV ≥99 mL).

Previous studies have suggested that 2-D echocardiographic methods systematically underestimate LAV compared to CT or MRI quantitation.[56,57,58] Thus, 2-D echocardiography is limited for assessing the LAV by significant geometric assumptions and has low reproducibility due to the diverging position and orientation of image planes. The recent advances in 3-D echocardiographic technology may make it possible to measure the LAV accurately. In contrast, 2-D echocardiography can measure the LAD easily, simply, and similarly among every hospital or medical center, which may standardize the value of the LAD as a guideline for patient selection for AF ablation.

The value of LA function as a marker of structural remodeling was investigated using imaging modalities because LA dysfunction leads to LA enlargement in patients with AF. However, it is difficult to accurately diagnose the degree of LA dysfunction because the wall motion is smaller in the LA compared to the LV. The peak LA appendage (LAA) emptying flow using TEE has been previously validated as an indicator of LA function. Previous studies showed that a peak LAA emptying flow of <20 cm/s is associated with higher rates of AF recurrence, [59] whereas values >30 cm/s may predict the success of direct-current cardioversion. [60] Recently, the intracardiac echocardiography has been used to obtain on-line acquisition of anatomic information regarding left atrial and PV during catheter ablation, [61] potential

to assess hemodynamic function and the monitoring of acute complications, such as pericardial effusion and PV occlusion. [62] Using intracardiac echocardiography in 102 patients with only persistent AF, Verma et al. [63] showed a velocity of only 19 cm/s in those with AF recurrence versus 29 cm/s in those without recurrence from 1 month to 6 months after PVAI (Table 1). These results indicate that <20 cm/s of LAA flow on Doppler echocardiography is a marker of AF recurrence. Chao et al. [64] showed using the time interval from the initiation of p-wave deflection to the peak of the mitral inflow a-wave (PA-PDI) on the pulse-wave Doppler imaging as a marker of atrial remodeling in 132 paroxysmal patients with CPVI and elimination of all non-PV triggers of AF including isolation of the SVC that a PA-PDI >160 ms had a sensitivity of 80.6% and a specificity of 70.8% for AF recurrence. Ultrasound-based, 2-D, speckle-tracking imaging allows for noninvasive quantification of the LA-myocardial deformation properties during the heart cycle, [65, 66, 67] and 2-D speckle-tracking imaging analysis of the LA has been shown to correlate with the extent of structural LA remodeling in patients with AF. [68] Previous studies reported that LA deformation estimated using 2-D, speckle-tracking imaging predicted AF recurrence in patients undergoing either external cardioversion of AF[65] or ablation procedures.[69] More recently, Hammerstingl et al.[70] demonstrated in 103 combined AF patients (76 with paroxysmal and 27 with persistent AF) with PVAI that assessing global LA strain with 2-D speckle-tracking identified patients at high risk for AF recurrence (sensitivity >85% and specificity >90.5%). Kupahally et al. [71] also showed that LA deformity using 2-D speckle tracking LA peak strain correlated with the quantity of LA fibrosis measured by MRI in patients with AF. These unique data using Doppler echocardiography or 2-D, speckle-tracking imaging was reported as a predictor of AF recurrence, but in addition to the angle dependency of Doppler imaging and difficult analysis of LA systole with 2-D stain, it is hard to obtain strain imaging due to the distance from the chest wall and the presence of pulmonary veins or the fossa of ovalis; therefore, the technique used to obtain the image and the analysis of the obtained images may require an expert with special software.

Iodine-123 Meta-iodobenzylguanidine Scintigraphy

Molecular cardiovascular imaging using iodine-labeled radiotracers has an important role in imaging rhythm disorders at both the molecular and cellular levels. [72, 73] Cardiac iodine-123 meta-iodobenzylguanidine (^{123}I-MIBG) uptake on scintigraphy represents the function of the cardiac sympathetic nervous system. In 2011, Arimoto et al. [74] showed using ^{123}I-MIBG scintigraphy that the washout rate of cardiac ^{123}I-MIBG uptake at 4 hours after intravenous injection of tracer was a more powerful predictor of an AF recurrence after extensive PVAI with line ablation and/or SVC ablation with an hazard ratio of 2.0 for every 7.7% increase of washout rate than LAD measured by M-mode echocardiography with hazard ratio of 1.75 for every 7 mm in 88 combined AF patients (48 with paroxysmal and 40 with persistent AF) during a mean follow-up period of 13.5 ± 2.2 months with a 1-month blanking period (Table 1). They showed that 25.1% of the washout rate was a threshold value for AF recurrence with a 64% of sensitivity and 80% of specificity. Sympathetic innervation is associated with PV triggers for AF recurrence in addition to the influence of structural remodeling on LA enlargement. [75] Our study previously showed that sympathetic innervation correlates to the LAD measured by M-mode echocardiography in patients with paroxysmal AF and is associated with the development of AF. [6]

The differences in cardiac ^{123}I-MIBG uptakes by the different scintigraphic machine, including collimator type, and different scintigraphic protocols, including the time from the tracer injection to the collection, may make multi-center comparisons of ^{123}I-MIBG values difficult, and single-center results may not easily be extrapolated to other hospitals.

Three-dimensional Computed Tomography

Recently, MDCT has allowed multi-dimensional reconstruction of patient-specific cardiac anatomy.[76] Quantitative analysis of cardiac chamber geometry is an essential component of a complete cardiac evaluation using 3-D cardiac imaging, such as MDCT with iodine contrast medium. [77, 78] In the area of arrhythmogenic heart disease, 3D cardiac image registration using MDCT is cur-

rently being investigated and used clinically for AF catheter ablation.[79,80] Computed tomography-rendered volumes add 3-D to an otherwise 2-D ablation procedure, allowing for better delineation of the complex LA anatomy with precise volume estimation and increased electroanatomic mapping accuracy.[78, 81] Abecasis et al. [82] used 64-MDCT in combined AF patients (78 with paroxysmal, 14 with persistent, and 7 with permanent AF) over 16.7 +/- 6.6 months (6-month minimum) with an excluded blanking period of 3 months after PVAI with line ablation and demonstrated that a LAV >145 mL had a sensitivity of 78% and specificity of 74% for AF recurrence (Table 1). Their study patients included 51.5% with HT, 9.1% with ischemic heart disease, and 5.1% with diabetes. They measured the LAV using semi-automatic software with atrium endocardial contours, automatic detection and operator correction. Using 16-MDCT, Helms et al. [83] also demonstrated in a 12-month follow-up study with an excluded blanking period of 1 month in combined AF patients that the sensitivity of a LAV >135 mL for predicting AF recurrence after repeated PVAI with line ablation was 36%, and the specificity was 96%. Their study patients included 48% with HT, 15% with ischemic heart disease, 11% with diabetes, and 14% with mitral valve disease. They measured the LAV by multiplying the area of each slice on the 2-D image by its thickness and summing all of the volumes for each slice (i.e., the Simpson method). Parikh et al. [54] also showed by a similar method to Helms at al. using 64-MDCT in American patients with combined AF patients that a LAV ≥117 mL was associated with an odds ratio (OR) for AF recurrence of 4.8. Their study patients included 60.2% with HT, 10.2% with ischemic heart disease, 8% with diabetes, and 3 patients with prior valve surgery. In contrast, in our study, [39] each atrial volume (RAV ≥87 mL or LAV ≥99 mL) using 64-MDCT was predictive of AF recurrence (RAV: sensitivity 81.3%, specificity 75.5%; LAV: sensitivity 81.3%, specificity 69.4%) over 6 months with a 1-month blanking period in Japanese patients with only paroxysmal AF. We used quantitative 3-D measurement software (OsiriX software) to measure both the LAV and RAV before extensive PVAI. Our study patients included 48% with HT, 13.8% with diabetes, and no one with a history of ischemic heart disease or significant valve disease. The LAV values for AF recurrence in the latter 2 studies were less than those in the former 2 studies.

The 3-D MDCT is a best tool for spatial and especially in temporal resolution. It is possible to assess atrial volume enlargement accurately with less influence from the technique, software, and expert used because of high reproducibility. However, the accurate volume measurement may cause uneven result due to the differences in patient backgrounds, such as the history of structural heart disease, AF type, and ablation procedure. First, using atrial enlargement as a powerful predictor of AF recurrence was intended for only patients with paroxysmal AF. In contrast, excluding patients with paroxysmal AF reduces [84] or eliminates[85, 86] the value of atrial enlargement for predicting AF recurrence because persistent or permanent AF is a predictor of AF recurrence itself. Paroxysmal AF is frequently a purely trigger-dependent phenomenon with structural remodeling, whereas permanent AF is generally mechanistically complex, implicating a more diffuse abnormality of the atrial substrate. [1] In other words, the role of both atrial electrical and structural remodeling is predominant over triggers in patients with persistent or permanent AF. [87] This difference is confirmed by the fact that a longer history of AF or shorter AF cycle length [84,85] is superior for predicting the recurrence of persistent AF to LA enlargement as a marker of structural remodeling although the present image modalities have not a capacity to assess the characteristics of occurrence of AF. Second, successful catheter ablation may be related to the ablation lesion targeting the substrate-roof line, mitral isthmus line, or CFAE ablation, particularly in permanent AF. Therefore, for patients that develop AF, different technical protocols or procedures may result in the different predictors of AF recurrence and different cut-off values for the predictors. Atrial enlargement on the whole represents structural remodeling, but a dilated atrium does not always lead to AF recurrence.

Park et al. [88] examined regional LAV using 3-D spiral CT in 70 combined AF patients. When each LA image on 3D spiral CT was divided into the venous atrium (VA), anterior LA (ALA), LA appendage (LAA), and antrum, recurrence after paroxysmal AF ablation was more common in patients with a disproportional enlargement of the

anterior portions of the LA than those with no recurrence after PVAI with line ablation. Measuring regional volume on 3-D CT is unique, and these results indicate that the difference in regional LA enlargement may change the ablation strategy or ablation target lesion.

Delayed Enhanced Magnetic Resonance Imaging

Atrial fibrosis or scarring have been invasively detected by contact voltage mapping with a multipolar circular catheter in the LA and have been evaluated by 3-D electroanatomic mapping. However, atrial fibrosis was recently estimated noninvasively from delayed enhanced cardiac magnetic resonance (DE-MRI) imaging. DE-MRI is an established method for visualizing tissue necrosis in cardiac disease processes, including myocardial infarction and myocarditis. [89-91] Contrast enhancement occurs as a result of altered washout kinetics of gadolinium relative to normal surrounding tissue, which may reflect increased fibrosis or tissue remodeling of the myocardium.[89] Oakes et al. [33] recently showed using a 1.5 Tesla scanner 3-D DE-MRI in 81 combined AF patients (41 with paroxysmal and 40 with persistent AF) that the extent of LA enhancement predicted AF recurrence after PVAI and posterior wall and septal debulking during an average follow up of 9.6 +/- 3.7 months (range from 6 to 19 months) (Table 1). They showed that the rate of AF recurrence was 6 patients (14.0%) with minimal enhancement (<15% of the LA wall), 13 (43.3%) with moderate enhancement (>15% and <35% of the LA wall), and 6 (75%) with extensive enhancement (>35% of the LA wall, p<0.001), and extensive LA enhancement predicted more accurately the AF recurrence with an OR of 4.88 compared to a large LAV (>116.13 mL) measured by MRI with an OR of 1.02. The extent of LA enhancement correlated with the electroanatomical voltage mapping data, which reflects the fibrosis. CARTO-based voltage mapping studies have been associated with a high degree of spatial error, from 0.5 to 1.0 cm, in comparative studies.[92,93] In contrast, reconstruction with DE-MRI provides information on the anatomy and location of pathology without spatial distortion. Akoum et al.[50] examined the relationships of atrial fibrosis before ablation and atrial scarring after ablation to AF recurrence in 144 patients who were staged by the percent of fibrosis quantified with DE-MRI relative to the LAV (minimal or Utah stage 1, <5%; mild or Utah stage 2, 5–20%; moderate or Utah stage 3, 20-35%; and extensive or Utah stage 4, >35%). All patients underwent PVAI and posterior wall and septal debulking, LA scarring was quantified, and the PV antra were evaluated for circumferential scarring 3 months post ablation. The extent of LA scarring post ablation was comparable across the 4 stages, and most patients had either no (36.8%) or 1 (32.6%) of the 4 targeted PV antrums circumferentially scarred. However, the extent of atrial fibrosis before ablation positively correlated with persistent AF (Utah stage 1, 40%; Utah stage 2, 55%; Utah stage 3, 65%; and Utah stage 4, 75%) and with AF recurrence after ablation (Utah stage 1, 0%; Utah stage 2, 28%; Utah stage 3, 35%; and Utah stage 4, 56%). More important in their study was the fact that the achievement of circumferential PV antral scarring caused by ablation predicted ablation success in mild LA fibrosis, while the achievement of posterior wall and septal scarring was needed for success in moderate fibrosis. This result confirms that isolation of PV triggers may be acceptable in paroxysmal AF, whereas patients with more clinically advanced AF are likely to have a better long-term outcome with more extensive ablation. [94-96] Determining the extent of atrial fibrosis before ablation provides an opportunity to characterize the stage of disease. On the basis of the DE-MRI results, AF ablation in patients with extensive LA structural remodeling is offered with a reduced expectation of long-term success. Surely, this result would have been proposed by Natale et al. [21]

DE-MRI is a most anticipated image modality for predicting AF recurrence by directly detecting LA myocardial fibrosis. However, the presence of respiratory navigator artifacts and MRI noise may lead to the inappropriate detection and quantification of fibrosis because of comparably longer examination time and LA wall thinning. Furthermore, the algorithm used to detect and quantify fibrosis requires an experienced observer to choose the threshold levels. Significant improvements in LA wall imaging with greater spatial resolution and improved signal-to-noise ratio are expected in the future. In the near future, DE-MRI will be used for estimating the extent of atrial fibrosis and determining the ablation point.

Conclusions

Atrial remodeling, particularly structural remodeling, plays an important role in AF recurrence. These non-invasive imaging modalities are significant tools for estimating atrial enlargement to improve patient selection for AF ablation at the point of paroxysmal AF and for estimating atrial fibrosis to select the AF treatment including ablation strategy at the point of development to persistent or permanent AF.

Disclosures

No disclosures relevant to this article were made by the author.

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