

## Left Atrial Diastolic Dysfunction following Catheter Ablation of Atrial Fibrillation

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### Abstract

Radiofrequency catheter ablation (RFCA)-induced thermal injury may cause and/or worsen left atrial (LA) diastolic dysfunction leading to pulmonary hypertension and heart failure in patients with atrial fibrillation (AF), the incidence of which is probably more common than is generally realized. Biplane 2-dimensional echocardiography coupled with tissue Doppler (velocity) imaging and Doppler-derived strain (rate) imaging can be applied to provide quantitative assessment of the LA function (both systolic and diastolic) relative to pulmonary venous circulation and left ventricular function. Information so obtained is useful for guiding follow-up management of patients undergoing RFCA of AF.

### Introduction

Radiofrequency catheter ablation (RFCA) has evolved to become an important treatment modality for drug refractory symptomatic paroxysmal and persistent atrial fibrillation (AF).<sup>1</sup> The success rate RFCA of AF is estimated to be 60-80 % in a worldwide survey.<sup>1</sup> Although short-term follow-up studies have shown that RFCA significantly improves the quality of life in patients suffering from such an arrhythmia, its long term effects on the incidence of stroke and heart failure and the overall mortality remain to be determined.<sup>1,2</sup> Recently, Gibson et al.<sup>3</sup> used right heart catheterization to investigate 19 patients (out of 1380 consecutive patients) who had developed unexplained dyspnea with "less than mild" mitral regurgitation on echocardiography after RFCA of AF. They demonstrated "new or worsening" pulmonary hypertension alongside diastolic dysfunction of the left atrium

(LA) reflected as large V waves recorded on pulmonary capillary wedge or LA pressure tracings in the absence of significant mitral regurgitation in these patients. These findings were indicative of LA diastolic dysfunction, consistent with the so-called "stiff LA syndrome" originally observed in patients, status post-surgical replacement of the mitral valve.<sup>4</sup> Despite the incidence being relatively small (1.4%), they implied that RFCA-induced scarring of the LA was the culprit and the "stiff LA syndrome" could have accounted for pulmonary hypertension and symptoms of heart failure in these patients. Since the LA diastolic function is seldom contained in the evaluation of patients following RFCA of AF, we aim to review the subject and propose the use of two-dimensional (2-D) echocardiography along with tissue Doppler imaging and Doppler-derived strain (rate) imaging for noninvasive quantitative assessment of the LA function<sup>5,6</sup> in managing this subset of patients.

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### Effects of Radiofrequency Catheter Ablation on Systolic Function of Left Atrium

RFCA of AF is considered a relatively invasive and complex procedure. It requires trans-septal placement of mapping and ablation catheters from the right atrium to the LA and application of radiofrequency energy to produce thermal injury to the LA tissue.<sup>1,7</sup> An extensive area of RFCA seems required for successful elimination of AF.<sup>8</sup> However, because of the complexity of the trigger/substrate of AF, the exact extent of the area and the amount of tissue needed to be ablated in the LA remain debatable. Consequently, the procedure strategy varies greatly among different centers.<sup>1,7</sup> In general, for effective restoration of sinus rhythm, a “stepwise approach” is preferred, i.e., circumferential pulmonary vein (PV) isolation followed by ablation lines created in the roof, anterior wall, septum, mitral isthmus, and/or posterior annulus, and if deemed necessary, additional ablation of fractionated atrial electrograms is performed.<sup>1</sup> As such, it is hoped that sufficient scar tissue can be created in the LA to prevent initiation of any sustainable reentrant arrhythmias.

It has been shown that RFCA can produce scarring and fibrosis of the atrial wall with subsequent thinning.<sup>9</sup> To assess the effect of scar tissue so created on the LA function, Wylie et al.<sup>10</sup> performed cardiovascular magnetic resonance imaging (MRI) in 33 consecutive patients with paroxysmal or persistent AF before and after (mean 48 days) circumferential PV isolation. They noted that the maximum LA volume decreased by 15% ( $P < 0.001$ ), whereas LA ejection fraction decreased by 14% ( $P < 0.001$ ) in 16 patients of the study cohort in whom high spatial resolution late gadolinium enhancement MRI images of LA scar were obtained. Of note, the decrement in LA systolic function correlated well with the amount of LA scar presumably produced by RFCA (mean LA scar volume  $8.1 \pm 3.7$  ml;  $r = -0.75$ ,  $P < 0.001$ ). They concluded that that LA scar produced by RFCA could adversely affect the LA systolic function and thus raised concern that procedures with extensive RFCA might increase the risk of post-procedural thromboembolism. No LA diastolic function relative to the amount of LA scar was evaluated in the study.

Numerous clinical studies have attempted to ad-

dress the effects of the RFCA procedure on the LA. Jeevanantham et al.<sup>11</sup> identified 17 out of 192 studies, enrolling 869 patients, in which primary outcomes had been set forth for changes in the LA size or volume and/or function before and after RFCA; fixed- and random-effects meta-analyses were used to weigh mean differences for changes in LA diameter, LA maximum volume, LA minimum volume, LA ejection fraction, and LA active emptying fraction. They found that decreases in LA diameter and LA volumes were significant in those without but not in those with AF recurrence and that while LA ejection fraction and LA active emptying fraction decreased in patients with AF recurrence, they did not decrease in patients without AF recurrence. They surmised that successful RFCA in patients with AF significantly decreased the LA size and volume but did not seem to adversely affect the LA systolic function. As had been pointed out by Gibson et al.<sup>3</sup> most of these studies included in this meta-analysis used variable RFCA strategies and were mostly retrospective in nature using consecutive and relatively small sampling designs, and none of them had systemically addressed the issue of RFCA effects on the diastolic function of LA.

### Mechanical Function of the Left Atrium in the Presence of Normal and Abnormal Left Ventricular Function

Bridging between the PV system and the left ventricle (LV), normally the mechanical function of LA consists of three phases during the cardiac cycle, serving as a pump, a reservoir, and a conduit, and thereby modulating intermittent filling of the LV.<sup>12</sup> First, the LA contracts right before the onset of the systolic phase of LV establishing the LV end-diastolic volume. Second, it becomes a reservoir that stores PV return during LV contraction and isovolumic relaxation after the closure and before the opening of the mitral valve. Third, the LA provides a conduit that directs its contents into the LV via an LA-LV pressure gradient after the mitral valve opens while continuing to passively transfer PV blood flow during LV diastasis.<sup>11</sup> The relative contribution of the LA pump function to the filling of the LV is estimated to be 25%, whereas those of the reservoir, and conduit functions, are 40% and 35%, respectively.<sup>13</sup> Nevertheless, these 3 phasic functions of the LA can be affected by changes in

LV function and age.<sup>14,15</sup> The booster pump contribution to the cardiac output becomes increasingly important to the preservation of cardiovascular performance in patients with LV dysfunction. In the presence of LV diastolic dysfunction (i.e., abnormal relaxation), the relative contribution of LA pump and reservoir functions increase and that of conduit function decreases because of attendant reduction of the LA-LV pressure gradient during early diastole. As LV filling pressure progressively increases due to further deterioration of LV diastolic dysfunction, pump and reservoir functions of the LA can be severely impaired, leaving the LA to serve predominantly as a conduit.<sup>13</sup> Hence, LA function is in a close interdependence with LV function and as a result, LA remodeling is related to LV remodeling.<sup>15</sup> Clinically, when the enhanced significance of LA systole to LV filling is compromised because of severe LV dysfunction or due to AF (loss of atrial pump contribution), patients could then develop signs and symptoms of heart failure. In the latter situation caused by AF, these adverse effects can be reversed or lessened with subsequent restoration of normal sinus rhythm and LA contraction.<sup>13</sup> On the other hand, aging causes structural changes of the LA wall that increase fatty tissue, collagen and fibrosis, leading to progressive remodeling; functionally, the LA reservoir function remains relatively unchanged, whereas its conduit function decreases, which can be an expression of LV diastolic dysfunction.<sup>15</sup>

### Imaging Techniques for Evaluation of LA function

There are several imaging methods that can be used for assessing LA anatomy and function.<sup>5</sup> Both multi-slice computed tomography (MSCT) and cardiovascular MRI generate accurate LA and PV anatomy thereby providing useful information prior to RFCA. However, the former contains radiation exposure and the use of contrast agents, and the latter requires relatively long acquisition time and arduous data analysis. More significantly, the cost and the lack of bedside availability preclude them to be the first-line use in the evaluation of LA function.<sup>5</sup> Even in the follow-up care of patients, these two imaging methods are employed only in selected patients. While clinically it is also impractical to routinely perform right heart catheterization,

the change of the LA function in different phases can be non-invasively assessed by 2-D echocardiography along with tissue Doppler imaging and Doppler-derived strain (rate) imaging.<sup>5,6</sup> The major shortcoming of the latter techniques is that they are computationally intensive; analysis and interpretation of velocity, strain and strain rate need to be done by well trained specialists.

### Two-Dimensional Echocardiography and the Doppler Method for Assessment of LA function

Another area of consideration when referring to LA volumes is that these volumes are usually calculated from apical four- and two-chamber views of the LA using the biplane technique.<sup>5</sup> The LA volume calculated by 2-D echocardiography provides a more accurate measure of the LA size than that of the conventional M-mode echocardiography.<sup>5</sup> Moreover, various LA volumes can be used to describe LA phasic function.<sup>16</sup> Specifically, total LA emptying volume (i.e., an estimate of reservoir volume) can be calculated as the difference between maximum LA and minimum LA volumes; LA passive emptying volume as the difference between maximal LA volume and the LA volume preceding atrial contraction; LA active emptying (contractile) volume as the difference between pre-atrial contraction LA volume and minimum LA volume; LA (passive) conduit volume as the difference between LV stroke volume and the total LA emptying volume and lastly, the LA ejection fraction as the difference between the maximum LA volume and the minimum LA volume divided by the maximum LA volume.

Tissue Doppler imaging quantifies regional tissue motion velocity, whereas Doppler-derived strain and strain rate depict local tissue deformation and measure the rate of deformation, respectively.<sup>5,6,17,18</sup> These two technologies have been validated for the assessment of both global and regional LV function and have recently been extended to the evaluation of regional LA function.<sup>5,6,17,18</sup> Using standard pulsed-wave tissue Doppler imaging, mitral inflow velocities are recorded at the tips of the mitral valve leaflets in an apical four-chamber view.<sup>5,6</sup> The pulsed Doppler profile of trans-mitral inflow is composed of an early (E wave) and late (A wave) diastolic flows.

The E wave represents LV filling in early diastole, which is a combination of passive and active LV function when LA acts as a conduit. The trans-mitral A wave reflects LA contractile function. PV flow velocities are measured from the apical four-chamber view usually by sampling the right upper PV. Spectral pulsed Doppler of PV can be used to evaluate LA function as well.<sup>19,20</sup> The first positive wave (PVs wave) during LV systole indicates the reservoir function of LA, and the 2nd positive wave (PVd wave) after the opening of mitral valve acts as LA conduit function. The reversal wave (PVa wave) after P wave on electrocardiogram represents LA contraction which is usually combined with trans-mitral A wave to describe the booster pump function of the LA. Although the Doppler technique is an easy and reproducible way to evaluate LA function, it has been shown to be dependent on the LA loading condition, LA contractile state, and LV function.<sup>20</sup> Therefore, these potential limitations should be taken into consideration while attempting to interpret the LA function using these indices.

To obtain LA Doppler-derived strain (rate) data, a small sample volume of interest, usually less than 12 mm in length, is placed on each mid-segment of the LA wall in four- and two-chamber views.<sup>5,6,17,18</sup> With the use of the trans-mitral Doppler profile of the aortic and mitral valves, different cardiac phases of systole and of early and late diastole can be accurately identified. Peak strain and strain rate are calculated at each of several mid-LA segments (e.g., septal, lateral, anterior, inferior). The LA appendage is a highly contractile structure which provides important reservoir function of the LA, especially when the LA pressure or volume is significantly increased.<sup>21</sup> Due to its anatomical location, the trans-esophageal approach confers better assessment of its structure and function (e.g., the size, emptying and filling velocities).<sup>5,6,17,18</sup> Analysis of velocity and strain (rate) of the desired atrial segment includes measurements during ventricular systole (Sa), early ventricular diastole (Ea) and late ventricular diastole (Aa). The Aa-wave is regarded as a direct measure of regional active atrial contraction and the Sa and Ea waves represent the passive expansion and emptying components of the LA function. Strain reflecting regional myocardial lengthening is usually expressed as a positive value and strain reflecting regional myocar-

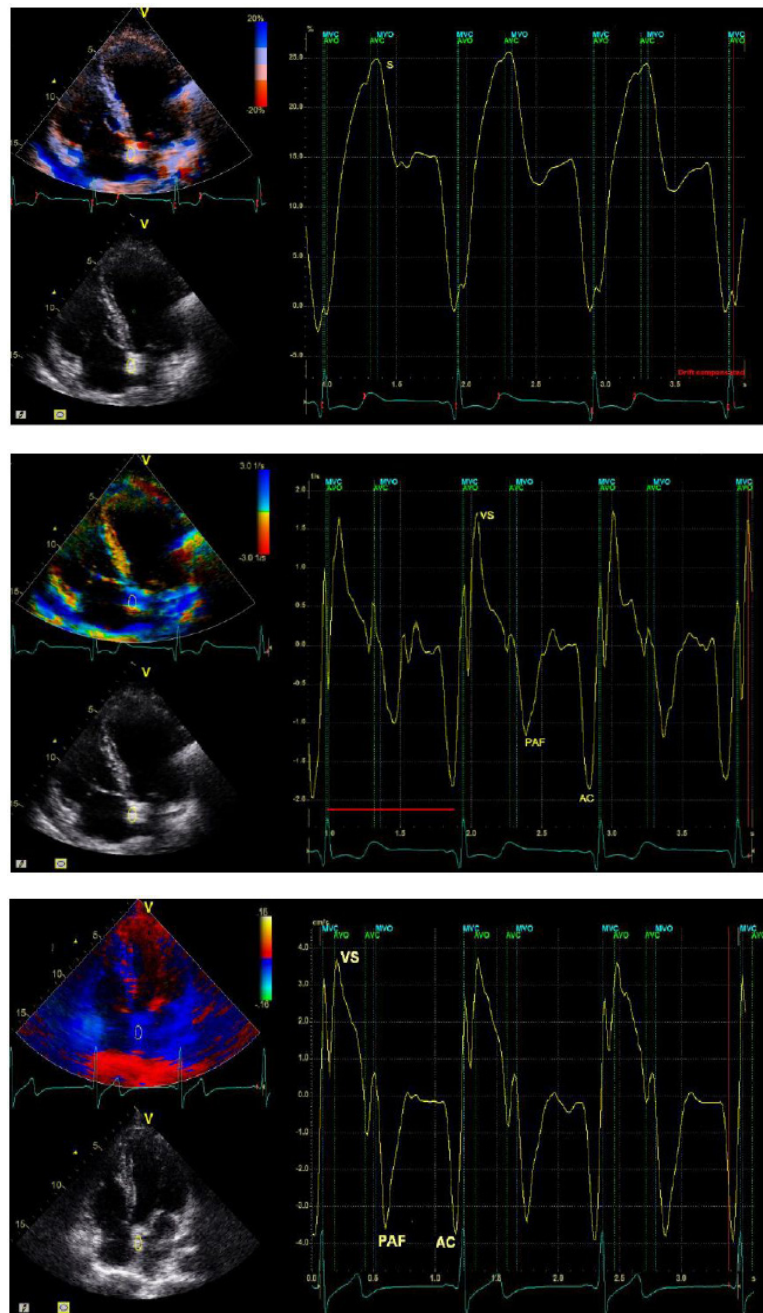
dial shortening a negative value (Figure 1).<sup>5,6,17,18</sup>

### Relevant Clinical Studies Using the Doppler Method for LA Function Evaluation

Several studies have demonstrated the value of regional atrial strain (rate) in the analysis of patients undergoing external cardioversion. In 65 patients with lone AF for at least 3 months, Salvo et al.<sup>23</sup> demonstrated that these AF patients had significantly reduced atrial myocardial properties compared with healthy controls (velocity,  $3.2 \pm 1.4$  vs.  $5.7 \pm 1.3$  cm/s; strain,  $23.3 \pm 19$  vs.  $92 \pm 26\%$ ; strain rate,  $2 \pm 0.9$ -1 vs.  $4.2 \pm 1.8$  seconds<sup>-1</sup>;  $P < 0.0001$ ). Using multivariable analysis, they also showed that patients with higher LA strain and strain rate (especially, inferior wall peak systolic strain rate and septal peak systolic strain) had a greater likelihood of maintaining sinus rhythm after external cardioversion. Similarly, in 52 patients with AF for less than 1 year, Wang et al.<sup>24</sup> found that compared with healthy controls, the LA velocity measured during ventricular systole ( $2.36 \pm 1.04$  vs.  $3.68 \pm 0.99$  cm/s,  $P < 0.001$ ) and early diastole ( $2.78 \pm 1.26$  vs.  $3.50 \pm 1.11$  cm/s,  $P < 0.05$ ), and the strain rate calculated during ventricular systole ( $2.05 \pm 0.96$  vs.  $2.83 \pm 0.73$  seconds<sup>-1</sup>,  $P < 0.01$ ) were markedly reduced in AF patients. Moreover, the strain rate calculated during ventricular early diastole was significantly lower in patients who failed to respond or had AF recurrence when compared with those without AF recurrence within 4 weeks after external cardioversion ( $2.32 \pm 0.95$  vs.  $3.17 \pm 0.93$  seconds<sup>-1</sup>,  $P < 0.01$ ). Additionally, they noted that a lower early diastolic strain and larger transverse LA diameter were independent predictors of failure of external cardioversion (HR, 95% CI: 0.36, 0.14-0.88 and 2.85, 1.33-6.10, respectively).

In patients with chronic AF (>3 months and <1 year), Thomas et al.<sup>25</sup> showed that atrial strain was significantly decreased immediately after external cardioversion compared to healthy controls and despite that there was gradual recovery with maximal changes observed in the initial 4 weeks, atrial pump function failed to normalize over time. These latter findings confirmed that atrial stunning,<sup>26</sup> characterized by reduced atrial mechanical function after restoration of sinus rhythm from AF could occur, thereby increasing the risk of thrombo-embolism. Kaya et al.<sup>27</sup> also studied patients with chronic AF and noted that

**Figure 1:** Representative atrial myocardial velocity (upper panel), strain (middle panel) and strain rate (lower panel) tracings are obtained from the left atrial septum. Four-chamber echocardiograms are displayed at the left and ECG at the bottom of each panel. A time interval (red line) depicting R-R of the ECG is shown in the lower panel. AC= atrial contraction; PAF= passive atrial filling; S= strain and VS= ventricular systole.



LA (transthoracic approach) and LA appendage (transesophageal approach) strain and strain rates were significantly lower one day after cardioversion ( $5.0 \pm 2.8\% / 2.3 \pm 1.0$ ;  $7.6 \pm 3.6\% / 1.6 \pm 0.7$ , respectively), which subsequently improved 10 days post-cardioversion. These sequential changes in the LA strain and strain rate were in parallel to those changes in the emptying and filling velocities of the LA appendage (e.g., LA systolic strain and LA appendage emptying velocity,  $r = 0.73$ ,  $P =$

$0.007$ ). Thus, these investigators had clearly demonstrated that there was a significant decrease in LA compliance in patients with AF, affecting the reservoir and conduit functions as well as that of the booster pump which is virtually lost during AF. They further advocated that regional LA function as assessed by combined tissue Doppler (velocity) imaging and Doppler-derived strain (rate) imaging could provide insightful information for predicting success or failure for external

cardioversion and for guiding anticoagulation and anti-arrhythmic therapy in these AF patients. More relevant to the present subject, Schneider et al.<sup>17</sup> applied Doppler-derived strain (rate) to evaluate 118 patients (74 paroxysmal AF, 44 persistent AF) before and after RFCA for AF. With peak strain rate (SR) and strain (S) measured during systole (LAs) and at early (LAe) and late diastole (LAa), they noted that while both groups of patients had decreased atrial myocardial properties compared with controls after RFCA (Controls:SR-LAs 4.1 seconds<sup>-1</sup>, S-LAs 88%, SR-LAa 22.9 seconds<sup>-1</sup>), the extent of decrement was more severe in those with persistent AF (SR-LAs 2.3 seconds<sup>-1</sup>, S-LAs 25%, SR-LAa 21.9 seconds<sup>-1</sup>) than those with paroxysmal AF (SR-LAs 2.5 seconds<sup>-1</sup>, S-LAs 30%, SR-LAa 22.2 seconds<sup>-1</sup>) ( $P < 0.011$ ). Moreover, these parameters increased in patients who had maintained sinus rhythm in contrast to patients who had had AF recurrence during a 3-month follow-up ( $P < 0.001$ ) and the best predictors for maintaining sinus rhythm were cut-off values of 2.25 seconds<sup>-1</sup> for septal and inferior SR-LAs and of 19.5% for inferior S-LAs ( $P < 0.001$ ). They concluded that Doppler-derived strain (rate) imaging could be applied to quantitatively assess LA function and data so obtained could be used as a potential marker of atrial reverse remodeling after RFCA. Of interest, using delayed-enhancement MRI to quantify and visualize the extent of scar tissue in atrial myocardium, Kuppahally et al.<sup>28</sup> studied 65 patients with paroxysmal AF (44%) or persistent AF (56%), in whom 2-D echocardiography and Doppler-derived LA strain (rate) had been obtained. They demonstrated that fibrosis values correlated inversely with LA mid-lateral strain ( $r = -0.5$ ,  $P = 0.003$ ) and strain rate ( $r = -0.4$ ,  $P < 0.005$ ). Patients with persistent AF seemed to have more fibrotic scar compared to those with paroxysmal AF ( $22 \pm 17\%$  vs.  $14 \pm 9\%$ ,  $P = 0.04$ ) and lower mid-septal ( $27 \pm 14\%$  vs.  $38 \pm 16\%$ ,  $P = 0.01$ ) and mid-lateral ( $35 \pm 16\%$  vs.  $45 \pm 14\%$   $P = 0.03$ ) LA strains. Furthermore, multivariable regression showed that mid-lateral strain ( $r = -0.5$ ,  $P = 0.006$ ) and strain rate ( $r = -0.4$ ,  $P = 0.01$ ) inversely correlated with the extent of fibrosis independent of other echocardiographic parameters. Based on these results, they suggested that 2-D echocardiography conjoined with the Doppler method could provide accurate information to reflect LA structural and functional changes related to AF.

## Practical Considerations

Despite RFCA being an effective means for eliminating AF, this approach is limited by potentially serious complications, the rate of which is in the range of 3.5 to 5%.<sup>29-31</sup> Among these are pneumothorax, pericardial effusion/cardiac tamponade, stroke/transient ischemic attack, femoral pseudoaneurysm, valvular damage, arteriovenous fistula, phrenic nerve injury, pulmonary vein thrombosis, atrio-esophageal fistula and death. Less well recognized are silent cerebral microembolism<sup>32-34</sup> and recently described LA diastolic dysfunction.<sup>3</sup> The incidence of silent cerebral microembolism has been reported to be more than 10% (ranging from 4.3 to 37.5 % depending on the RFCA technology used) as documented by cerebral diffusion-weighted MRI.<sup>32-34</sup> On the other hand, it is difficult to determine the exact incidence of diastolic LA dysfunction produced by RFCA of AF as it may coexist with systolic LA dysfunction. Although Gibson et al.<sup>3</sup> reported that the incidence of the "stiff LA syndrome" presumably caused by RFCA-induced scar was only 1.4%, the study was confined to symptomatic patients with "less than mild" mitral regurgitation on echocardiography. Judging from effects of thermal injury to the atrium,<sup>9</sup> and considering complex pathophysiology of AF,<sup>35-39</sup> the exact incidence of RFCA-induced LA diastolic dysfunction is likely to be more prevalent than is generally realized. First, many patients have pre-existing atrial scar (fibrosis/low-voltage tissue) caused by aging and AF.<sup>15,35</sup> Experimentally, AF and LA fibrotic scar (electrical and structural remodeling) have been shown to be mutually causative, accounting for "AF begets AF".<sup>36-39</sup> Clinically, tachycardia-induced atrial cardiomyopathy manifested as atrial stunning is not infrequently seen following conversion to sinus rhythm with surgery, antiarrhythmic drugs, electrical cardioversion and RFCA.<sup>15,25,26,40</sup> Second, LA diastolic dysfunction with pulmonary hypertension has been demonstrated in some of AF patients without prior RFCA.<sup>41</sup> Third, up to 40% of patients require a second RFCA for recurrence of AF and/or development of atrial flutter/atrial tachycardia.<sup>1</sup> Lastly, many of these AF patients have significant co-morbidities (e.g., heart failure, hypertension, stroke, sleep apnea, chronic obstructive pulmonary disease, etc.), all of which, with or without as-

sociated LV dysfunction, can result in atrial myocardial degeneration with AF progression and/or LA dilatation with mechanical dysfunction.<sup>1,42,44</sup> Under these circumstances, RFCA-induced scar will certainly further add to the impairment of systolic and/or diastolic function of the LA.

Also noteworthy, creation of linear lesions during RFCA of AF, especially the septal line, may inadvertently isolate the LA appendage thereby delaying its activation.<sup>44,45</sup> Since the LA appendage plays an important role in the LA reservoir function and is the most common site of thrombus formation,<sup>21,46</sup> whether this latter complication by itself, or as part of global LA dysfunction is serious enough to predispose to forming thrombus despite elimination of AF has been raised as an issue of concern.<sup>44,45</sup>

Taken together, while either MSCT or cardiovascular MRI may be needed for guiding the RFCA of AF procedure, we propose that biplane two-dimensional echocardiography along with tissue Doppler imaging and Doppler-derived strain (rate) imaging be systematically obtained before and periodically after RFCA of AF for evaluation of the LA function (both systolic and diastolic) in this subset of patients. Early detection of any new or worsening LA dysfunction function and/or pulmonary hypertension should prompt physicians to appropriately institute a therapeutic regimen of preload and/or afterload reduction for preventing development of heart failure which is also one of independent risks of severe stroke.<sup>47</sup>

Also of clinical relevance, because mechanisms underlying thrombogenesis in AF are complex and only partly understood, the answer to the question as to whether anticoagulation therapy can be discontinued after apparent success of RFCA remains uncertain and debatable.<sup>48,49</sup> In general, warfarin is recommended for all patients for at least 2 months after the RFCA procedure and decisions regarding the use of warfarin thereafter are based on the risk stratification for stroke even after seemingly successful restoration of sinus rhythm. Discontinuation of warfarin therapy is generally not recommended in patients who have a CHADS2 score (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack) > 2.50. Herein, we advocate that alteration of the

LA function after RFCA of AF be additionally taken into consideration during follow-up evaluation of these patients. Specifically, anticoagulation therapy should be continued in patients with spontaneous echo contrast which is usually found in the LA appendage,<sup>46</sup> and those with low LA ejection fraction, reduced or absent emptying and filling velocities of the LA, especially the LA appendage.<sup>46</sup>

## Conclusion

From an electromechanical perspective, 2-D echocardiography along with tissue Doppler (velocity) imaging and Doppler-derived strain (rate) imaging can be noninvasively used to provide a better understanding of the LA function and its relationship with LV function as well as PV circulation. Routine and systematic application of these technologies before and after RFCA of AF will allow early detection of LA dysfunction, both systolic and/or diastolic, in the presence or absence of associated LV dysfunction. It is anticipated that proper initiation of preload and/or afterload reduction therapy can prevent or minimize new or worsening heart failure and pulmonary hypertension and that prudent anticoagulation therapy may reduce the risk of thromboembolism in this subset of patients.

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