Atrial Fibrillation Pathophysiology and Prognosis
Insights From Cardiovascular Imaging

Konstantinos C. Siontis, MD; Jeffrey B. Geske, MD; Bernard J. Gersh, MB, ChB, DPhil

Atrial fibrillation (AF) is the most common sustained arrhythmia and is characterized by ineffective atrial contractions and often rapid ventricular response rates. It has been recognized that the risk of AF increases with age and the rise in AF incidence in recent decades is at least partly accounted for by the aging population in addition to the increase in other risk factors, including obesity.1,2 The global estimated prevalence of AF was >33 million in 2010,3 and projections indicate that its incidence and prevalence could potentially increase >2.5-fold by 2030.4 Although aging, hypertension, body mass index, structural heart disease, heart failure, and pulmonary disease are recognized clinical risk factors for the development of AF,5,6 advances in cardiovascular imaging, including novel echocardiographic techniques, cardiac MRI (CMR), computed tomography (CT), and positron emission tomography, have provided novel insights into AF pathogenesis, prediction, and natural history.

Despite the use of novel imaging technologies and the use of sophisticated invasive ablative techniques and newer antiarrhythmic strategies, AF still comprises a considerable public health burden and results in major morbidity and expenditures.7,8 Thromboembolism and its sequelae account for much of this burden. Ineffective atrial contraction in the setting of LA dilatation and electric remodeling constitutes a substrate for development of AF via the increase in activation sources at the junction between the pulmonary veins (PV) and the LA in a sheep model. On the other hand, long-standing ineffective atrial contraction in the setting of persistent AF worsens LA dilatation and electric remodeling and can perpetuate the arrhythmia (AF begets AF).15,16 LA dimension assessed by M-mode echocardiography was found to be predictive of incident AF in the Framingham Heart Study17 and the Cardiovascular Health Study.6 However, LA volume assessed by biplane 2-dimensional (2D) echocardiography has superior accuracy18 and stronger association with cardiovascular outcomes19,20 compared with 1D measurements and is the recommended method for determining LA size by the American Society of Echocardiography.21 In the Olmsted County, MN, population, Tsang et al22 demonstrated the value of echocardiographic LA volume (biplane area–length method) in predicting the occurrence of AF incrementally to clinical risk factors (congestive heart failure, myocardial infarction, and diabetes mellitus) and M-mode LA dimensions (Figure 1). The same investigators also identified LA volume as an independent predictor of AF after cardiac surgery.23 In addition, LA volume index is a powerful predictor of stroke in AF,24,25 In general, LA size may be a marker of the state of vasculature as it also predicts adverse cardiovascular outcomes regardless of AF.26,27 Although echocardiography remains the most commonly used modality for the volumetric assessment of the LA in AF, CT and CMR imaging also provide volumetric measures. Notably, CT and CMR consistently yield higher values of LA volume compared with 2D echocardiography, and a gold-standard modality has not been established.28 The same holds true for comparisons of 3D echocardiography and CMR.29

Received March 11, 2015; accepted April 21, 2015.
From Department of Medicine (K.C.S.), Division of Cardiovascular Diseases (J.B.G., B.J.G.), Mayo Clinic College of Medicine, Rochester, MN.
Correspondence to Bernard J. Gersh, MB, ChB, DPhil, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905.
E-mail gersh.bernard@mayo.edu
(Circ Cardiovasc Imaging, 2015;8:e003020, DOI: 10.1161/CIRCIMAGING.115.003020.)
© 2015 American Heart Association, Inc.
Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org
DOI: 10.1161/CIRCIMAGING.115.003020
LA enlargement is often accompanied by LA shape remodeling. The LA roof shape assessed by CT imaging (deep-V, shallow-V, or flat) can help determine the possible sites of AF triggers, as triggers from the PVs become less common as the LA roof shape flattens (Figure 2). Also, recent data from CMR imaging suggest that assessment of the sphericity of the LA may be useful in predicting the risk of AF recurrence after catheter ablation and thus selecting the best candidates for such therapy. Specifically, a spherically deformed LA may be more susceptible to AF recurrence.

LA Function
LA function was more predictive of adverse patient outcomes than LA structure in a general population from the Dallas Heart Study. In patients with AF, the decrease in LA reservoir function (determined by the total LA emptying fraction [LAEF]) has also been shown to be predictive of AF. In a study of 574 subjects without AF at baseline, the 30 subjects who developed AF after a mean follow-up 1.9 years had significantly lower LAEF compared with the rest (38% versus 49%). The prognostic association remained significant even after adjustment for established AF predictors. Prolonged atrial conduction time determined by tissue Doppler imaging was also a strong predictor of the development of AF independently of LA size in a study by De Vos et al. In another study, Kojima et al used velocity vector imaging echocardiography to assess global and regional LA function by measuring LAEF and strain rate, respectively. Patients with paroxysmal AF had significantly more global and regional dysfunction even when they were in sinus rhythm compared with patients without a history of AF. The impairment in LA function was present even before the development of LA enlargement, suggesting that functional changes may precede structural remodeling. This was replicated in a study of patients with varying AF burden (paroxysmal, persistent, or permanent) where ≈1 in 5 patients had impaired LAEF in the presence of a normal LA size. In the same study, worsening of LA contractile function (as assessed by LAEF and tissue Doppler A’ velocities) and compliance (LA expansion index=[maximum−minimum LA volume]/minimum LA volume) correlated significantly with increasing AF burden. Overall, LAEF has shown the greatest promise among the LA function parameters, owing both to its relatively straightforward measurement and its incremental ability to predict adverse outcomes. Among patients with AF, reduced LA strain has also been independently associated with increased stroke risk.

It should be noted that LA function is almost universally assessed by echocardiography in clinical practice, but echocardiography may be limited in accurately assessing the function of the thin and asymmetrical LA wall. Agner et al showed that the correlation of LAEF measurements derived by echocardiography is rather poor compared with those derived by CT and CMR. However, the recent development of a CMR technique that tracks LA wall motion using cine CMR imaging has shown promise as a good alternative for LA function assessment. Further validation specifically in patients with AF is necessary.

Atrial Wall Fibrosis
The altered architecture of the atrial ultrastructure is a substrate for the initiation and perpetuation of AF via formation of local conduction heterogeneities, which in turn increase the risk of reentry circuit formation. Clinicopathologic studies have demonstrated that patients with persistent AF have significantly higher percentage of interstitial fibrosis of both the left and right atria, as well as the PVs, compared with...
The extent of fibrotic changes may actually be greater in patients with a history of permanent rather than paroxysmal AF. Although areas of atrial scarring had been previously characterized invasively with electroanatomic voltage mapping in patients undergoing AF ablation, more recently the role of the noninvasive evaluation with delayed-enhancement CMR (DE-CMR) imaging has been characterized. On T1-weighted imaging, delayed gadolinium washout from fibrotic atrial tissue generates high signal intensity compared with normal atrial tissue, and the ensuing image contrast renders the fibrotic areas discernable. In the study by Oakes et al, the average extent of LA enhancement in 6 healthy volunteers was significantly lower (1.7±0.3%) compared with 81 AF with mild (8.0±4.2%), moderate (21.3±5.8%), and severe (50.1±15.4%) LA enhancement. In all patients with AF, there was anatomic correlation of DE areas and electroanatomically mapped low-voltage areas. The proposed Utah classification denotes the degree of LA fibrosis: Utah I ≤5%, Utah II >5% and ≤20%, Utah III >20% and ≤35%, and Utah IV >35% LA wall enhancement. In a study combining DE-CMR and echocardiographic imaging, Kuppahally et al demonstrated a significant negative correlation between the extent of LA wall fibrosis and strain measured by velocity vector imaging echocardiography which, as discussed above, is an emerging marker of LA dysfunction in AF (Figure 4). The same study demonstrated that atrial fibrosis was more prominent in persistent compared with paroxysmal AF (22±18% versus 14±9%).

Finally, in a large, multicenter, prospective study of patients with paroxysmal and persistent AF undergoing catheter ablation, atrial fibrosis identified by DE-CMR was a significant predictor of AF recurrence and the likelihood of recurrence increased with increasing extent of fibrosis (Figure 5). The potential challenges of DE-CMR should be acknowledged, specifically pertaining to its less than ideal spatial resolution, which can affect the imaging of the thin LA wall. It can be argued, however, that invasive CARTO-based mapping may be associated with more significant spatial error. In addition, the challenge of spatial resolution may be overcome by the expanding use of scanners with superior magnetic field strengths.

Beyond DE-CMR, which can be technically challenging to perform and present issues with image resolution, T1 mapping has more recently emerged as another promising CMR technology for atrial fibrosis assessment. Although DE-CMR detects fibrosis qualitatively, postcontrast T1 mapping allows for direct signal quantification. Beinart et al performed T1 mapping in 51 patients with AF and 16 healthy volunteers and demonstrated a significant correlation between the T1 relaxation time of the LA posterior wall and the intracardiac electrogram voltages (a surrogate of fibrosis). The median LA T1 relaxation time was significantly shorter in patients with AF. This observation was replicated in a larger subsequent study where the interatrial septum was the anatomic site of interest. The relationship of atrial fibrosis and AF is complex and incompletely understood. The degree of atrial fibrosis has
been shown to be similar in patients with lone and nonlone AF, and there seems to be no significant effect of patient age. This is in concordance with the autopsy study by Platonov et al, where there was no association between age and histological atrial fibrosis. However, these observations contradict the well-established relationship between age and AF risk and raise questions about the causality of atrial fibrosis and AF.

LA Appendage
The LAA, a long, tubular, and trabecular LA structure, is a central focus of imaging assessment in patients with known or suspected AF. Even though it was previously considered to be an insignificant remnant of embryonic development, the role of the LAA is now well recognized in the pathology of cardiac diseases, mainly AF. The ineffective contraction of the LA in AF promotes stasis, which, along with the procoagulable state in AF, results in an increased likelihood of thrombi to form within the LAA. A historic study in postmitral valve surgery patients from the 1950s showed that LAA thrombi were much more common in patients who suffered embolic events compared with those who did not. In addition, a review of 23 echocardiographic studies in patients with rheumatic and nonrheumatic AF found that LA thrombi were present in 13% and 17% patients, respectively. In the patients with nonrheumatic AF, >90% of the thrombi were localized in the LAA. More recent evidence suggests that non-LAA thrombi are common in valvular AF (>50% of all LA thrombi) whereas thrombi are much less commonly found outside the LAA in nonvalvular AF (>10%).

There are several approaches to imaging the LAA. Transesophageal echocardiography (TEE) is the main diagnostic modality used in clinical practice to assess LAA morphology, function, and presence of thrombus. TEE has been shown to have near-perfect sensitivity and specificity for the detection of LAA thrombi. In cases where spontaneous echo contrast may render the identification of thrombi difficult, tissue Doppler imaging with or without echocardiographic contrast injection may improve thrombus detection. Beyond detection of thrombus, TEE provides assessment of LAA structure. 3D TEE has been shown to be superior to 2D TEE for delineation of LAA geometry, which has obvious implications for LAA closure device implantation.

Although TEE is the most commonly used imaging tool for LAA assessment, a recent meta-analysis indicated that cardiac CT has comparable diagnostic accuracy in evaluating for LAA thrombus. CT imaging also offers novel insights into LAA morphology. Wang et al categorized LAA morphology as chicken wing, windsock, cauliflower, or cactus using CT. A later study by the same group suggested that the chicken wing morphology portends a lower risk of embolism. Subsequent studies focused on determination of thromboembolic risk after AF catheter ablation have failed to replicate or have even contradicted this observation (Figure 6).

Use of CMR to assess the LAA would be of clinical interest, especially given the unique ability to assess LA fibrosis, as outlined previously. CMR has also shown promise for the characterization of LAA anatomy, but results have been less convincing about its current ability to detect LAA thrombi.

Pulmonary Veins
The PV ostia are well recognized sources of electric activity that initiates AF and therefore constitute the primary target of all modern catheter ablation techniques. Both the diameter and the degree of atrial myocardium extension into the PVs have been implicated as arrhythmogenic factors.
Albeit not routinely used, preoperative CT, echocardiography or MRI of the PVs can not only guide procedural planning but also provide reference information for the evaluation of postablation PV stenosis, one of the most serious complications of catheter ablation (Figure 7). Head-to-head comparisons of the different techniques suggest that CT likely provides the most accurate assessment of PV anatomy and is therefore the most common modality for PV stenosis evaluation. On the other hand, echocardiography and lung ventilation-perfusion scanning can help determine the functional significance of PV stenosis. Therefore, a multimodal approach should be used when PV stenosis is suspected. Finally, although diagnostic guidelines on the topic are not established, routine screening imaging postablation for PV stenosis is not recommended.

Imaging Beyond the LA

Left Ventricular Systolic Function
AF may be both a cause and a result of left ventricular (LV) systolic dysfunction. Uncontrolled ventricular rates secondary to AF can result in tachycardia-induced cardiomyopathy, which often demonstrates at least partial reversibility after improvement of ventricular response. Tachycardia-induced cardiomyopathy portends a better prognosis when compared with patients with idiopathic dilated cardiomyopathy and secondary AF. Preexisting LV systolic dysfunction is associated with a 4.5-fold increased risk of AF in men and a 5.9-fold increased risk in women. Also, the development of AF in the setting of antecedent reduced LV systolic function leads to adverse outcomes. Ongoing trials of sinus rhythm restoration with catheter ablation in patients with concomitant AF and LV dysfunction, such as Randomized Ablation-based Atrial Fibrillation Rhythm Control Versus Rate Control Trial in Patients With Heart Failure and High Burden Atrial Fibrillation (RAFT-AF; NCT01420393) and Catheter Ablation Versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF), may help clarify this association. Regardless, objective assessment of LV systolic function should be obtained in all patients with new-onset or recalcitrant AF.

LV Myocardial Tissue Characterization
Beyond global assessment of LV systolic function, myocardial tissue characterization provides further insight with regard to AF assessment. In patients with no history of previous myocardial infarction, both the presence and extent of delayed myocardial enhancement on CMR have been demonstrated to be univariate predictors of all-cause mortality in patients with AF. When quantified with full-width at half maximum criteria, each 1% increase in DE was associated with a 15% increase in the risk of death in multivariate analyses. Furthermore, in patients with AF and LV systolic dysfunction but no DE, ventricular function normalizes after restoration of sinus rhythm. Detection and quantification of diffuse myocardial scar, as seen in myopathic processes, can be challenging using current delayed gadolinium enhancement techniques. Ventricular T1 mapping may provide incremental value and has been shown to differ across patients without AF, with paroxysmal AF, and with persistent AF in the absence of late gadolinium enhancement (Figure 8).

LV Diastolic Dysfunction
Impaired relaxation of the LV chronically loads the LA, may promote progressive LA dilatation, and can predispose to AF. Diastolic dysfunction progresses with age and is more prevalent in patients with hypertension. Both aging and hypertension are shared risk factors between AF and diastolic dysfunction. Is there, however, an independent contribution of diastolic dysfunction to the risk for AF? Although the optimal method
of assessing the LV diastolic dysfunction is still a matter of debate,\textsuperscript{64,85} several studies have examined its association with AF. In a population of 840 patients with nonvalvular AF from the Olmsted County, MN, Tsang et al\textsuperscript{86} demonstrated that a predictive model including echocardiographically determined diastolic function had superior predictive power compared with models based on other clinical factors and diastolic dysfunction remained a significant predictor of incident AF in multivariate analysis. Also, the same study noted significantly worse overall survival in patients with restrictive diastolic pattern compared with pseudonormal, abnormal relaxation, and normal patterns. The independent association between diastolic dysfunction and AF risk was replicated in the Framingham Heart Study population where an increase of the E/A ratio by 1 was related to a 41% increase in the risk of AF after adjusting for age, sex, systolic blood pressure, left ventricular ejection fraction, diabetes, atrial fibrillation, and atrial hypertrophy in older patients.\textsuperscript{87} More recently, a large-scale analysis of the Cardiovascular Health Study demonstrated that the peak E-wave velocity and the A-wave velocity time integral showed a positive nonlinear and U-shaped association with AF, respectively.\textsuperscript{88}

The association between diastolic dysfunction and AF has been of considerable interest in postmyocardial infarction patients. In an analysis of the Cardiac Arrhythmias and Risk Stratification After Myocardial Infarction (CARISMA) study, diastolic dysfunction was the only significant AF predictor in patients after postmyocardial infarction.\textsuperscript{89} Numerous other investigations have described the association of myocardial infarction and AF.\textsuperscript{90–92}

Not all evidence, however, suggests an independent association of diastolic dysfunction and AF in general. A study in elderly patients aged ≥65 years from the Olmsted County, MN, showed abnormal diastolic relaxation to be predictive of AF only in those with an enlarged LA (≥27 mL/m\textsuperscript{2}).\textsuperscript{91} This may suggest that diastolic dysfunction in the elderly is not a sufficient cause of AF in the absence of atrial remodeling, whereas in younger patients other yet unidentified mechanisms may precipitate AF in the presence of diastolic dysfunction. The relationship between diastolic dysfunction and AF may be dependent on more than age. A study of diabetic patients by From et al\textsuperscript{92} showed that although patients with diastolic dysfunction had higher incidence of AF, this association did not remain significant after adjustment for clinical and echocardiographic factors. Overall, although the association of diastolic dysfunction and AF has been replicated in several studies, causality remains unclear and there are certain patient subgroups where pathogenic mechanisms are likely multifactorial.

### Aortic Stiffness

Similar to diastolic dysfunction, aortic stiffness increases LV afterload predisposing to AF. Pulse wave velocity, the gold-standard noninvasive measure of aortic stiffness, has been traditionally quantified by applanation tomography, but modern imaging technologies, including echocardiography and MRI, have demonstrated favorable diagnostic characteristics and are increasingly used.\textsuperscript{93} In everyday practice, aortic stiffness is easily assessed by using the peripheral pulse pressure (PP) as a surrogate (a larger value suggests greater aortic stiffness). Peripheral PP offered incremental value in the prediction of incident AF beyond established clinical and echocardiographic AF risk factors in the Framingham Heart Study.\textsuperscript{94} This was replicated in subsequent studies, resulting in speculation that aortic stiffness may be a useful AF predictor.\textsuperscript{95–97} Also, increases in PP correlate with increases in LA size.\textsuperscript{98} However, peripheral blood pressure measurements tend to overestimate central hemodynamics.\textsuperscript{100} The association between aortic stiffness and AF was questioned in a recent report of the Multi-Ethnic Study of Atherosclerosis where aortic distensibility was measured with MRI imaging.\textsuperscript{101} Although aortic distensibility correlated with PP ($r=-0.34$; $P<0.001$) and PP was again identified as a risk factor for AF with moderately large effect sizes in all adjusted models, aortic distensibility was not independently predictive of AF. No other studies have examined associations of aortic stiffness quantified by MRI with incident AF and it should be cautioned that this MRI assessment has not been well-validated, although seems promising.\textsuperscript{102} No evidence exists on associations between echocardiographically defined aortic stiffness and AF risk.

### Epicardial Adipose Tissue

Epicardial adipose tissue does not simply serve as an insulator. Epicardial adipose lies directly adjacent to myocardium and has been implicated in coronary atherosclerosis via release of inflammatory cytokines in multiple studies. In patients with AF, epicardial adipose tissue has been demonstrated to have increased inflammatory activity on 18-fluorodeoxyglucose positron emission tomography compared with controls\textsuperscript{103} and may also be implicated in the autonomic stimulation of the atria resulting in the triggering and maintenance of AF.\textsuperscript{104} Pericardial fat volume has been highly associated with paroxysmal and persistent AF independent of age, LA size, hypertension, sex, valvular heart disease, LV ejection fraction, diabetes mellitus, and body mass index (Figure 9).\textsuperscript{105} Furthermore, total epicardial adipose volume and thickness have both been associated with LA volume.\textsuperscript{106} Although these associations do not necessarily prove a causal relationship between an inflammatory cascade driven by the epicardial tissue and the genesis of AF, extent of epicardial adipose tissue has also been related to AF recurrence after ablation\textsuperscript{107} and may thus be a clinically useful marker in the evaluation of AF.

### Conclusions and Future Directions

AF is a highly prevalent condition with substantial morbidity and mortality. Established and novel cardiovascular imaging technologies continue to enhance our understanding of AF risk factors and natural history and identify patients at the highest risk for adverse outcomes and those who are most likely to
benefit from advanced therapies, thus facilitating a more personalized approach in AF. Such an approach tailored to the individual patient may help current and future therapies meet the yet unmet goal of substantial survival improvement in the AF population. Multimodality cardiac imaging remains a key aspect of care of patients with AF. Assessment of LV systolic function is a cornerstone of patient management. LAA assessment, LA size, and evaluation of LA fibrosis are increasingly being used clinically to guide AF management. Specific to ablation management, the comprehensive preoperative echocardiographic evaluation of LV function, LA volume, LAA anatomy, and any potential structural heart disease that could affect procedural planning and decisions for the intensity of postprocedural antiarrhythmic therapy are of special importance. Other advanced imaging techniques, such as aortic stiffness and epicardial fat assessment, show promise but remain largely investigational. Similarly, techniques at even earlier stages of scrutiny, such as cardiac sympathetic activity quantification with iodine-123 meta-iodobenzylguanidine scintigraphy, may prove valuable in improving risk stratification in AF and patient selection for catheter ablation. In addition to continued discovery of new imaging risk factors, there remains a need for large scale, systematic, prospective investigation of the novel imaging techniques described herein to clarify their role in clinical decision-making, healthcare utilization and patient outcomes.

Disclosures

None.

References


C, Dragulescu SI. Left atrial remodeling: assessment of size and shape and regional function in patients with paroxysmal atrial fibrillation has


De amjcard.2008.01.051.


84. Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care. *Circulation*. 2009;120:802–809. doi: 10.1161/CIRCULATIONAHA.109.869602.


Keywords: atrial fibrillation • physiopathology • prognosis.
Atrial Fibrillation Pathophysiology and Prognosis: Insights From Cardiovascular Imaging
Konstantinos C. Siontis, Jeffrey B. Geske and Bernard J. Gersh

Circ Cardiovasc Imaging. 2015;8:
doi: 10.1161/CIRCIMAGING.115.003020

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/8/6/e003020

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org/subscriptions/