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Evaluating the Atrial Myopathy Underlying Atrial Fibrillation: Identifying the Arrhythmogenic and Thrombogenic Substrate

Jeffrey J. Goldberger, MD, MBA[1], **Rishi Arora, MD**[1], **David Green, MD, PhD**[2], **Philip Greenland, MD**[3], **Daniel C. Lee, MD, MSc**[1], **Donald M. Lloyd-Jones, MD, ScM**[3], **Michael Markl, PhD**[4], **Jason Ng, PhD**[1], and **Sanjiv J. Shah, MD**[1]

[1]Division of Cardiology, Feinberg School of Medicine, Northwestern University, Chicago, IL

[2]Division of Hematology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

[3]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

[4]Department of Radiology, Feinberg School of Medicine, Northwestern University, Chicago, IL

Abstract

Atrial disease or myopathy forms the substrate for atrial fibrillation (AF) and underlies the potential for atrial thrombus formation and subsequent stroke. Current diagnostic approaches in patients with AF focus on identifying clinical predictors with evaluation of left atrial size by echocardiography serving as the sole measure specifically evaluating the atrium. Although the atrial substrate underlying AF is likely developing for years prior to the onset of AF, there is no current evaluation to identify the pre-clinical atrial myopathy. Atrial fibrosis is one component of the atrial substrate that has garnered recent attention based on newer MRI techniques that have been applied to visualize atrial fibrosis in humans with prognostic implications regarding success of treatment. Advanced ECG signal processing, echocardiographic techniques, and MRI imaging of fibrosis and flow provide up-to-date approaches to evaluate the atrial myopathy underlying AF. While thromboembolic risk is currently defined by clinical scores, their predictive value is mediocre. Evaluation of stasis via imaging and biomarkers associated with thrombogenesis may provide enhanced approaches to assess risk for stroke in patients with AF. Better delineation of the atrial myopathy that serves as the substrate for AF and thromboembolic complications might improve treatment outcomes. Furthermore, better delineation of the pathophysiologic mechanisms underlying the development of the atrial substrate for AF, particularly in its earlier stages, could help identify blood and imaging biomarkers that could be useful to assess risk for developing new onset AF and suggest specific pathways that could be targeted for prevention.

Address for Correspondence: Jeffrey Goldberger, M.D., Northwestern University Feinberg School of Medicine, Center for Cardiovascular Innovation, 645 N. Michigan Avenue, Suite 1040, Chicago, IL 60611, Tel: 312-695-0363, Fax: 312-926-6295, j-goldberger@northwestern.edu.

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Atrial fibrillation (**AF**) affects >2 million Americans[1–3] with projections that it will affect 8–12 million people in the US by 2050.[1, 4] The incremental cost related to AF in the US is estimated at $6–26 billion per year.[5] It is associated with reduced quality of life[6–8] and increased risk of stroke[9] and death.[10] Despite this overwhelming and growing health burden, it is striking that for decades, there has been essentially **no change** in the recommended initial clinical evaluation of patients with AF. The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society (AHA/ACC/HRS) Guideline for the Management of Patients With Atrial Fibrillation recommends that the initial evaluation includes history and physical examination, ECG, transthoracic echocardiogram, and blood tests of thyroid, renal, and hepatic function.[11] This initial evaluation focuses on identifying clinical factors that predispose to or may precipitate AF. Typical cardiovascular causes include hypertension, valvular heart disease, heart failure, and coronary artery disease, but these diagnoses do not indicate the degree of involvement of the heart, or more specifically the left atrium (LA) in the disease process. With the exception of LA size, no other LA features are evaluated. To date, LA size has not proven to be useful for clinical decision making.

Once AF is diagnosed, treatment addresses the precipitating cause (if identified), restoration/maintenance of sinus rhythm (versus rate control), and prevention of thromboembolic complications. The risk models used to identify candidate patients for anticoagulation include the commonly used $CHADS_2$ and CHA_2DS_2-VASc scores (defined in Table 1). They demonstrate only mediocre predictive values with C statistics ranging from 0.55–0.64.[12] In another large cohort of patients, the CHA_2DS_2-VASc score was noted to have a C statistic of only 0.67[13] but it is currently recommended by guidelines.[11] Similarly, rhythm control treatment options have only mediocre success. A meta-analysis[14] reported antiarrhythmic drug efficacy of 52% compared to 25% for placebo and catheter ablation success rate of 71% after multiple procedures. A recent report[15] noted a 5 year arrhythmia-free survival of 63% after the last catheter ablation procedure. Thus, for both rhythm management and stroke prevention there are opportunities to improve our understanding of the underlying disease process in the atrium with the aim of improving treatment outcomes. The need for better characterization of the atrial substrate has been promoted by the European Heart Rhythm Association[16] and the AHA/ACC/HRS.[11] As there may be significant overlap among the pathophysiologic determinants of response to rhythm control treatments and thrombus formation in patients with AF, this report will summarize some of the newer approaches that are available to advance our understanding of the underlying atrial myopathy that forms the substrate for AF.

Pathogenesis of AF

There is increasing recognition that one of the contributing abnormalities to the development of AF is atrial fibrosis.[17–24] Importantly, it has recently been demonstrated that the degree of

fibrosis has therapeutic implications.[25] The DECAAF study[26] established that the degree of atrial fibrosis is (inversely) associated with the successful outcome of catheter ablation for treatment of AF. As LA fibrosis is one of the pathogenic pathways for the development of AF, and it likely develops over some period of time prior to the clinical appearance of AF, delineation of the various stages of disease progression may help develop better diagnostic and therapeutic approaches to AF. Just as breakthroughs in the prevention and treatment of coronary artery disease and acute myocardial infarction resulted directly from ascertaining the role of coronary atherosclerosis, especially in its pre-clinical phases, and atherosclerotic plaque rupture in the pathogenesis of myocardial infarction, longitudinal assessment of the development of the substrate for AF could alter the diagnostic and therapeutic landscape.

Figure 1 provides a schematic for a disease progression model that focuses on the development of atrial fibrosis. Four disease stages are shown – no disease, early disease that is not detectable, detectable substrate without AF (i.e. pre-clinical substrate), and manifest AF. Potential mediators known to promote fibrosis in the atrium include pressure and volume overload, aging,[27] atrial stretch,[19] inflammation,[28, 29] and oxidative stress.[28, 30] As the atrial myopathy progresses, it can lead to atrial dysfunction that may be detectable by currently available diagnostic tests. The role of atrial dysfunction in the pathogenesis of stroke in patients with atrial myopathy without AF is also of interest.

What is the atrial substrate underlying AF?

AF may be associated with structural as well as electrophysiological remodeling. Some of these remodeling changes may be detectable prior to the onset of clinical AF. Structural remodeling may incorporate changes in LA size and the development of atrial fibrosis. Various reports have highlighted the role of fibrosis[17–24] in the pathogenesis of AF. Fibrosis may contribute to the substrate for reentry by increasing heterogeneity of conduction in the atria. Oakes et al[25] introduced delayed enhancement MR imaging of the LA to detect fibrosis, demonstrating that areas of delayed enhancement corresponded to areas of low voltage during intracardiac mapping. Others have applied this technique as well to evaluate LA fibrosis.[31–33]

Electrophysiologic remodeling has multiple manifestations. The concept that “AF begets AF”[34] reflects the shortening of atrial refractory periods that occurs with repeated bouts of pacing or AF that further promotes AF. Changes in ion channel function, calcium loading, and conduction are components of atrial electrical remodeling that are usually noted after the development of AF.[35] However, electrical changes may also precede the onset of AF. In the ASSERT trial,[36] serial noninvasive programmed atrial stimulation was performed in 458 patients with implanted pacemakers and demonstrated no change in refractory periods in those who went on to develop atrial tachyarrhythmias while P wave prolongation and increased vulnerability to induction of AF was noted. Conduction slowing and increased vulnerability to AF have also been noted in patients with hypertension without AF.[37]

An important contributor to electrophysiological remodeling is the autonomic nervous system. Autonomic remodeling occurs in a variety of disease processes and can serve as an important substrate for AF, with both the parasympathetic and sympathetic nervous system

playing roles in the genesis and maintenance of AF.[38–40] The parasympathetic nervous system may have a more dominant contribution to AF substrate – primarily by leading to shortening and heterogeneity of refractoriness in the atria – with the sympathetic nervous system playing a more modulatory role. The pulmonary veins, often involved in the pathogenesis of AF, are much more densely innervated - with both parasympathetic and sympathetic nerves – than the rest of the LA.[41] While catheter ablation to achieve denervation in the region of the pulmonary veins[42] has been shown to improve outcomes, this finding has not been consistent. Significant interest remains in the role of catheter ablation of the autonomic ganglia.[43]

Identifying the pre-clinical atrial myopathy

Though not currently part of clinical practice, it is conceivable that identification of the early stages of atrial myopathy might allow for early preventive treatments to prevent progression of atrial disease and AF. A variety of treatments have in fact been evaluated. Emerging data show that there are a number of upstream therapies – ACE inhibitors/angiotensin receptor blockers,[44] aldosterone blockers,[45] statins,[46–49] and omega-3 polyunsaturated fatty acids[50, 51] – that might prevent AF in susceptible populations, but few prospective studies have been performed, the data are not consistent, and the effect of these therapies on the atrium have not been evaluated in humans.[52–57] Statins and aldosterone blockers appear to be the most promising agents. Statins may prevent early atrial electrical remodeling,[56] even if they may not be effective in the treatment of established AF.[57] In a meta-analysis[49] of 20 studies with 23577 patients evaluating both primary and secondary prevention of AF, statin use was associated with a reduced incidence of AF (5.72% versus 7.38% for placebo, odds ratio 0.49, 95% CI 0.37–0.65); a larger effect was noted for secondary versus primary prevention. Aldosterone has been shown to cause atrial fibrosis.[58] Spironolactone has been shown to reduce LA fibrosis (and P wave duration) in a post-myocardial infarction rat model of heart failure.[59] The EMPHASIS-HF study reported a substantial reduction in new onset AF in patients with heart failure who were treated with eplerenone versus placebo (2.7% versus 4.5%, hazard ratio 0.58, 95%CI 0.35–0.96).[45] While not specifically evaluated in this study, it is likely that at entry the bulk of the patient population had some substrate for AF,[60] as they were older (mean age 68–70 years) and all had heart failure, 2/3 had hypertension, and 1/3 had diabetes. If one accepts the notion that these patients had pre-clinical substrate, including LA fibrosis, the ability of eplerenone to reduce new onset AF is impressive and suggests that there is a role for this therapy even when the atrial substrate for AF is already present. Thus, to enable trials of targeted treatment for early atrial myopathy, better tools are needed to identify this substrate and track treatment effects.

A number of previous observational studies (Table 2)[61–65] have assessed risk factors for new AF in people without clinical history of prior AF. These studies have focused on clinical factors associated with AF (not anatomic findings nor direct assessment of potential mechanisms) and all prior studies have been limited to clinically-detected AF, leaving a gap in our understanding of the pathogenesis of asymptomatic AF, an increasingly recognized important health problem. Several multivariable quantitative risk models have been validated in external cohorts. The Framingham Heart Study (FHS) model[66] was validated in 2 cohorts [The Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study and

Cardiovascular Health Study]. Validation confirmed that risk of incident AF in community-dwelling whites and African-Americans can be assessed by clinical variables and accounted for up to 64% of the overall AF risk.[67] In the Atherosclerosis Risk in Communities (ARIC) study,[68] the same risk factors were studied to determine population attributable risk. During 17 years of follow-up, 1,520 incident AF cases were identified. Overall, 57% of AF cases could be accounted for by having ≥1 borderline or elevated risk factors. Attributable risks in these ranges suggest there could be a role for additional mechanistic factors. An additional study was conducted by Alonso et al[69] (CHARGE-AF consortium). They collected individual-level data from 3 US cohorts (ARIC; CHS; FHS), including 18,556 men and women aged 46 to 94 years (19% African Americans, 81% whites) to derive predictive models for AF using clinical variables. Validation of the derived models was performed in 7,672 participants from AGES and the Rotterdam Study. A 5-year predictive model including age, race, height, weight, systolic and diastolic BP, smoking, use of blood pressure medication, diabetes, and history of MI and heart failure had good discrimination (C-statistic, 0.765; 95% CI, 0.748 to 0.781). Adding standard variables from the resting ECG (i.e., PR interval and ECG-LVH) did not improve the overall model discrimination.

Obesity is a particularly relevant risk factor for development of AF given the growing obesity epidemic. In the Framingham cohort, obesity was associated with a 4% increased risk in incident AF per unit increase in BMI in both men and women.[70] Obesity encompasses a heterogeneous set of risk factors that may predispose to developing AF, including the associated medical conditions that are intimately linked to risk of AF, such as hypertension and diabetes. Obesity may have direct effects on the LA substrate mediated by increases in inflammation, oxidative stress, and left atrial volume.[71–73] Epicardial fat, in particular, is associated with increased prevalence of AF[74] or AF burden.[75] The role of obesity in the pathogenesis of AF was demonstrated in the ARREST-AF study[76] in which a cohort of patients underwent a structured risk factor management program following catheter ablation for treatment of AF. Compared to a control group who did not participate in the program, these patients experienced a 13% decrease in BMI with significant declines in blood pressure and LA volume index. Over a two-year follow-up, there was substantially higher freedom from AF in the risk factor management group (multivariable hazard ratio 4.8, 95%CI 2.04–11,4, p<0.001). Given the potentially large impact of risk factor management in the secondary prevention of AF, it is possible that better delineation of the multiple pathophysiologic pathways that are responsible for the development of the pre-clinical atrial substrate could form the basis for a more informed strategy for addressing these modifiable risk factors for primary prevention of AF, in addition to the other cardiovascular benefits.

Very few studies have examined the physiologic or detailed anatomic mechanisms that might underlie AF development in previously healthy people. One such study was reported in 2012 based on an analysis of echocardiographic diastolic parameters from the CHS.[77] AF was ascertained by self-report, annual study ECG for the first 9 years of CHS, and reports from hospitalizations. For the first time, this study found that atrial factors beyond LA size were associated with new onset of AF. In addition to LA diameter, the most significant predictors of incident AF were Doppler peak E-wave velocity (HR 1.5 (CI 1.3–1.9) for

highest vs. lowest quintile), and Doppler A-wave velocity time integral, which displayed a U-shaped relationship with risk of AF (HR 0.7 (CI 0.6–0.9) for middle vs. lowest quintile).

Techniques for evaluating atrial myopathy - substrate for AF

There are several techniques for evaluating the atrial myopathy, as shown in Figure 2. These include echocardiography, cardiac MRI, ECG waveform analysis, and biomarker analyses. Echocardiography has been the imaging technique of choice for evaluating the LA because of its widespread availability and ease of use. LA dimension/volume has been consistently shown to be a predictor of incident[78] and recurrent AF.[79–81] Yet, the LA size or volume has not been used clinically for treatment decisions. There are other echocardiographic techniques that could better delineate the presence of atrial myopathy; these include assessment of LA chamber function (e.g., LA ejection fraction, LA function index [LAFI]); tissue Doppler imaging (i.e., a' velocity) for evaluation of the ability of LA contraction to affect the longitudinal velocity of the basal LV in late diastole; speckle-tracking strain analysis (for the evaluation of LA mechanics); and 3D echocardiography (for the evaluation of LA size, shape, and function). Echocardiographic assessment of LA function provides novel insight into LA pathophysiology in the setting of AF. The LAFI, a rhythm-independent marker of LA function that incorporates LA size and the left ventricular outflow tract velocity-time integral (a marker of left ventricular stroke volume), is associated with adverse outcomes in patients with coronary disease, and provides a measure of LA function independent of underlying rhythm.[82, 83] The tissue Doppler a' velocity, which is measured at the septal and lateral mitral annulus, conveys information on both the LA contractile function and the stiffness of the LV at ventricular end-diastole.

Measurement of LA strain is a novel technique that quantifies segmental and global LA myocardial mechanics in both sinus rhythm and AF. LA strain evaluates the longitudinal shortening and lengthening of segments of the LA myocardium throughout the cardiac cycle. The resultant strain curves quantify the LA conduit function (peak positive LA strain), booster function (peak negative strain [in patients with coordinated atrial contraction]), and the reservoir function (total LA strain). Decreased LA strain (indicative of worse LA mechanical function) has been associated with the development of AF. In addition, LA strain has been used to predict AF recurrence after AF ablation and future stroke risk in the setting of AF, and worse LA strain parameters correlate with reduced exercise capacity, higher CHADS2 score, and increased risk of adverse cardiovascular events.[84–90]

As noted above, delayed enhancement MRI has been used to detect atrial fibrosis in vivo. The technical challenges of this technique to image fibrosis in the thin walled LA are well appreciated. T1 mapping has been developed to identify diffuse myocardial fibrosis and has recently been applied to the LA[91, 92] with good correlation to intracardiac LA electrogram voltage. 4D flow MRI (3D flow velocity measured over time) is a novel technique for the comprehensive assessment of cardiovascular hemodynamics in the heart and great vessels.[93–97] 4D flow MRI is uniquely suited for evaluation of LA flow velocities (an index of atrial function) as it can provide blood velocity in 3 orthogonal directions with full volumetric coverage of the LA throughout the cardiac cycle with a single, free-breathing 10–15 minute acquisition.[94, 97–99] The 3D segmentation of LA volume enables quantitative

analysis of 3-directional velocities inside the entire LA over all time frames of the cardiac cycle.[99] Recent studies demonstrated low inter-observer variability and good test-retest reliability for the quantification of blood flow velocities and other hemodynamic parameters.[100–102] We have demonstrated the potential for this technique to identify different flow patterns in patients with AF, even for those not in sinus rhythm during imaging.[99, 103]

Even the standard ECG recorded during AF is an underutilized tool. It is typically used only to make a diagnosis of AF with no further analysis of the waveform. There is, in fact, significant electrical information in the f waves of the AF ECG. As shown in figure 3, close examination of the ECG can clearly identify differences in rate and other features. Frequency analysis of the f waves can be done to quantify features such as rate. It has been demonstrated that f wave analyses are associated with clinical AF outcomes such as the response to anti-arrhythmic drugs,[104] catheter ablation,[105, 106] and maintenance of sinus rhythm after cardioversion.[107, 108] Dofetilide drug effect – slowing of the dominant frequency – can be detected on the standard 12 lead ECG.[109] After the first dose of dofetilide, the AF dominant frequency was reduced (6.46±0.87 vs 4.92±0.62 Hz, $p<0.0001$). Importantly, drug effect on the atrium was not correlated with its effect on the ventricle as measured by the rate corrected QT interval. In addition, many current approaches to evaluate the atrial substrate focus on intracardiac electrogram properties such as amplitude, frequency, and complexity[37, 110–113] as surrogates of the actual anatomic substrate. These parameters are also likely reflected in the surface ECG, but standardized approaches are needed to define optimal techniques, leads for analysis, and measures that provide clinically useful information.

Advanced ECG, echocardiographic, and MRI techniques are available to characterize atrial abnormalities that could be important factors affecting treatment efficacy. None of these advanced techniques has yet become a routine part of clinical practice. An understanding of how the results of these tests can affect therapeutic results, as recently demonstrated for fibrosis detected by MRI and its effect on ablation outcomes,[26] is needed.

Atrial myopathy and stroke risk

While several AF studies have shown an association between atrial fibrosis and either stroke or predictors of thrombus formation/stroke,[114–116] a causal link has yet to be demonstrated. The factors implicated in thrombogenesis are described by the classic Virchow's triad and consist of endothelial/endocardial damage or dysfunction, stasis, and hypercoagulability which describes the major factors conducive to thrombogenesis. There is evidence supporting each of these factors in AF.[117] Further studies may elucidate the link between these abnormalities and the atrial myopathy of AF. It is noteworthy that in addition to the relationship between markers of coagulation and stroke in AF, there is also a relationship to other clinical outcomes in AF.

Stasis, as noted by the echocardiographic display of smoke or diminished LA appendage flow velocities by echocardiography,[118–122] has been shown to be associated with stroke in patients with AF. Studies utilizing transesophageal echocardiography (TEE) have shown

that decreased flow in the LA and particularly LA appendage (LAA), which is the typical site of thrombus formation, are independent risk factors for stroke in AF.[120, 122, 123] Furthermore, the presence of spontaneous echo contrast, a marker of blood stasis, has been shown to be an independent predictor for thromboembolism.[118, 124] Specifically, a prior TEE study found that peak LAA emptying velocity <0.2m/s was associated with increased risk for atrial thrombus formation and embolic stroke.[120] Multivariate analysis including clinical risk factors found that peak LAA emptying velocity <0.2m/s was independently associated with LAA thrombus (relative risk 2.6, $p = 0.02$). While the velocities were significantly lower in patients with AF versus sinus rhythm at the time of imaging (0.33±0.20 m/s versus 0.61±0.35 m/s, $p<0.001$), there was significant overlap in the distribution of velocities, indicating that even patients with prior AF but in sinus rhythm at the time of imaging may have significantly depressed LAA emptying velocity. Other studies have shown that LA size and LAA geometry may be additional parameters influencing thromboembolic risk.[125–127]

Stasis can also be detected by the novel 4D flow MRI technique.[99] This technique can noninvasively display complex 3D blood flow patterns in-vivo and has facilitated insight into complex normal and altered cardiovascular hemodynamics previously limited by other imaging strategies.[128–130] Preliminary findings demonstrate that 4D flow MRI can detect individual physiologic changes in LA flow velocities in patients with AF that are not conveyed by the standard CHA_2DS_2-VASc clinical risk score.[131–133] We have demonstrated an inverse relationship between flow and the CHA_2DS_2-VASc score. As with TEE, flow velocities in patients imaged during sinus rhythm were higher than those imaged in AF, but were significantly depressed compared to a similarly aged cohort without a history of AF. Almost by definition, the atrial myopathy underlying AF is likely responsible for the diminished flow observed in patients with AF imaged when in sinus rhythm. In addition, there may be a dynamic change in LA flow velocities in sinus rhythm depending on degree of atrial myopathy, frequency and duration of AF episodes, and time from the most recent episode of AF. In addition, other factors such as LA geometry may affect the tendency for areas of stasis and thrombus formation. In a study[127] evaluating the LA appendage by CT and MRI, stroke risk differed depending on anatomic details of the LA appendage, but AF occurrence was not reported. The relationship of stasis to other atrial substrate parameters and to clinical outcomes requires further study.

Despite a large body of work demonstrating an increase in prothrombotic factors in patients with AF, these are usually not incorporated in the clinical diagnostic evaluation of stroke risk. Hemostasis occurs in three general phases: initiation, propagation, and termination.[134] *Initiation* is characterized by platelet adherence and aggregation at the site of vascular injury and trace thrombin formation. Larger amounts of thrombin are formed during the *propagation* phase, and thrombin formation is curtailed by inhibitors during the *termination* phase, which includes activation and inhibition of fibrinolysis.

Von Willebrand factor (VWF) is a multimeric plasma glycoprotein that plays a central role in hemostasis and participates in angiogenesis, cell proliferation, and inflammation[135] and is active during the initiation phase of hemostasis. The highest molecular weight (HMW) multimers are the most thrombogenic.[136] Within minutes of the onset of AF, atrial blood

shows evidence of platelet and endothelial cell activation.[137] The activated endothelium, under shear, extrudes VWF from its Weibel-Palade bodies. The hemostatic potential of the VWF increases with its size (extent of multimerization) and the magnitude of the applied hydrodynamic shear.[138] The HMW multimers become anchored to the cell surface where they unravel and bind platelets, initiating thrombus formation.[139] The unraveling of the multimers exposes a cleavage site between aminoacids 1605 and 1606 (tyrosine/methionine) that is attacked by the protease, ADAMTS13 (a disintegrin-like and metalloprotease domain with thrombospondin type-1 motif, number 13). There are conditions that result in resistance to proteolysis; for example, alterations in glycosylation[140] and oxidative stress.[141] The latter might be particularly relevant to patients with AF, in whom oxidative stress secondary to disturbed atrial circulation could result in resistance of VWF to ADAMTS13, an increase in HMW multimers, and thrombosis. In healthy persons, the ratio of VWF antigen to ADAMTS13 is unity, reflecting the balance between VWF and its protease. Ratios are significantly higher in patients with chronic AF than in those with paroxysmal AF ($P<0.01$) or controls ($P<0.0001$).[142] In addition, there are significant correlations between the ratio and the LA diameter ($P=0.0002$) and LA appendage flow velocity ($P=0.002$). A high ratio of VWF:ADAMTS13 independently predicts major adverse cardiovascular events in patients with AF (hazard ratio 2.17, $P=0.007$).[143] After cardioversion, the ratio was an independent predictor of recurrent AF (HR 1.88, $P=0.03$).[144]

VWF[145–148] is increased in patients with nonvalvular AF as compared to those in sinus rhythm, irrespective of a history of stroke. In the ARIC Study, VWF was associated with AF independent of other CV risk factors.[149] In multivariable Cox models, the hazard ratio for incident AF associated with a 1-standard deviation increase in VWF was 1.17 (95% CI 1.11–1.23). Conway et al[150] and Krishnamoorthy et al[151] reported that raised VWF levels in patients with AF predicted stroke and vascular events, and Roldan et al[152] found that high VWF levels are an independent risk factor for adverse events in AF patients on anticoagulant therapy. The concentrations of VWF in LA blood are increased in patients with persistent AF and are higher than in the LA of those with paroxysmal AF or controls.[153] They are also associated with spontaneous echocardiographic contrast, and are higher in AF patients with than without LA thrombi (200 vs 155 IU/dl, $P=0.0006$).[154] The level of VWF is also associated with the extent of periatrial epicardial fat, but not body mass index or epicardial adipose tissue, suggesting local adiposity affects VWF concentrations.[155]

A variety of other prothrombotic abnormalities have been noted in patients with AF. These include alterations in D-dimer, platelet factor-4, thrombin-antithrombin complexes, and plasminogen activator inhibitor-1 (PAI-1). D-dimer has been evaluated most extensively; significant associations between D-dimer levels and the risk of stroke, cardiovascular death, and major bleeding outcomes were reported in the ARISTOTLE trial.[156] In those with new onset AF, D-dimer levels increase above the normal range within 12 hours, and reach a plateau at the 18th hour.[157] In patients with chronic AF, the range of D-dimer increase is characteristic for each patient and is stable over time.[158] In patients with chronic AF, elevated levels of platelet factor-4 are observed.[145, 147, 148, 159, 160] There is evidence of thrombin generation in AF, as detected by increases in thrombin-antithrombin complexes and prothrombin fragment 1+2.[161, 162]

Why do thrombi occur more often in the left than right atrium? There may be greater tendency to stasis and/or procoagulant factors in the LA. Activated protein C is one of the most potent natural anticoagulants; protein C binds to the endothelial protein C receptor where it is activated by a complex of thrombin and thrombomodulin. Cervero et al[163] reported a significant underexpression of thrombomodulin by the left as compared to the right atrial endocardium, and less than half the ability to activate protein C. In pigs with induced AF, PAI-1 protein expression was increased in the LA but not the right atrium, and the LA increase was accompanied by a decrease in nitric oxide.[164] In patients with chronic AF, thrombin generation is increased in the LA compared to the periphery.[165] Platelet and leukocyte activation, and leukocyte platelet aggregates were observed in the LA blood of patients with spontaneous echocardiographic contrast.[166]

It is evident that procoagulant factors in AF are associated with AF and atrial disease. VWF, ADAMTS13, thrombomodulin, and PAI-1 are all either synthesized or released from the endothelium, and are affected by diseases that attack the endothelium. There is considerable evidence of endothelial dysfunction in AF; for example, nitric oxide synthase and NO bioavailability are decreased[164] and levels of MMP-2 and sVCAM-1, markers of endothelial remodeling, are increased.[167] The complex interplay of hemostatic and anatomic factors in the LA may underly a prothrombotic state more localized to the LA.

Recent data raise the possibility that there is a complex relationship between thromboembolic risk and AF. The RACE trial[168] noted that “patients with risk factors may have a stroke after cessation of anticoagulant therapy, despite maintenance of sinus rhythm”. The TRENDS study[169] showed that most of the 40 patients with AF and implanted devices who experienced cerebrovascular events or systemic emboli did not have AF episodes proximal to the event. Additionally, a retrospective analysis of 568 continuously monitored patients demonstrated an interaction between AF duration and $CHADS_2$ score, such that patients with scores≥3 were at increased stroke risk regardless of AF duration, those with scores of zero were at low risk regardless of AF duration, and those in between had risk profiles that depended on the duration of AF episodes.[170] Data from the Multi-Ethnic Study of Atherosclerosis[171] and the Cardiovascular Health Study[172] have identified an association between P wave terminal force in V1 (left atrial abnormality) and stroke that is independent of AF. These observations support the conjecture that the atrial myopathy underlying the development of AF may also directly affect the risk of thrombosis via effects on atrial flow and/or the hemostatic profile, thereby increasing the risk for thromboembolism, even in the absence of AF (this potential pathway is illustrated in Figure 1). In addition, the disease processes underlying the development of the atrial myopathy may also be associated with stroke etiology unrelated to emboli from the left atrium. More detailed understanding of the atrial myopathy, specifically its impact on atrial flow velocities or stasis, as well as the prothombotic factors present in individual patients might enhance risk stratification currently assessed by the clinically-based CHA_2DS_2-VASc score.

Other biomarkers in AF

While biomarkers are generally not specific to atrial myocardial disease, various biomarkers (in addition to the coagulation biomarkers described above) spanning myocyte injury/stress,

inflammation, and fibrosis have been linked to outcomes in AF[173] and have been reported to be elevated in AF or predictive of development of AF.[174] The natriuretic peptides, troponin, CRP, IL-6, among others, have been related to outcomes in AF.[173, 175–182] It is not yet known which of these markers is most predictive of treatment outcomes, but there is strong evidence for the role of inflammation in AF[28, 29] and emerging evidence for the prognostic importance of the natriuretic peptides and troponin.[174, 175, 178, 183–185] Persistent elevation of troponin and NT-proBNP in the RELY trial was associated with adverse outcomes.[186] Serial changes in biomarkers of inflammation (CRP, IL-6), natriuretic peptides (ANP, BNP), and collagen turnover (MMP-2, TIMP-2) have been reported after ablation[187] or medical therapy.[57] Thus, baseline evaluations of these biomarkers could indicate the involvement of the specific pathways and serial study could provide evidence of salutary effects of medical therapy on atrial substrate.

Conclusion

A clear delineation of the atrial myopathy that serves as the substrate for AF might improve treatment outcomes. Stroke and major bleeding complications associated with anticoagulation remain significant concerns in patients with AF. Better assessment of stroke risk can improve the risk-benefit ratio of current and future therapies. Current pharmacological treatments for rhythm control of AF have only modest efficacy and suffer from potentially life-threatening side effects. While the AF guidelines do provide an algorithm for choosing anti-arrhythmic drugs, this is based on the presence and severity of a patient's underlying heart disease, and designed to limit proarrhythmic complications rather than matching specific treatments to the underlying atrial substrate for AF. Current ablative and surgical approaches to AF, though somewhat more successful, use an anatomic, 'one-size fits all' strategy (with some minor variations), focusing on pulmonary vein isolation, that does not address the specific mechanisms underlying this complex arrhythmia. Moreover, in the STAR AF II randomized clinical trial,[188] there was no significant benefit to adding either ablation of complex fractionated electrograms or additional LA linear lesion sets compared to pulmonary vein isolation alone in patients with persistent AF. Better delineation of the atrial myopathic substrate and its relationship to arrhythmia mechanisms in individual patients could potentially substantially improve the results of catheter ablation, as defining the primary arrhythmia substrate for other types of supraventricular tachycardias has been associated with success rates exceeding 95%.[189] As noted by the European Heart Rhythm Association consensus conference, it therefore is likely that "a new taxonomy of AF may be needed based on the pathophysiological type of AF to allow personalized management of AF to come to full fruition." Further evaluation will be required to confirm that treatment outcomes improve if a comprehensive evaluation of the atrial substrate is used to guide management decisions.

Finally, better delineation of the pathophysiologic mechanisms underlying the development of the atrial substrate for AF, particularly in its earlier stages, could help identify blood and imaging biomarkers that could be useful to assess risk for developing new onset AF. Primary prevention strategies could potentially target specific mechanisms and novel treatments could be tested in appropriate higher risk groups. In addition, these blood and

imaging biomarkers might serve as surrogate endpoints for early assessment of novel interventions designed for the primary prevention of AF.

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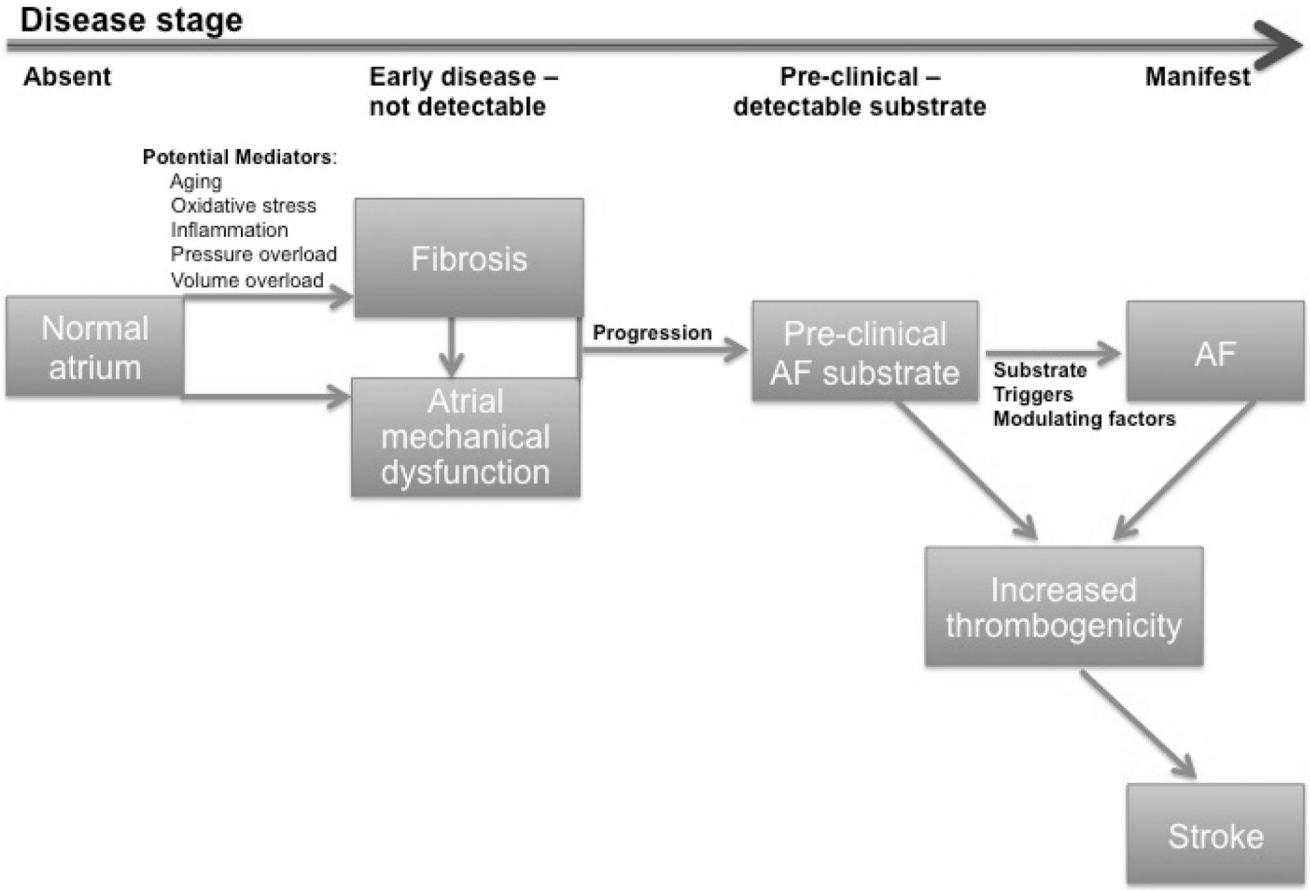

Figure 1.
Schematic of the progression of disease in patients who are developing the substrate for AF.

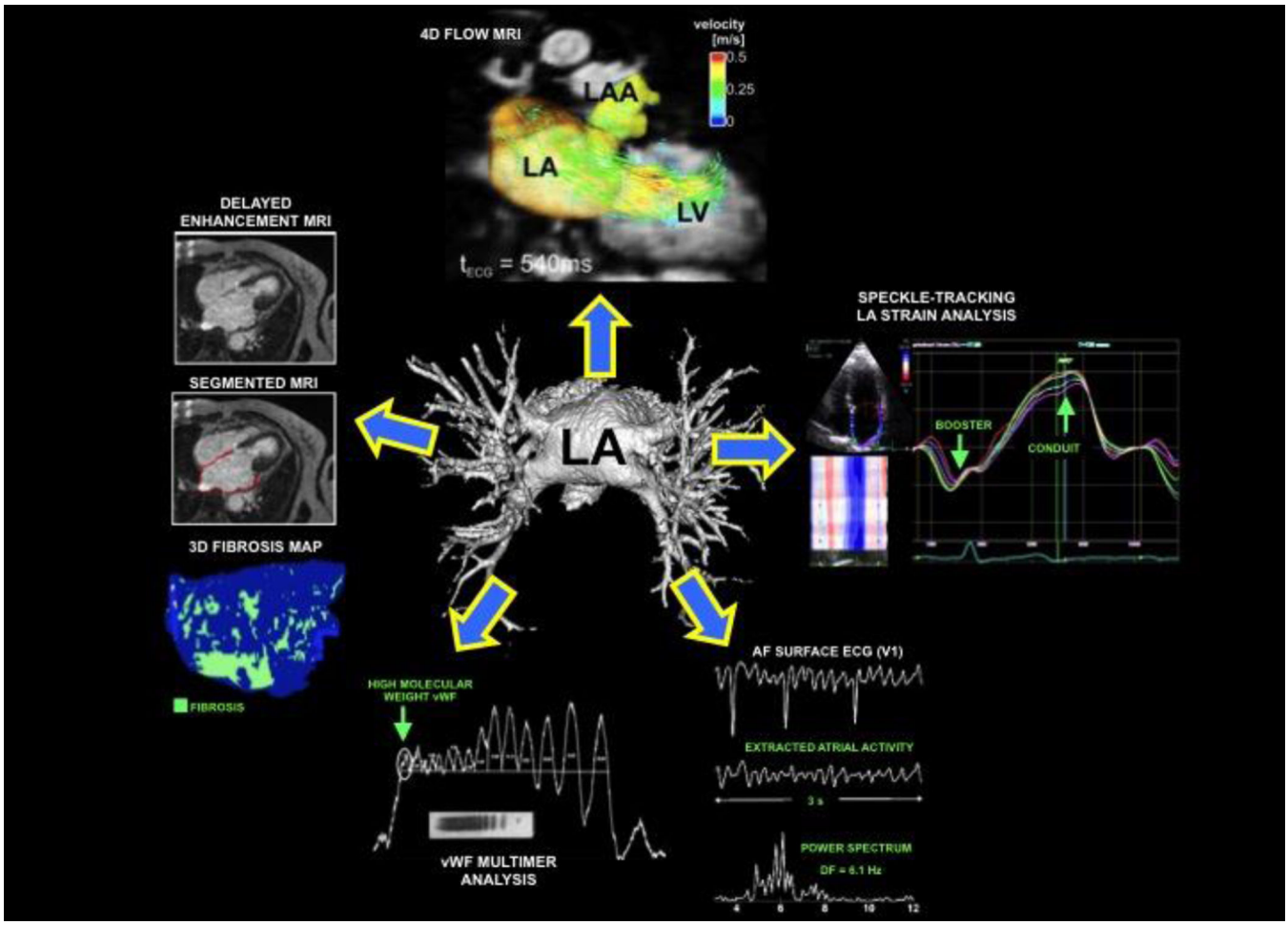

Figure 2.
Multiple noninvasive techniques to evaluate the left atrium in patients with atrial fibrillation.

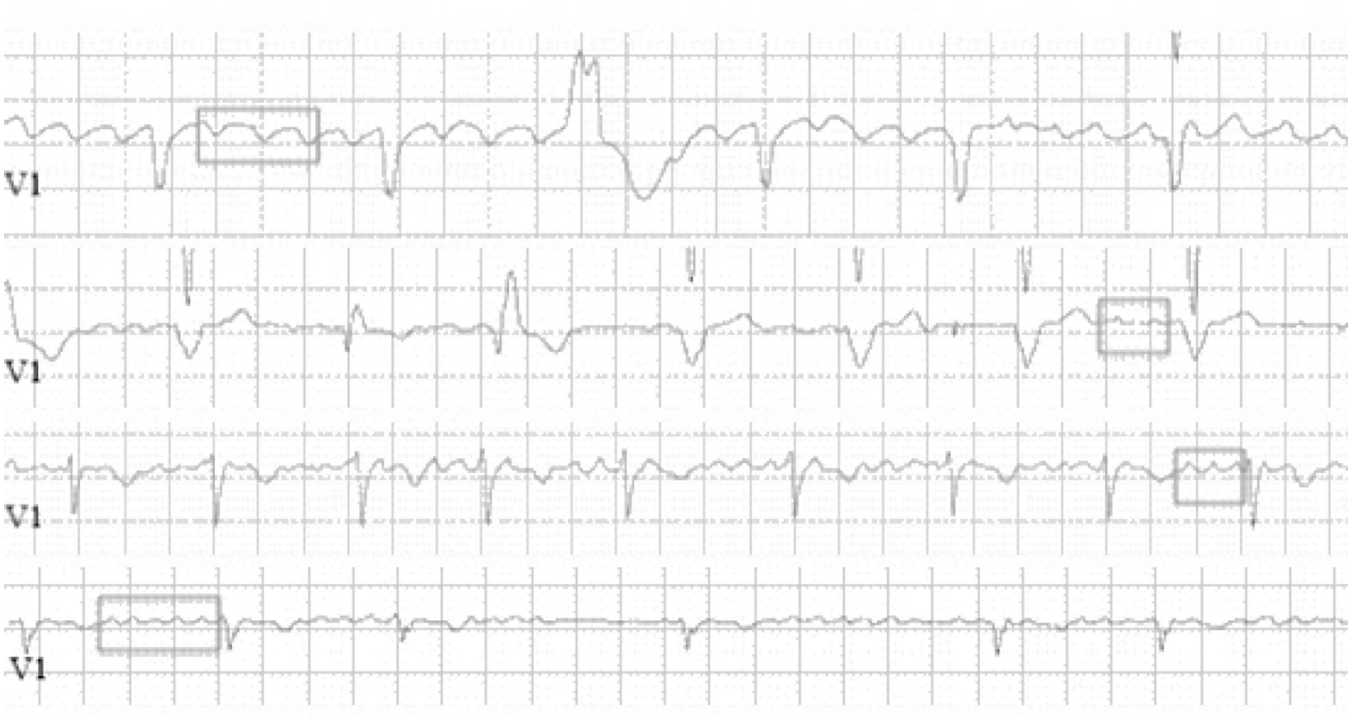

Figure 3.

ECG V1 lead recordings from 4 different patients with AF showing f waves. Although f waves in AF are variable throughout a recording, they are sometimes well-visualized, allowing the variation in their rate and amplitude to be characterized. Differences in f wave rate can be appreciated in some parts of these recordings. In the 1st and 4th tracings, the same size box encompasses 3 and 5 F waves, respectively; in the 2nd and 3rd tracings, the same size box encompasses 2 and 3 F waves, respectively. Other characteristics differ, as well – F wave amplitude and consistency of activation.

Table 1

Calculation of $CHADS_2$ and CHA_2DS_2-VASc scores. The indicated number of points are added up for each condition that exists.

	$CHADS_2$	CHA_2DS_2-VASc
Congestive heart failure	1	1
Hypertension	1	1
Age		
65–74 years	1	1
≥75 years	1	2
Diabetes mellitus	1	1
Stroke or TIA	2	2
Vascular disease		1
Sex category = female		1

Table 2

Previous epidemiologic studies of risk factors for incident atrial fibrillation.

Author (Ref No.)	Study Name	Number in Study	Ages (years)	Follow-up length	Detection Methods	Primary Risk Factors
Psaty ([61])	Cardiovascular Health Study (CHS)	4844	65+	3 years	Self-report (SR); Exam ECG; Hospital Discharge Info	Age; male sex; diuretic use; history of CHD or valve disease; SBP; height; glucose; LA size (Echo)
Schnabel ([66])	Framingham Heart Study (FHS)	4764	45–95	10 years	Exam ECG; physician records; Hospital discharge data	Age; male sex; BMI; SBP; treatment for hypertension; ECG PR-interval; clinically significant cardiac murmur; heart failure. Echocardiogram findings not additive.
Chamberlain ([62])	Atherosclerosis Risk in Communities Study (ARIC)	14546	45–64	10 years	Exam ECG; Hospital discharge data; Death Certificates	Age; race; height; smoking; SBP, BP medication use; precordial murmur; ECG LVH; LA enlargement (by ECG); diabetes; CHD; heart failure.
Heeringa ([63–65])	Rotterdam Study	6808	55+	7–8 years	Exam ECG; Medical records; National registration system of all hospital discharges	Age; gender; BMI; hypertension; SBP; cholesterol; diabetes; LVH by ECG; MI; heart failure; cigarette smoking; asymptomatic TSH levels in the “normal range”; carotid intima-media thickness.

SBP=systolic blood pressure; LA=left atrial; ECG=electrocardiogram; BMI=body mass index; LVH=left ventricular hypertrophy; CHD=coronary heart disease; MI=myocardial infarction; TSH=thyroid stimulating hormone