MAYO CLINIC

REVIEW

Atrial Fibrillation and Endothelial Dysfunction: A Potential Link?

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and coronary atherosclerosis is the leading cause of death in the United States and worldwide. Endothelial dysfunction is the earliest clinically detectable form of atherosclerosis. Control of shared AF and coronary atherosclerosis risk factors improves both AF-free survival and vascular endothelial function. Decades of AF research have yielded fundamental insight into AF pathophysiology, but current pharmacological and catheter-based invasive AF therapies have limited long-term efficacy and substantial side effects, possibly because of incomplete understanding of underlying complex AF pathophysiology. We hereby discuss potential mechanistic links between endothelial dysfunction and AF (risk-factor–associated systemic inflammation and oxidative stress, myocardial ischemia, common gene variants, vascular shear stress, and fibroblast growth factor-23), explore a potential new vascular dimension to AF pathophysiology, highlight a growing body of evidence supporting an association between systemic vascular endothelial dysfunction, AF, and stroke, and discuss potential common effective therapies.

 ■ Mayo Clin Proc. 2020;■■(■):1-13

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Atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States, with progressively increasing incidence and prevalence. In fact, incidence of AF is projected to double by 2030.[1] Morbidity and mortality secondary to AF are also increasing worldwide owing to associated decrease in functional capacity and quality of life, altered hemodynamics, and increased thromboembolic risk in an aging population.[2] Interestingly, the majority of established and extensively studied AF risk factors to date (including aging, male sex, hypertension, valvular heart disease, left-ventricular dysfunction, obesity, alcohol consumption, smoking, diabetes, and obstructive sleep apnea)[3] overlap with coronary artery disease (CAD) risk factors. On the other hand, physical fitness, aggressive lifestyle modifications (healthy diet and exercise), and control of the aforementioned CAD and AF risk factors have shown to improve AF-free survival. Examples include the impact of cardiorespiratory fitness on recurrence of arrhythmia in obese patients with atrial fibrillation (CARDIO-FIT) study,[4] the aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation (ARREST-AF),[5] and the long-term effect of goal-directed weight management in an atrial fibrillation cohort (LEGACY) long-term follow-up study.[6]

Although AF has been associated with subclinical coronary atherosclerosis, defined as coronary calcium score >0,[7] and advanced obstructive CAD detected on multislice computed tomography coronary angiography,[8] the mechanistic link among CAD, vascular dysfunction, and AF remains largely unknown. Coronary endothelial dysfunction (CED), is the earliest clinically detectable form of atherosclerotic CAD[9] and shares the same risk factors for AF and CAD.[10] It is the result of increased vascular inflammation and oxidative stress and is characterized by abnormal coronary reactivity caused by an imbalance between endogenous vasoconstrictive and vasodilatory molecules.[11] Coronary endothelial dysfunction has been associated with coronary plaque progression,

ARTICLE HIGHLIGHTS

- Mechanistic links between endothelial dysfunction and atrial fibrillation (AF) suggest a potential new vascular dimension to AF pathophysiology.
- Association of AF and stroke may also be mediated or worsened by vascular endothelial dysfunction.
- Prognostic role of endothelial dysfunction early detection and treatment on incident AF and stroke needs in-depth evaluation.

presence of rupture-prone vulnerable plaque, and increased risk of major adverse cardiovascular and cerebrovascular events, thrombotic events, and congestive heart failure.[10,12,13] It is becoming evident that microvascular endothelial dysfunction is a systemic disease involving not only the heart but also other organs including the brain, retina, kidneys, subcutaneous fat, and femoral vasculature.[10,11] Interestingly, it has been recently shown that patients with AF have significantly impaired peripheral endothelial dysfunction and that maintenance of sinus rhythm by catheter ablation in those patients can improve peripheral endothelial function successfully.[14]

In this review, we will discuss the potential mechanistic links between endothelial dysfunction and AF, explore a potential new vascular dimension to the pathophysiology of AF, and highlight the growing body of evidence supporting an association among systemic vascular dysfunction, atrial endothelial dysfunction, and AF.

LIMITED PROGRESS IN UNDERSTANDING THE DIVERSE PATHOPHYSIOLOGY OF AF

Several decades of detailed investigation have yielded fundamental insights into the pathophysiology of AF and the associated alterations in the cellular, molecular, electrophysiological, and atrial structure. Initial work has focused on the "trigger and substrate" theory for AF pathophysiology, whereby rapidly firing ectopic foci in the pulmonary or nonpulmonary veins (superior vena cava, coronary sinus, left atrial appendage, ligament of Marshall, crista terminalis, and left-atrial posterior free wall) trigger AF, which is subsequently maintained by the presence of vulnerable atrial electrical substrates (shortening of refractory period and changes in resting potential caused by membrane abnormalities in atrial cells and impaired electrical impulse conduction caused by altered expression and cell−cell connexins coupling in atrial myocytes) or structural remodeling (left-atrial enlargement or fibrosis).[15] Central to the mechanism of electrical and structural remodeling in AF is intracellular Ca^{2+} overload, which can be caused by increase in oxidative stress and inflammation and release of endothelial vasoactive agents. The structural remodeling in AF can be considered a form of "tachycardia-induced" atrial cardiomyopathy.

Current pharmacological and catheter-based invasive therapeutic options for AF have limited long-term efficacy and substantial side effects, possibly because of an incomplete understanding of the complex pathophysiology of AF.[16,17] Moreover, different subtypes of AF have different responses to antiarrhythmic therapy and catheter ablation, suggesting a potential range of pathophysiological mechanisms underlying different subtypes of AF. For example, although catheter-based AF ablation is suggested to be superior to antiarrhythmic drug therapy in patients with paroxysmal AF (PAF) and persistent AF (PeAF),[18] the long-term success of AF ablation varies considerably from 50% to 80%,[19,20] In fact, the 4-year rate of recurrence of AF was 70% with antiarrhythmic drug therapy and 50% after catheter ablation in the Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest among Patients with Atrial Fibrillation (CABANA Randomized Clinical Trial).[21] The findings of CABANA indeed imply that the 2 current rhythm-control treatment options for AF are suboptimal in preventing recurrence possibly—at least in part—because of under-appreciated and under-explored pathophysiologic etiologies of AF.

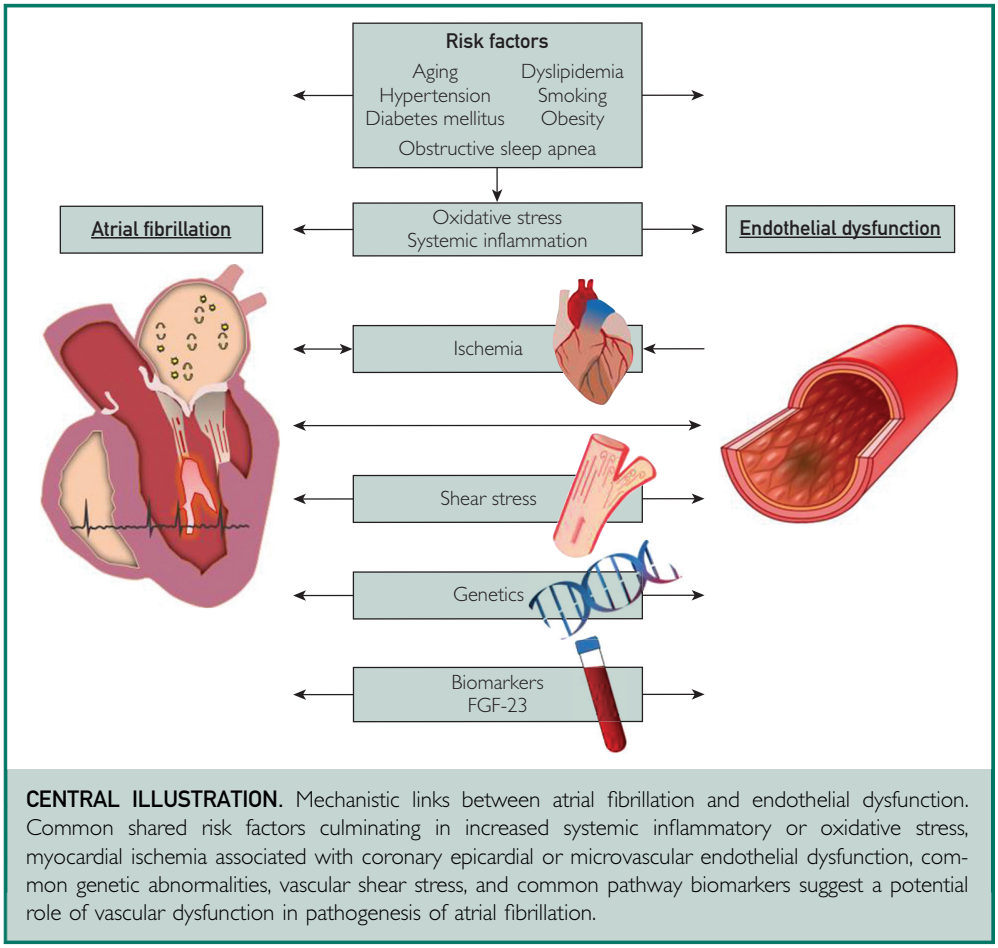
Recently, oxidative stress-mediated atrial remodeling has been implicated to provide

substrate for the development of AF.[22] Genetic predisposition is likely to play a role, and 151 candidate genes were suggested to be involved in AF pathogenesis;[23] patients with family histories of AF have a 40% greater risk of incident AF.[24] Moreover, a growing body of evidence supports that AF may be a systemic disease associated with systemic inflammation, oxidative stress, and endothelial dysfunction.[25] In that sense, endothelial dysfunction may be related to one type of AF more than the other (ie, paroxysmal trigger-dependent AF in young and otherwise healthy patients vs longstanding persistent substrate-predominant AF in older patients with multiple cardiometabolic comorbidities), and thus future studies investigating this relationship should independently study the association of endothelial dysfunction with different types of AF.

AF AND ENDOTHELIAL DYSFUNCTION

Potential Role of Endothelial Dysfunction in Genesis of AF

Experimental and clinical studies have shown that AF is associated with systemic vascular and atrial endothelial dysfunction through multiple mechanisms including (1) altered hemodynamics, (2) shear stress on endothelial cells, (3) reduced nitric oxide bioavailability, (4) increased oxidative stress and inflammation, (5) renin-angiotensin axis abnormalities, and (6) intracellular Ca^{2+} overload.[26-28] Paroxysmal and persistent AF have both been shown to be independent predictors of systemic endothelial dysfunction (independent of common risk factors), whereas restoration and maintenance of sinus rhythm by catheter ablation can improve peripheral endothelial function successfully.[14,29-31] Similarly, cardioversion improved flow-mediated dilatation in patients with lone AF but not in patients with diabetes mellitus.[32] This is partly explained by AF-mediated systemic turbulent flow and decreased endocardial nitric oxide synthase expression and nitric oxide bioavailability, coupled with increased plasminogen activator inhibitor-1 expression in left atria of pigs with induced AF.[26] Conversely, worse peripheral microvascular endothelial dysfunction was associated with higher recurrence of AF following catheter ablation. Importantly, the impact of endothelial dysfunction on recurrence of AF was more significant in young patients (<50 years) with fewer cardiovascular risk factors than older patients, indicating that endothelial dysfunction plays a more prominent role or is more clearly unmasked in AF genesis in the young population.[33] Similarly, an elegant study by Lim et al demonstrated that atrial myocardial damage by radiofrequency catheter ablation of AF provoked coronary microvascular endothelial dysfunction (characterized by increased index of microvascular resistance in the left-anterior descending artery postablation) along with systemic decrease in nitric oxide levels.[34] Indeed, induction of AF increases asymmetric dimethylarginine (marker of endothelial dysfunction) and soluble CD40 ligand (indicator of platelet-derived inflammation) compared with control patients in sinus rhythm or those with rapid atrial pacing at 150 beats per minute.[35] Furthermore, a recent clinical study demonstrated that lone AF (in the absence of other conventional risk factors) was also associated with increased left-atrial platelet activation and systemic endothelial dysfunction, with a significant stepwise worse endothelial function paralleling increasing severity from controls to lone AF to AF with comorbidities.[36] Importantly, a previous study from our group has demonstrated that systemic endothelial dysfunction, measured by peripheral arterial tonometry, was associated with recurrence of AF following pulmonary-vein isolation in young patients.[33] More recently, we have also shown that compared with patients with similar CAD and AF risk-factor profiles but normal endothelial function, patients with CED have 5.8-fold increased risk of developing AF over 10.5 years of follow-up.[37] Taken together, these findings underscore a strong bidirectional association, potentially feeding a vicious cycle that leads to worse endothelial dysfunction (atrial, coronary, or systemic) and persistent AF and suggest a potential role of endothelial dysfunction in genesis of AF.



CENTRAL ILLUSTRATION. Mechanistic links between atrial fibrillation and endothelial dysfunction. Common shared risk factors culminating in increased systemic inflammatory or oxidative stress, myocardial ischemia associated with coronary epicardial or microvascular endothelial dysfunction, common genetic abnormalities, vascular shear stress, and common pathway biomarkers suggest a potential role of vascular dysfunction in pathogenesis of atrial fibrillation.

Endothelial Function Assessment and Limitations of Current Available Data

Atrial endothelial dysfunction has mostly been defined by surrogate systemic or local atrial biomarker levels such as nitric oxide synthase and plasminogen activator inhibitor-1 expression nitric oxide bioavailability. Noninvasive peripheral endothelial function assessment is performed by flow-mediated dilation (FMD) of brachial artery assessed by ultrasound imaging or reactive hyperemic-peripheral arterial tonometry (RH-PAT) assessed by plethysmography. Both techniques evaluate the ability of peripheral arterial endothelial cell lining to produce and secrete nitric oxide in response to limited arterial flow by suprasystolic blood pressure cuff inflation around the arm, with resultant peripheral arterial dilation and hyperemia. Invasive coronary endothelial-function assessment is performed by evaluation of coronary artery diameter change (spasm) and change in coronary blood flow in response to intracoronary acetylcholine infusion. Therefore, it is important to note that available studies discussed in this review are heterogeneous regarding atrial vs arterial (peripheral and coronary) endothelial-dysfunction assessment and diagnosis, which constitutes a limitation of current available data.

POTENTIAL MECHANISTIC LINKS BETWEEN AF AND ENDOTHELIAL DYSFUNCTION

We herein discuss and present available data on 5 potential mechanistic links between atrial fibrillation and endothelial dysfunction (Central Illustration).

TABLE. Summary of Individual Studies and Meta-Analyses of Common AF Interventions Effect on Endothelial Function

Author	Year	Sample size	AF intervention	Effect on endothelial function
Shahin et al[49]	2011	1129	Blood pressure control, mainly with angiotensin converting-enzyme inhibitors and angiotensin receptor blockers	Improvement in peripheral endothelial dysfunction by FMD
Shuang et al[48]	2014	590		
Williams et al[50]	2005	73	Weight loss	Improvement in peripheral endothelial dysfunction by FMD
Gokce et al[51]	2005	41		
Reriani et al[52] (meta-analysis)	2011	2706	Statins	Improvement in both peripheral (by FMD) and coronary (by acetylcholine- challenge testing) endothelial function
Kohler et al	2013	64	Continuous positive airway pressure for obstructive sleep apnea	Improvement in peripheral endothelial function by FMD and clinical outcomes
Kohler et al[53]	2011	41		
Nguyen et al[54]	2010	18		
Ip et al[55]	2004	27		
Oda et al[56]	2016	2734	Decreased alcohol intake	Improvement in peripheral endothelial function by FMD
Johnson et al[57]	2010	1504	Smoking cessation	Improvement in peripheral endothelial function by FMD and RH-PAT; Increase circulating endothelial progenitor cells
Xue et al[58]	2019	166		
Kondo et al[59]	2004	29		
Shin et al[14]	2011	160	Rhythm control by catheter ablation or cardioversion	Improvement in peripheral endothelial function by FMD and RH-PAT
Skalidis et al[60]	2007	71		
Okawa et al[30]	2017	245		
Guazzi et al[27]	2007	50		

AF, atrial fibrillation; FMD, flow-mediated dilation; RH-PAT, reactive hyperemia-peripheral arterial tonometry.

Shared Systemic Risk Factors Associated with Inflammation and Oxidative Stress

Atrial fibrillation and endothelial dysfunction share common systemic risk factors and may thus share—and be the result of—common systemic inflammatory and oxidative stress pathogenic pathways. In fact, control of the of 7 modifiable CAD risk factors listed in the American Heart Association Life Simple 7 Guide (cholesterol level, blood pressure, blood glucose, smoking, physical activity, diet, and body mass index [BMI]) demonstrated that each 1-point increase in Life Simple 7 score was associated with a 5% reduction in risk of incident AF in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study cohort and by 17% in the Atherosclerosis Risk in Communities (ARIC) study cohort.[38,39]

Age is the most prominent risk factor for AF.[40,41] Recently, an epidemiological study showed distinct demographics between patients with AF <65 years and >65 years of age. Interestingly, patients <65 years of age with AF have been found to have fewer cardiovascular risk factors, indicating the presence of under-recognized risks for AF in this patient population such as endothelial dysfunction and genetic variance.[42]

Hypertension is another strong independent risk factor for AF.[43-45] In the ARREST-AF study, strict blood pressure control, along with other risk-factor modification,

increased the arrhythmia-free survival interval in patients who had undergone AF ablation.[5] Similarly, a recent meta-analysis demonstrated a 20% to 40% reduction in incidence of AF in patients with left-ventricular hypertrophy or dysfunction treated with inhibitors of the renin-angiotensin-aldosterone pathway.[46] This finding is consistent with the known properties of angiotensin II as an inflammatory modulator leading to increased oxidative stress and sympathetic system drive, which can, in turn, increase atrial fibrosis and remodeling and ultimately development of AF.[47] Indeed, blood pressure control in hypertensive patients, mainly with angiotensin converting-enzyme inhibitors and angiotensin receptor blockers, has shown to improve peripheral endothelial function as measured by FMD[48,49] (Table).

Ample evidence exists linking obesity and AF, and several studies showed that weight loss decreases incidence of AF. In the LEGACY cohort, long-term sustained weight loss $\geq$10% resulted in a 6-fold greater probability of arrhythmia-free survival compared with those with <10% weight loss.[6] Further subanalysis in the ARREST-AF study showed that the same group had an 88% reversal rate from persistent to paroxysmal or no AF ($P<.001$), indicating that weight-loss management and risk-factor modification reverses the type and natural progression of AF.[61] Furthermore, bariatric surgery reduces the risk of AF by 31% in men and women with a baseline BMI of >34 and >38, respectively, with a greater risk reduction in younger patients.[62] Similarly, weight loss significantly improve endothelial dysfunction in humans[50,51] (Table).

Diabetes is also a strong independent predictor of AF and CAD.[63] The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial demonstrated that hypertensive patients who developed diabetes during a 4.2-year follow-up period also had 49% increased risk of developing incident AF.[64] A separate meta-analysis by Huxley et al demonstrated that patients with diabetes had a 25% relative risk increase in developing AF after adjusting for other AF risk factors.[50] Abnormal glucose metabolism triggers cardiac autonomic dysfunction and increases oxidative stress, leading to not only endothelial dysfunction but also atrial electrical and structural remodeling.

The role of hyperlipidemia in the development of AF remains unclear and mostly attributable to associated comorbidities and metabolic syndrome. Analysis from the Multi-Ethnic Study of Atherosclerosis (MESA) and Framingham Heart Study (FHS) cohorts showed a protective role against AF for higher levels of high-density lipoproteins, no effect for low-density lipoproteins and total cholesterol levels, and a higher risk for AF with elevated triglycerides.[63] Metabolic syndrome, partially defined by elevated triglycerides, was also found to be associated with a higher incidence of AF.[64] On the other hand, statins—commonly used for treatment of CED (Table) and prevention of progression of atherosclerosis—have shown to decrease incidence and recurrence of AF, as discussed later in the Atrial Fibrillation, Endothelial Dysfunction and Common Effective Therapies section of this review.

The relationship between obstructive sleep apnea (OSA) and both AF and endothelial dysfunction has also been studied. Murine models of OSA manifest a 43% increase in interstitial collagen fraction in the atria but not ventricles.[65] Cardiac remodeling, fibrosis, and increased atrial inflammatory marker interleukin-6 associated with OSA play important role in development of AF.[65,66] The Sleep Heart Health Study reported a significantly increased incidence of nocturnal AF in patients with OSA,[67] which, in turn, along with anteroposterior left-atrial diameter, was an independent predictor of failure of AF ablation.[68] Similarly, in a meta-analysis of studies with a total of approximately 4000 patients undergoing AF ablation, OSA was associated with 25% increased risk of AF recurrence.[69] Although our group did not find a link between OSA and CED,[70] Kadohira et al have shown a significant correlation between severity of OSA and rate of coronary vasoconstriction in

response to intracoronary acetylcholine infusion.[71] Interestingly, OSA was recently shown to be associated with peripheral endothelial dysfunction,[72] whereas treatment of OSA with continuous positive airway pressure therapy was associated with improved endothelial function[72,53-55] (Table), suggestive of a possible systemic link between AF and vascular endothelial dysfunction beyond the heart.

Finally, substance abuse—both excess alcohol intake[73] and tobacco use[74,75]—constitute risk factors for AF. Moderate intake (>2 drinks per day) of alcohol in otherwise healthy women increased the risk of AF,[76] whereas, conversely, a reduction in alcohol use contributed to improved AF ablation outcomes in the ARREST-AF trial,[5] and alcohol abstinence was associated with reduced recurrences of arrhythmias in regular drinkers with AF.[77] Similarly, a subanalysis of the ARIC cohort showed a dose-response relationship between smoking and risk of AF[78] and current smoking status compared with smoking history, showed stronger association with incident AF.[79] On the other hand, decreased alcohol intake and weight loss have both shown to improve peripheral endothelial dysfunction by FMD and RH-PAT, along with increase in endothelial progenitor cells (Table).[56-59]

MYOCARDIAL ISCHEMIA

Experimental atrial ischemia promotes AF in dogs and pharmacological treatment with beta blockers and calcium channel blockers suppress ischemia-induced AF in the same animal model.[80,81] Similarly, experimental left-atrial ischemia induces spontaneous focal discharges and re-entry, leading to AF in sheep,[82] whereby increased oxidative stress in the ischemic zone results in altered ryanodine receptor 2 and calmodulin-binding property with subsequent increase in calcium leak from ryanodine receptor 2. Administration of dantrolene normalizes calmodulin response, prevents induction of spontaneous focal discharged in the left atrium, and thus blunts initiation of AF. In addition to ischemia-induced focal triggers, epicardial CAD may be accompanied by interatrial block, which has been linked to AF substrates such as fibrosis and changes in the electrical properties of the atrial myocytes, leading to development, maintenance, and recurrence of AF.[83-86] These studies highlight the mechanistic role of myocardial ischemia caused by obstructive CAD in triggering AF. However, not only epicardial CAD, but also coronary microvascular dysfunction, can induce myocardial ischemia. Indeed, patients with AF and no obstructive CAD, compared with controls in sinus rhythm, have impaired baseline and stress myocardial blood flow secondary to coronary microvascular dysfunction.[87,88] Moreover, this reduction in myocardial blood flow was shown to be proportional to the degree of left-ventricular and left-atrial impairment.[88] Another elegant study by Skalidis et al[60] demonstrated that isolated atrial myocardial perfusion abnormalities, secondary to coronary microvascular dysfunction in the left-atrial circumflex artery branch, were associated with lone recurrent AF. Interestingly, coronary flow reserve measured in the left-atrial circumflex artery is significantly lower than that in the proximal left-circumflex coronary artery in the same patients with lone AF. Their findings underscore the potential important role of coronary endothelial and nonendothelial microvascular dysfunction-induced ischemia in the pathogenesis of AF.

Common Gene Variants

Some patients develop AF despite the apparent absence of known risk factors, suggesting that genetic variants provide important background predisposition for the development of AF. In a small study with 10 patients, a higher than expected recurrence of lone AF postablation in pediatric patients (<21 years of age) without conventional cardiovascular risk factors is also suggestive of genetic predisposition for AF or atrial tissue more refractory to AF substrate modification.[89] Moreover, the presence of AF in only 1 parent was associated

with 85% increased risk of offspring AF in the Framingham Heart Study[90] and 40% greater risk of incident AF in offsprings with family histories of AF in a separate study.[24] Genome-wide association studies showed that some genetic variants linked to AF are related to ion channels and cardiac morphogenesis.[91-96] Other studies further identified predisposing genes to AF related to the renin-angiotensin system[97] and inflammation.[98] Also, genetic variants affecting endothelial functions, such as endothelial nitric oxide synthase and caveolin-1, have been linked to AF.[99-101] In fact, administration of endothelial nitric oxide synthase inhibitor heightened AF inducibility by epicardial catheter stimulation in rabbits, potentially via calcium overload mechanism.[102] These genetic variants might play an important mechanistic link between vascular diseases and AF in young patients.

Vascular Shear Stress

Another potential mechanism in which AF affects endothelial dysfunction is reduced shear stress caused by rapid and irregular pulse. Experimental rapid atrial pacing in rabbits results in decreased shear stress with a subsequent decrease in production of endothelial nitric oxide and increased oxidative stress markers.[103]

Fibroblast Growth Factor-23

Fibroblast growth factor (FGF)-23 is a phosphate and calcium-regulating hormone, primarily secreted by osteocytes and osteoblasts, which is elevated with decreasing kidney function and is associated with major cardiovascular events in patients with chronic kidney disease.[104] However, FGF-23 is also an emerging biomarker to detect AF[105,106] independent of kidney function.[107] Fibroblast growth factor-23 promotes myocardial remodeling and cardiac hypertrophy. Therefore, FGF-23 may cause hypertrophy-related ectopic activity and automaticity, leading to AF.[108,109] Interestingly, FGF-23 has been independently associated with impaired vascular reactivity and increased arterial stiffness,[110] thus suggesting another possible link between FGF-23 levels as a marker of endothelial dysfunction and AF.

AF, ENDOTHELIAL DYSFUNCTION, AND STROKE

A growing body of evidence suggests that endothelial dysfunction is a systemic disease affecting multiple organ systems including the heart, brain, kidneys, retina, and even subcutaneous and visceral fat.[11,111] Also, systemic endothelial dysfunction has been associated with increased risk of major adverse cardiovascular events, including patients with minimal traditional cardiovascular risk factors.[112] The endothelium is a prime site for the effects of cardiovascular risk factors. Thus, in assessing the effects of these risk factors that are associated with inflammation and oxidative stress, endothelial function can be viewed as an integrated index and sensitive marker of cardiovascular risk.[113] Indeed, the determinants of the CHA2DS2-VASc score, which is a commonly used stratification scheme for assessing the risk of thromboembolic stroke in patients with nonvalvular AF, are conditions associated with endothelial dysfunction. We, and others, have previously reported that coronary and peripheral endothelial dysfunction could predict future risk of cardiovascular events, including cardiovascular death, acute coronary syndrome, coronary revascularization, heart failure, peripheral artery disease, and stroke.[12,13,114] We have also previously reported that coronary endothelial dysfunction is independently associated with increased venous and arterial thrombosis and adverse cerebrovascular events in similar patient populations.[115,116]

Atrial fibrillation is a well-known risk factor of cardioembolic stroke, and anticoagulation reduces the risk of stroke. However, in the Stroke Prevention in Atrial Fibrillation (SPAF) trial, only 52% of strokes in AF were estimated to be cardioembolic.[117] Similarly, 57% of patients had cardioembolic stroke, and 36% of patients had lacunar mechanisms in Asymptomatic Atrial Fibrillation and the Atrial Fibrillation Reduction in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial pacing (ASSERT) trial.[118] Importantly,

the risk of stroke in AF was not necessarily temporally associated with the periods of AF, whereby in a subanalysis of the ASSERT trial, Brambatti and colleagues[119] have elegantly shown that the majority of strokes were not preceded by AF. These observations suggest an epidemiological association between AF and stroke that is independent of cardiac rhythm, perhaps indicating an underlying vascular etiology of strokes in AF.

This underlying vascular etiology may potentially involve endothelial dysfunction. Atherosclerosis is a major determinant in large-vessel, noncardioembolic strokes, and endothelial dysfunction is the earliest detectable form of atherosclerosis. In addition to the associations of endothelial dysfunction with stroke discussed here, a previous report showed that circulating level of von Willebrand factor and soluble E-selectin, considered to be markers of endothelial activation, and damage and dysfunction, respectively, are increased in patients with AF (compared with control subjects in sinus rhythm) and may be contributory to a hypercoagulable state predisposing to stroke in AF.[120] This hypothesis is supported by an important study demonstrating that increased levels of circulating von Willebrand factor and soluble E-selectin are associated with the increased risk of ischemic stroke in real-world patients with AF.[121] Finally, significant positive correlations between markers of fibrinolysis and prothrombotic state (such as fibrinogen) and markers of endothelial dysfunction in patients with AF also suggest that endothelial dysfunction could be 1 of the determinants of thrombogenesis and potentially stroke in this patient population.[122]

AF, ENDOTHELIAL DYSFUNCTION, AND POTENTIALLY COMMON EFFECTIVE THERAPIES

Beneficial effects of aggressive common risk factors control and statin therapy on both endothelial function and incidence of AF and recurrence postablation lends credence to a common underlying pathophysiology and the potential mechanistic links between these 2 disease entities. Lifestyle interventions that reduce incidence and recurrence of AF, including weight loss, smoking cessation or abstinence, avoidance of excessive alcohol and caffeine intake, and eating a heart-healthy diet, have also shown to improve endothelial function, as summarized in the Table. Moreover, statins have also shown beneficial effects on both peripheral and coronary endothelial dysfunction[52] and AF (Table). Rosuvastatin significantly reduced risk of incident AF, compared with placebo, in a large (17,000 patients) exploratory analysis of the JUPITER trial,[123] and statin therapy was associated with lower recurrence of AF and burden following dual-chamber pacemaker implantation in 185 patients with paroxysmal AF.[124] The role of statins in prevention of AF was further shown in a meta-analysis by Fang et al.[125] Although our previous randomized controlled trial of high-intensity atorvastatin therapy for prevention of atrial fibrillation postpulmonary catheter ablation was negative (125 patients),[126] a very recent meta-analysis rate in 4 pooled randomized controlled trials (488 patients), including ours,[127] did show that statins significantly lowered recurrence of AF post-catheter ablation. Accordingly, large-scale, high-quality randomized controlled clinical trials investigating statins and other common therapeutic targets for both AF primary or secondary prevention and endothelial function improvement are certainly warranted.

In addition, whether early aggressive medical therapy for atrial, peripheral, or coronary endothelial dysfunction could prevent incident AF in this young patient population also warrants further investigation, based on data presented in this review. Moreover, randomized clinical trials evaluating AF ablation vs medical therapy alone effect on endothelial function would also be important to help answer the question of whether successful restoration of sinus rhythm post-AF ablation leads to direct endothelial function improvement (through restoration of laminar flow and improved NO bioavailability) or whether the improvement in endothelial function seen in observational

studies of AF ablation are mere secondary to confounding multimodal pharmacological and nonpharmacological interventions implemented after ablation procedures.

CONCLUSION

A growing body of evidence links AF to atrial, coronary and systemic endothelial dysfunction. Data presented in this review strongly suggest a potential role of endothelial and vascular dysfunction in genesis of AF, or at least a bidirectional association between these diseases, potentially feeding a vicious cycle that leads to worse endothelial dysfunction and persistent AF. Mechanistic links between AF and endothelial dysfunction include common shared risk factors, culminating in increased systemic inflammatory or oxidative stress, myocardial ischemia associated with coronary epicardial or microvascular endothelial dysfunction, common genetic abnormalities, vascular shear stress, and common pathway biomarkers. Finally, the association of AF and stroke may also be mediated or worsened by vascular endothelial dysfunction independently associated with arterial thrombosis. Large prospective studies are warranted to evaluate these hypotheses and study the potential benefit of early detection and treatment of endothelial dysfunction on development of AF and prevention of ischemic stroke.

Abbreviations and Acronyms: **AF** = atrial fibrillation; **ED** = endothelial dysfunction; **CAD** = coronary artery disease

Grant Support: The authors report no grant support for this article.

Potential Competing Interests: The authors report no competing interests.

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