CORONARY ENDOTHELIAL DYSFUNCTION IS ASSOCIATED WITH INCREASED RISK OF INCIDENT ATRIAL FIBRILLATION

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BACKGROUND: Coronary artery disease risk factors are associated with atrial fibrillation (AF) and coronary endothelial dysfunction (CED). We hypothesized that CED is associated with increased risk of incident AF among patients with chest pain and nonobstructive coronary artery disease.

METHODS AND RESULTS: Three hundred patients with chest pain, nonobstructive coronary artery disease, and no history of AF underwent intracoronary acetylcholine infusion for evaluation of baseline epicardial (decrease in mid–left anterior descending coronary artery diameter in response to acetylcholine) and microvascular (<50% increase in coronary blood flow in response to acetylcholine) CED. Primary outcome was incident AF over a mean follow-up period of 10.5±5.5 years. Mean age was 53.3±10.8 years, and 70% were women. Baseline clinical and echocardiographic characteristics were similar between patients with CED (n=256) and those with normal endothelial function (n=44). Overall, 35 of 300 (12%) patients developed AF, among whom 34 of 35 (97%) had CED at baseline. Compared with normal endothelial function, the presence of CED was associated with 11% increased absolute risk and 5.8-fold increased relative risk of incident AF. Moreover, CED (odds ratio, 3.87; 95% CI, 1.27–47.0) and increased (>34 mL/m²) left atrial volume index (odds ratio, 3.87; 95% CI, 1.60–9.11) were independent predictors of incident AF.

CONCLUSIONS: Patients with normal coronary endothelial function, as compared with those with CED and similar AF risk factors, have significantly lower incidence of AF on long-term follow-up. The potential mechanistic link between vascular dysfunction and AF development warrants further investigation.

Key Words: atrial fibrillation, coronary artery disease, coronary endothelial dysfunction

Atrial fibrillation (AF) is the most commonly encountered sustained arrhythmia in clinical practice, with progressively increasing incidence, prevalence, and associated mortality and morbidity worldwide. The estimated lifetime risk of developing AF for individuals 40 to 55 years of age is 22% to 24%.1 Multiple traditional and nontraditional risk factors and predictors of AF have been extensively studied, including age, sex, hypertension, valvular heart disease, congestive heart failure, congenital heart disease, obesity, diabetes mellitus, sleep apnea, smoking, alcohol consumption, chronic kidney disease, inflammation, and genetics. There is considerable overlap between the risk factors for AF and coronary artery disease (CAD); however, the nature of the pathophysiologic link between these disease processes is unknown.

Coronary endothelial dysfunction (CED) is the earliest clinically detectable form of atherosclerosis.2 CED is characterized by abnormal coronary vasoreactivity and is associated with coronary plaque progression, presence of rupture-prone vulnerable plaque, and increased risk of major adverse cardiovascular and cerebrovascular events, thrombotic events, and congestive heart failure.3–5
Patients with AF have been demonstrated to have higher rates of advanced obstructive CAD detected on multislice computed tomography coronary angiography compared with patients without AF. Furthermore, a higher prevalence of subclinical CAD, defined as coronary calcium score >0, has been reported in asymptomatic AF patients without history of CAD. Moreover, 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 successfully improve peripheral endothelial function.

Whether AF is a vascular disease or part of a syndrome that starts with CED and progresses to advanced CAD also remains unknown. Improved understanding of the underlying mechanisms and pathophysiology of AF and its association with earliest detectable forms of atherosclerosis are certainly needed to develop more efficient strategies for AF prevention and management. We hypothesized that the presence of CED is associated with increased long-term risk of incident AF in patients with chest pain and nonobstructive CAD, independent of other CAD risk factors.

CLINICAL PERSPECTIVE

What Is New?
• In 300 patients with chest pain and nonobstructive coronary artery disease, absence of baseline coronary endothelial dysfunction was associated with significantly lower absolute and relative risks of developing incident atrial fibrillation over 10.5 years of follow-up.
• Coronary endothelial dysfunction and increased left atrial volume index were independent predictors of incident atrial fibrillation.

What Are the Clinical Implications?
• Findings suggest a potential mechanistic link between vascular dysfunction and atrial fibrillation development.

Nonstandard Acronyms and Abbreviations

| Acronym | Definition |
|---------|------------|
| AF      | atrial fibrillation |
| CAD     | coronary artery disease |
| CED     | coronary endothelial dysfunction |
| LAVI    | left atrial volume index |
| OR      | odds ratio |
| TTE     | transthoracic echocardiogram |

Coronary Reactivity Testing

All patients withheld all prescription medications that could affect coronary vasoreactivity for at least 48 hours before coronary angiography and coronary reactivity testing. These medications included calcium channel blockers, β-blockers, long-acting nitrates, and phosphodiesterase inhibitors. Short-acting sublingual nitroglycerin for chest pain was only allowed >6 hours before the procedure. After diagnostic angiography and exclusion of patients with CAD ≥40%, endothelium-dependent and endothelium-independent coronary vasoreactivity were assessed as previously described. In brief, Doppler guidewire (Flowire, Volcano Therapeutics Inc, Rancho Cordova, CA) within a coronary-infusion catheter was positioned into the mid–left anterior descending coronary artery. Incremental intracoronary bolus injections of adenosine (18–72 μg) were administered until maximal hyperemia was achieved. Coronary endothelium-independent microvascular function was assessed by coronary flow velocity reserve calculated as hyperemic flow velocity/baseline flow velocity. Subsequently, coronary endothelial function was assessed by selective intracoronary infusion of escalating doses of acetylcholine [10⁻⁶, 10⁻⁵, and 10⁻⁴ mol/L for 3 minutes at each concentration] into the mid–left anterior descending coronary artery.

METHODS

Patient Population

We enrolled 401 consecutive patients with chest pain and nonobstructive CAD (<40% angiographic stenosis) on clinically indicated coronary angiography between 1993 and 2015. All patients underwent comprehensive invasive coronary reactivity testing for evaluation of epicardial and microvascular CED during the same catheterization procedure. All patients had no history of AF diagnosis at the time of the index procedure, confirmed by review of patients’ charts and baseline ECGs. Patients with acute coronary syndrome presentation and those with a history of myocardial infarction or cerebrovascular accident within the past 6 months, previous percutaneous coronary intervention or coronary artery bypass surgery, use of radiographic contrast agents within 12 hours before catheterization, valvular heart disease, advanced chronic kidney disease, cardiomyopathy (left ventricular ejection fraction <45%), active malignancy, local or systemic infectious disease within 4 weeks before catheterization, and inflammatory diseases were excluded. Pregnant patients and those unable to provide written informed consent were also excluded from this study. The study was compliant with the Declaration of Helsinki and approved by Mayo Institutional Review Board.
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artery. Hemodynamic data, Doppler measurements, and coronary angiograms were obtained after each infusion. Coronary artery diameter was measured by an independent investigator in the segment 5 mm distal to the tip of the Doppler wire offline using a quantitative coronary angiography program (Medis Corp., Leiden, the Netherlands), and epicardial CED was defined as any coronary artery vasoconstriction, percent change in coronary artery diameter <0%, in response to acetylcholine infusion. Coronary blood flow in the left anterior descending coronary artery was calculated from the Doppler-derived time velocity integral and vessel diameter, where coronary blood flow =πt×(coronary artery diameter/2)²×(average peak velocity/2), and microvascular CED was defined as <50% increase in coronary blood flow in response to acetylcholine infusion.

**Transthoracic Echocardiographic Assessment**

Transthoracic echocardiographic parameters of study patients were collected by chart review and time period, in days, between transthoracic echocardiogram (TTE) study and endothelial function study for each patient was recorded as a negative value if TTE was done before coronary reactivity testing or positive if done after coronary reactivity testing. Left ventricular ejection fraction, cardiac index, right ventricular systolic pressure, left atrial volume index (LAVI), and diastolic parameters, including mitral E and A velocities, E/A ratio, medial E/e’ and lateral E/e’ ratios, were collected.

**Follow-Up and Assessment for Incident AF**

Patients were assessed for new diagnosis of AF by administration of a questionnaire. Mean follow-up period from index coronary reactivity testing procedure was 10.5±5.5 years. We used a standardized questionnaire to assess incidence of AF on long-term follow-up. All patients were confirmed to have no history of AF by chart review and review of ECGs at time of baseline endothelial function testing. The primary end point was any new coronary artery vasoconstriction, percent change in coronary artery diameter <0%, in response to acetylcholine infusion. Coronary blood flow in the left anterior descending coronary artery was calculated from the Doppler-derived time velocity integral and vessel diameter, where coronary blood flow =πt×(coronary artery diameter/2)²×(average peak velocity/2), and microvascular CED was defined as <50% increase in coronary blood flow in response to acetylcholine infusion.

**Statistical Analysis**

Continuous variables are summarized as mean±SD or median (interquartile range), and differences between groups were tested using Student t test. Discrete variables are summarized as frequency (percentage), and Pearson’s chi-squared test was used to test for differences. When an expected value was <5, Fischer’s exact test was used to evaluate differences in the place of the chi-squared. Absolute and relative risks of incident AF are calculated in patients with normal endothelial function versus those with CED. Univariate analysis was performed to evaluate the relationship between traditional AF risk factors, CED, and incident AF. Multivariable logistic regression models, including CED, increased LAVI (>34 mL/m²), and age, were used to determine independent predictors of AF. Missing predictor values were imputed using random forest methods. Both the model with imputation and the complete case model are shown. An additional third model with important AF clinical predictors (CED, hypertension, and age) was fit, and results are reported. Because of the small sample size and possibility of separation, Firth’s bias reduction methods were used. All variables were first checked for multicollinearity using the variance inflation factor. There were no variance inflation factors in excess of 2. For all analyses, a 2-sided P<0.05 was considered statistically significant. A sensitivity analysis was conducted because of the potential of mortality being associated with missing AF data. Identical multivariable models were run assuming deaths were related to AF, and the results were compared with the models using the original data. Missing data attributable to incomplete surveys were assumed to be completely at random and excluded from all models. Analyses were done using R version 3.4 (R Core Team, 2017). Imputation was done using the RandomForest package (version 4.6–12), and the logistf package (version 1.23) was used for bias reduced multivariable logistic regression.

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data sharing is subject to limitations of the informed consent and Mayo Institutional Review Board approval.

**RESULTS**

**Patient Population**

A total of 101 patients of 401 patients were excluded from analysis: 16 (4%) patients were confirmed deceased by review of medical chart and national registries, and no information on incident AF was available, and 85 (21%) returned incomplete questionnaires with unknown AF status at time of...
follow-up. Three hundred (75%) of 401 patients returned complete questionnaires and were included in the present study. Mean age was 53.3±10.8 years, and body mass index 29.1±5.8 kg/m². Seventy percent were women, 48% had hypertension, 56% hyperlipidemia, 9% diabetes mellitus, and 6% were smokers. Mean percent angiographic stenosis was 12±14%. Of these 300 patients, 44 (15%) had normal endothelial function, and 256 (85%) had CED at baseline. Of the latter, 17 (7%) patients had isolated microvascular endothelial dysfunction, 75 (29%) had isolated epicardial endothelial dysfunction, and 164 (64%) had combined epicardial and microvascular endothelial dysfunction. Endothelium-independent coronary flow velocity reserve was similar between patients with normal endothelial function versus those with CED (2.9±0.7 versus 2.9±0.7; \( P = 0.59 \)). All baseline patient characteristics were similar between patients with normal coronary endothelial function and those with CED (Table 1). Mean follow-up period was 10.5±5.5 years.

**Transthoracic Echocardiographic Characteristics**

Median (interquartile range) time period between TTE and baseline coronary endothelial function testing was −2 (−22, +3) days. This time period was similar between patients with normal endothelial function −2 (−21, +1) and those with CED −2 (−23 to +24) days (\( P = 0.08 \)). Table 2 represents the baseline TTE characteristics of the study population. There were no significant differences in all TTE characteristics including LAVI in patients with normal versus abnormal endothelial function. However, mean LAVI was significantly larger in patients who developed AF (32.9±7.7 mL/m²; \( P = 0.04 \)) whereas left ventricular ejection fraction, cardiac index, right ventricular systolic pressure, and diastolic function parameters were similar between those who developed AF and those who did not (\( P = NS \) for all).

**Association of CED and AF**

A total of 35 (12%) patients developed AF during the follow-up period. Percent angiographic stenosis was similar between those who developed AF and those who did not (12±14 versus 14±13%; \( P = 0.63 \)). Among the 10 (29%) patients, who developed AF with no angiographic atherosclerosis at baseline, 7 patients had combined epicardial and microvascular CED, 2 had isolated epicardial CED, and 1 had normal coronary endothelial function.

Figure(A) shows distribution of incident AF diagnoses, and Figure(B) the absolute risk of new AF in patients with normal versus abnormal baseline coronary endothelial function. Thirty-four (97%) new AF diagnoses occurred in patients with baseline epicardial or microvascular CED, and 1 (3%) occurred in a patient with normal coronary endothelial function (\( P = 0.04 \)). Thus, incident AF was more frequent in patients with CED (13.3%) than in those with normal endothelial function (2.3%). As compared with patients with normal baseline coronary endothelial function, presence of CED was associated with an 11% absolute risk increase and 5.8-fold relative risk increase in AF on long-term follow-up. Among CED patients who developed AF, 24 (68.6%) had combined epicardial and microvascular dysfunction, 9 (25.7%) had isolated epicardial CED, and 1 (2.9%) had isolated microvascular CED.

**Table 1. Baseline Clinical Characteristics**

|                      | Normal Coronary Endothelial Function (n=44) | Coronary Endothelial Dysfunction (n=256) |
|----------------------|-------------------------------------------|------------------------------------------|
| Age, y               | 53.7±10.4                                  | 53.3±10.8                                |
| Women, n (%)         | 34 (77)                                    | 176 (69)                                 |
| Body mass index, kg/m² | 29.0±6.2                                   | 29.1±5.8                                 |
| Mean arterial pressure, mm Hg | 103±15                                    | 99±13                                    |
| Total cholesterol, mg/dL | 186±35                                    | 184±41                                   |
| Low-density lipoprotein, mg/dL | 106±28                                    | 103±36                                   |
| High-density lipoprotein, mg/dL | 58±19                                     | 55±18                                    |
| Triglycerides, mg/dL | 124±97                                     | 129±100                                  |
| Hypertension, n (%)  | 23 (52)                                    | 120 (47)                                 |
| Hyperlipidemia, n (%) | 23 (52)                                    | 145 (57)                                 |
| Diabetes mellitus, n (%) | 4 (9)                                      | 24 (9)                                   |
| Tobacco smoking, n (%) | 3 (7)                                      | 15 (6)                                   |

Values are mean±SD or n (%). All \( P \) values for comparison between groups are nonsignificant (>0.05).

**Table 2. Baseline Echocardiographic Characteristics**

|                      | Normal Coronary Endothelial Function (n=44) | Coronary Endothelial Dysfunction (n=256) |
|----------------------|-------------------------------------------|------------------------------------------|
| Left ventricular ejection fraction, % | 62±6                                      | 62±7                                     |
| Cardiac index, L/min per m²          | 3.2±0.7                                   | 3.2±2.4                                  |
| Right ventricular systolic pressure, mm Hg | 28.3±4.7                                  | 28.6±6.0                                 |
| Left atrial volume index, mL/m²      | 26.8±8.6                                  | 27.8±8.5                                 |
| Mitral E velocity, m/s              | 0.7±0.2                                   | 0.8±0.2                                  |
| Mitral E/A ratio                    | 1.1±0.5                                   | 1.3±0.8                                  |
| Medial E/e′ ratio                   | 9.5±2.7                                   | 9.4±3.0                                  |
| Lateral E/e′                       | 7.3±2.4                                   | 7.7±2.8                                  |

Values are mean±SD. All \( P \) values for comparison between groups are nonsignificant (>0.05).
Univariate analyses of AF predictors are shown in Table 3. In the multivariable analyses model with imputed data, coronary endothelial dysfunction (odds ratio [OR], 3.87; 95% CI, 1.27–47.0) and increased (>34 mL/m²) LAVI (OR, 3.87; 95% CI, 1.60–9.11) were independent predictors of AF (Table 4, model A) after adjusting for age. These results held using only complete case data (Table 4, model B). For a sensitivity analysis where missing because of death was assumed to be related to AF, the results held in the complete case analysis for coronary endothelial dysfunction (OR, 3.34; 95% CI, 1.01–17.27) but did not for the imputed analysis (OR, 2.59; 95% CI, 0.98–8.62). Additionally, CED remained an independent predictor of AF (OR, 4.51; 95% CI, 1.14–40.94) in a fit model adjusted for age and hypertension, the 2 strongest known clinical predictors of AF.

DISCUSSION

To our knowledge, this study is the first to show that normal coronary endothelial function compared with CED is associated with significantly lower absolute and

Table 3. Univariate Analyses for Risk Factors of Incident Atrial Fibrillation

| Variable                                | Univariate Odds Ratio (95% CI) | P Value |
|-----------------------------------------|--------------------------------|---------|
| Coronary endothelial dysfunction        | 6.59 (1.36 to >100)            | 0.07    |
| Increased left atrial volume index, >34 mL/m² | 3.75 (1.61–8.57)              | 0.002   |
| Age                                     | 1.03 (0.99–1.07)               | 0.07    |
| Sex, male                               | 1.10 (0.50–2.30)               | 0.81    |
| Hypertension                            | 1.25 (0.61–2.58)               | 0.54    |
| Body mass index                         | 0.98 (0.91–1.04)               | 0.45    |
| Diabetes mellitus                       | 1.30 (0.36–3.63)               | 0.65    |
| Hyperlipidemia                          | 0.97 (0.47–2.02)               | 0.93    |
| Obstructive sleep apnea                 | 1.47 (0.66–3.10)               | 0.33    |

Odds ratios and 95% CIs for univariate analyses. The following variables had the associated percentage of missing values: 26% for increased left atrial volume index, 1% for hypertension, and 1% for hyperlipidemia.

Table 4. Multivariable Logistic Regression Analyses for Independent Risk Factors of Incident Atrial Fibrillation

| Variable                                | Model A—Imputed Data (N=300) | Model B—Complete Case (N=221) |
|-----------------------------------------|-------------------------------|-------------------------------|
| Coronary endothelial dysfunction        | 5.13 (1.27–47.00)             | 14.1 (1.87 to >100)           |
| Increased left atrial volume index, >34 mL/m² | 3.87 (1.60–9.11)             | 3.77 (1.58–8.86)             |
| Age                                     | 1.02 (0.99–1.06)              | 1.02 (0.98–1.06)             |

Odds ratios and 95% CIs for multivariable analyses. Increased left atrial volume index variable had 26% missing values.
relative risk of long-term incident AF in relatively young patients with similar baseline AF risk factors. Moreover, CED and increased LAVI were found to be independent predictors of AF development. The current study further supports a potential mechanistic link between vascular dysfunction and AF.

Prior experimental and clinical studies have shown that AF is associated with systemic vascular and atrial endothelial dysfunction through multiple mechanisms including altered hemodynamics and shear stress on endothelial cells, reduced nitric oxide bioavailability, increased oxidative stress and inflammation, and renin-angiotensin axis abnormalities. Indeed, peripheral endothelial function, by arterial tonometry, has been previously shown to be significantly lower in patients with AF and that maintenance of sinus rhythm by catheter ablation in AF successfully improves peripheral endothelial function. On the other hand, an elegant small study by Skalidis et al 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. Their findings underscore a link between coronary microvascular dysfunction and AF. A prior study from our group has also demonstrated that peripheral endothelial dysfunction, measured by peripheral arterial tonometry, was associated with AF recurrence following catheter ablation in young patients. The current study builds on these findings and strongly suggest that CED, and potentially ischemia secondary to CED, may be a pathophysiological substrate of AF. Taken together, these data may also suggest bidirectional interactions between CED and AF, potentially feeding a vicious cycle that leads to worse endothelial dysfunction and persistent AF.

A growing body of evidence suggests that endothelial dysfunction is a systemic disease affecting multiple organ systems, including the heart, brain, kidneys, retina, and peripheral vasculature. Traditional CAD risk factors, oxidative stress, inflammation, and renin-angiotensin system abnormalities are not only the central known mediators of AF but are also involved in the development of CED. However, the fact that CED was an independent predictor of incident AF in this study after adjusting for age, hypertension, and LAVI sheds new light into the pathophysiology of AF. Furthermore, it raises the possibility that some of the prior clinical risk factor studies were confounded by underlying CED, or that CED is the mechanism by which these risk factors converge to induce AF. In turn, these results beg the question of whether AF, whose exact pathogenesis mainly in the younger population remains unknown, is a vascular disease and whether the increased thromboembolism and stroke risk in AF is directly related to vascular and atrial endothelial dysfunction. In addition to shared systemic risk factors associated with inflammation and oxidative stress, AF and endothelial dysfunction share other potential links including: myocardial ischemia, common gene variants, nonphysiologic vascular shear stress, and elevated novel biomarkers such as fibroblast growth factor. Furthermore, endothelial dysfunction has been independently associated with increased venous and arterial thrombosis and adverse cerebrovascular events in similar patient populations and the risk of stroke in AF is not necessarily temporally associated with periods of AF. A subanalysis of ASSERT (the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial), have shown that the majority of strokes were not preceded by AF, suggesting an epidemiologic association between AF and stroke that is independent of the rhythm—perhaps also indicating underlying vascular disease.

Results of this study may have important clinical ramifications. While preventive AF and CAD lifestyle measures and risk factors control (such as weight loss, smoking cessation/abstinence, avoidance of excessive alcohol and caffeine intake, and following a heart-healthy diet) should be advised in all patients at risk, the concomitant presence of CED among patients with chest pain but no obstructive epicardial CAD may help identify a subset of young patients who are at highest risk of developing AF and who might most benefit from not only CED-directed medical therapy (such as statin and L-arginine therapy) but also from closer clinical follow-up and potentially long-term rhythm monitoring with wearable devices for AF development. Moreover, while metabolic syndrome has been previously associated with incident AF, this is the first study to link coronary endothelial dysfunction (a potential by-product of the metabolic syndrome risk factors including obesity, elevated triglycerides, decreased high-density lipoprotein, hypertension, and impaired glucose metabolism) to AF development. Interestingly, rosuvastatin therapy significantly reduced incident AF risk, as compared with placebo, in an exploratory analysis of the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin Trial) trial, and statin therapy was associated with a reduced risk of AF recurrence and burden following dual-chamber pacemaker implantation in patients with paroxysmal AF. Importantly, the potential benefit of upstream statins in patients with CED/earliest form of CAD, has not been addressed by the 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society AF guidelines or by the 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society focused update of those guidelines. The 2014 guidelines...
only recommend upstream statins for primary AF prevention post coronary bypass surgery (Class IIb) and reports no benefit of statins in patients without cardiovascular diseases (Class III). This is not surprising because this high-risk patient population with CED has never been extensively studied before. Future, large-scale, high-quality randomized clinical trials on primary AF preventive, pharmacological, and nonpharmacological strategies in this high-risk group of patients with CED is certainly warranted.

Finally, the results of this study raise intriguing questions as to whether AF is in part a vascular disease or a simple complication of a syndrome that manifests as early CED and late AF development along with CAD progression in this relatively young cohort of patients.

LIMITATIONS

This study has some limitations worth noting. First, only patients with chest pain who were referred for a clinically indicated coronary angiography and endothelial function testing were included in this study, and therefore selection bias could not have been avoided and might affect generalizability of our results. While results of this study apply to a relatively young patient population with signs and/or symptoms of ischemia and no obstructive CAD on clinically indicated coronary angiogram, generalizability of results to other patient populations may be limited and need further evaluation. Second, this is a retrospective study in a relatively small but well-defined sample with a long follow-up period. This study design might have resulted in some inherent recall bias, and therefore confirmation of our results by larger prospective investigations is warranted. Importantly, the current study is not designed to show a causal effect relationship between CED and AF taking into account combined positive effects of multifactorial risk factor reduction programs, including sustained weight loss and increased physical activity, which have been shown to both reduce AF recurrence and improve CED. Future prospective studies specifically designed to actively monitor and evaluate time-dependent combined risk factor control effect on AF incidence and/or recurrence and endothelial function status may demonstrate whether vascular endothelial dysfunction is causal of AF development or a marker of higher-risk population for developing AF. Third, established strong clinical risk factors for AF—except for CED and increased LAVI—did not show independent prediction of AF in this study. While this might be regarded as a limitation in itself, it strengthens the role of CED as a stronger, more important predictor of incident AF in this younger patient population. Fourth, AF may be silent and asymptomatic in many patients. Thus, in the absence of continuous heart rhythm monitoring, silent AF might have been missed in this patient population. Future long-term validation studies with new wearable heart rhythm monitoring devices could overcome this limitation.

CONCLUSIONS

This study demonstrated that normal coronary endothelial function, in symptomatic and relatively young patients without obstructive CAD, is associated with a significantly decreased absolute and relative risk of developing AF over 10.5 years of follow-up. Moreover, CED and increased LAVI were independent predictors of AF development, suggestive of a potential mechanistic role of vascular dysfunction itself in AF development.

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