Calcified Pipes
You Better Call the Electrician Too

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Despite the high prevalence and morbidity of atrial fibrillation (AF), the mechanisms of the disease are multifactorial and remain poorly understood. The initiation of AF requires a trigger, and abnormal atrial substrate is necessary to sustain the arrhythmia. Although there are genetic predispositions to AF,1 more traditional cardiovascular risk factors such as age, diabetes mellitus, hypertension, obesity, and metabolic syndrome are also associated with AF.2 Among AF patients, weight loss has been associated with lower AF burden and improved maintenance of sinus rhythm.3 Reducing weight and blood pressure along with better glycemic and lipid management have been shown to improve arrhythmia-free survival after AF ablation.4

Nearly two thirds of patients with AF have concomitant coronary heart disease,5 which can contribute to the initiation and maintenance of AF through myocardial fibrosis, atrial dilatation, inflammation, and ischemia.6–9 Animal models of atrial ischemia have shown increased spontaneous atrial ectopic activity and slowing of atrial conduction, leading to initiation and sustained re-entry of AF. Coronary artery calcium (CAC) scores can identify vascular aging and patients at risk for acute coronary events.10 The CAC score was independently associated with the development of AF in the Multi-Ethnic Study of Atherosclerosis (MESA) study.11 In the MESA study, patients with higher CAC scores at baseline had a greater incidence of AF in follow-up. Relative to patients with a baseline CAC score of 0, the hazard ratios (HRs) for developing AF were 1.4 (95% confidence interval [CI], 1.0–2.0), 1.6 (95% CI, 1.1–2.4), and 2.1 (95% CI, 1.4–2.9) for CAC scores of 1 to 100, 101 to 300, and >300, respectively. In addition, CAC score improved the discrimination of AF risk scores.11 Questions remained about whether cardiac computed tomography and CAC could identify actionable risk.

In this issue of Circulation: Cardiovascular Imaging, O’Neal et al12 make an important contribution and describe the association between CAC progression and AF in MESA, which recruited patients without diagnosed cardiovascular disease from 6 geographic locations. There were 5612 patients with 2 CAC scores separated by a mean of 2.4±0.8 years. Among the study population, 203 (3.6%) patients developed incident AF over a median follow-up of 5.6 years. Patients with an increase in their CAC score from the first to the second scan were labeled as having CAC progression.

The cumulative incidence of AF was >3-fold higher among patients with CAC progression relative to those without CAC progression (10 versus 3 per 1000 patient-years; log-rank, P<0.0001). After multivariable adjustment including baseline CAC score, patients with CAC progression continued to have higher incidence of AF than patients without CAC progression (HR, 1.6; 95% CI, 1.1–2.2), and patients with a greater increase in CAC score had a higher incidence of AF in a dose-dependent fashion. To place these risks in perspective, the incidence of AF in those with a CAC increase of >300 (45.8 per 1000 patient-years) exceeded the incidence of AF among patients aged 80 to 84 years in the United States (38.3 per 1000 patient-years).13 CAC progression was also associated with a greater risk of new-onset AF in those <61 years (HR, 3.5; 95% CI, 1.3–9.7) than in patients ≥61 years (HR, 1.4; 95% CI, 1.0–2.0; interaction P=0.037). Although CAC progression was associated with an increased risk of AF, the risk of developing AF was similar for those with unchanged versus decreased CAC scores (HR, 1.0; 95% CI, 0.5–2.2).

How should clinicians interpret these results? Can CAC scores or serial CAC measurements identify actionable risk? Why is CAC progression associated with an increased risk of developing AF? Should the CAC score be used as a screening tool for risk prediction of AF in clinical practice? Despite statistically significant associations between (1) CAC score and AF and (2) CAC progression and AF, for the following reasons computed tomographic scans are not ready for widespread clinical use to determine CAC progression as a means of classifying the risk of incident AF.

First, there were several limitations to the study presented by O’Neal et al.12 In their study, AF was identified through phone calls to patients every 9 to 12 months or by inpatient Medicare claims data (without outpatient claims). This methodology likely resulted in limited ascertainment/diagnosis of AF; particularly in paroxysmal, recent onset, or minimally symptomatic AF. If CAC progression affects the severity of AF, patients with more severe CAC might have been more symptomatic and therefore more likely to have reported a given episode of AF. Also, the use of Medicare claims data may have affected the comparison between older and younger patients, as patients aged >65 years had greater AF ascertainment. Furthermore, it is possible that younger patients were
more active and symptomatic from vascular disease and AF, and this may have affected the diagnosis and recall of AF, partially explaining the greater association between CAC progression and AF in patients aged <61 years. Finally, although the authors accounted for many patient characteristics, they were unable to adjust for several important risk factors known to influence the risk of AF, including left atrial size, heart failure, and sleep apnea.

It is important to better understand why CAC progression was associated with AF. A previous study demonstrated an association between increased CAC score and larger left atrial and pulmonary vein size, but it remains unknown whether the processes common to CAC resulted in left atrial dilation or whether the AF resulted in the dilation. Given the association between CAC scores and coronary events, a more direct potential mechanism may be atrial ischemia. An association between sinus node ischemia and AF and AF has previously been established. A study by Simno et al evaluated induction and maintenance of AF after ligation of the right intermediate atrial artery in dogs. Repeat burst pacing was used to induce AF both at baseline and at serial intervals after ligation. The duration of induced AF and the AF burden were significantly greater after the establishment of coronary ischemia. Moreover, conduction was significantly slower in the atrial tissue supplied by the right intermediate atrial artery. These results raised the hypothesis that ischemia prolonged atrial myocardial conduction time, thus facilitating re-entry and fibrillation.

Human studies have examined the association between atrial ischemia and postoperative AF after coronary artery bypass grafting. Patients who developed AF after coronary artery bypass grafting had more obstructive disease in the sinoatrial artery (34% versus 21%; P=0.04) on preoperative angiograms when compared with those who did not develop postoperative AF. Another study of AF after myocardial infarction identified that coronary artery disease of the right and left atrial arterial branches was independently associated with postoperative AF. Both of these studies were limited by the complicated hemodynamic and inflammatory changes that accompany coronary artery bypass grafting and myocardial infarction, so they may not apply to ambulatory outpatient populations like the MESA cohort.

Before recommending a screening test for patients, it is important to understand the predictive value of that test, as well as the ability to intervene on the test results to prevent disease onset or progression. The Framingham Heart Study and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) are 2 risk scores that were developed to predict incident AF, and the addition of CAC scores to these risk models had a statistically significant effect on the C-statistic from 0.771 to 0.784 (P=0.005) and from 0.789 to 0.798 (P=0.003), respectively. Although including CAC scores statistically improved AF risk discrimination, it remains unknown whether CAC can meaningfully reclassify patients based on their risk of AF.

Even if CAC scores are valuable in risk prediction, there is not yet a target for prevention of AF in patients with elevated CAC scores. Put another way, what should clinicians do if they find elevated CAC scores or CAC progression? Should these patients get screened with prolonged outpatient rhythm monitoring? Should they receive additional medical therapy, such as a statin? Risk factor modification is emphasized in patients at risk for AF, but there are no proven therapies for the primary prevention of AF. Even if we could improve our prediction of AF, we have no effective therapies to alter disease progression. Unfortunately, the data from REMA were not encouraging for targeting primary prevention of AF because patients with CAC regression (change in CAC<0) had similar rates of AF as those with no progression (change in CAC=0). Furthermore, if the mechanisms of the association between CAC score and AF were vascular aging and coronary artery disease, one would expect statin therapy to prevent AF. There has been data to suggest that the use of statins was associated with a lower incidence of AF at the time of myocardial infarction. However, the Statin Therapy for secondary Prevention of Atrial Fibrillation (SToP AF) trial found no reduction in AF recurrence with atorvastatin. It is important to note that this was a small trial of 64 patients.

Given our rudimentary understanding and predictive abilities of incident AF, the findings from the MESA cohort are important. The apparent association and dose-dependent relationship between CAC and AF should inform future studies to improve our understanding of the mechanisms behind AF. Although the clinical use of CAC scores for the prediction of AF is not ready for prime time, it should be helpful in developing studies to test strategies to prevent AF in patients with vascular disease. Coronary artery calcium scoring with computed tomography provides a perspective on coronary vasculature disease, and in this interesting study, the extent of calcification and progression is associated with incident AF. The mechanisms behind this association require further clarification, but this new information offers the potential to explore strategies to mitigate the risk of AF.

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References
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