Predicting atrial fibrillation: can we shape the future?

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This editorial refers to ‘Prognostic impact of supraventricular premature complexes in community-based health check-ups: Rhe Ibaraki Prefectural Health Study’, by N. Murakoshi et al., on page 170

Atrial fibrillation (AF) is a major risk factor for cardio-embolic stroke, heart failure, and mortality including sudden death; anticoagulation in high-risk patients has been shown to lower the risk of stroke significantly. However, the arrhythmia may remain undetected in many patients and an embolic stroke or heart failure can be the initial presentation. The early recognition of AF is therefore of great importance. In the Framingham Heart Study, older age, male sex, hypertension, cardiac murmurs, and heart failure were predictors of AF. Premature atrial contractions (PACs) and repetitive atrial ectopic activity are frequently observed during ambulatory monitoring. In epidemiological studies, these have been associated with an increased risk for the development of AF, stroke, and mortality during long-term follow-up.

Murakoshi et al. have now contributed to the discussion of PACs and the risk for AF with data from the Ibraki Perfcutre Health Study, a government-sponsored community-based prospective cohort study from the Ibraki Prefecture in Japan. These authors examined the prognostic significance of the presence of PACs on a 12-lead electrocardiogram (ECG) recorded for ~15 s during a routine health check. Of a total of 192 125 participants in the study, a cohort of 63 197 individuals was chosen for analysis based on exclusions for prevalent AF, known heart disease, and inadequacy of follow-up. These individuals had at least one 12-lead ECG recorded over a 3-year period between 1993 and 1995 and were followed with annual ECGs to a mean follow-up of 14 years. Mean age of the cohort at entry was 59 years and 68% were female. PACs were documented in 6% of patients at baseline. There were significant differences in baseline characteristics between those with and without PACs. Importantly, patients with PACs were older, and more likely to be hypertensive and to have sustained a previous stroke. The incidence of AF in the cohort was 1 per 1000 patient-years. The primary endpoints of deaths from stroke, cardiovascular causes, and all causes were significantly higher in those with PACs. When adjusted for confounding risks in a propensity score-matched analysis, the group with the PACs had a higher stroke death in women and greater cardiovascular mortality in both men and women. In multivariate analysis, the presence of PACs was associated with a significantly higher risk of subsequent AF [hazard ratio (HR) 4.8 for men and 3.8 for women]. The study is commendable for its large population-based analysis and lengthy longitudinal follow-up. Limitations include the uncertain reliability of self-reported medical conditions and the absence of thyroid status in the database.

As in all observational studies, the pathophysiological relationship between cause and effect cannot be established from these data. The role of atrial ectopic activity in the initiation of AF is well established. Haissaguerre et al. in their seminal paper linked the onset of AF to ectopic activation of the atria by rapid spontaneous discharges from sleeves of muscle surrounding the pulmonary veins in the region of the veno-atrial junction. Indeed, muscle sleeves in the great thoracic veins including the superior vena cava, inferior vena cava, coronary sinus, and other sites have been implicated in the triggering of AF. In some patients, PACs may be a marker for foci that are or will later become capable of firing rapidly to initiate AF. Rapid and repetitive stimulation of the atrial muscle is known to alter its electrophysiological properties by shortening atrial refractoriness, and impairing rate adaptability of the atrial action potential, conditions conducive to the development and maintenance of AF. Down-regulation of potassium channels and alteration of calcium channels brought about by rapid atrial contractions further encourage the sustenance of fibrillation. Alternatively PACs may be a marker of developing atrial electrophysiological changes that promote AF, such as interstitial fibrosis and abnormal intracellular calcium handling. Fibrosis that diminishes coupling of atrial cells, including those around pulmonary veins, may promote automaticity and re-entry, causing PACs and setting the stage for AF (Figure 1).

It seems likely that the association of PACs with cardiovascular mortality is mediated through the association with AF. However, PACs may be a marker for other underlying heart diseases, virtually all of which are also associated with AF. Thus, the exact role of...
PACs in the genesis of AF and its deleterious consequences remains unclear.

What are the clinical implications? PACs sufficiently frequent to be detected in a 15 s ECG are not common; they occurred in 6% of middle-aged people in the present study. Although the lengthy time course from PAC detection to new AF together with the low incident rate for AF tempers any enthusiasm, from a clinical point of view, to target isolated PACs for therapy, detection of PACs provides an opportunity for evaluation of any underlying heart disease and to reassess and address risk factors for heart disease, including hypertension, diabetes, sleep apnoea, and obesity in an individual patient. Atrial ectopics and repetitive supraventricular activity may be the trigger for AF, but the myocardial phenotype and conventional AF risk factors, as in the CHADS-VASC scoring system, seem likely to be just as, if not more, important in determining outcomes related to AF.

Is additional monitoring for AF warranted in patients with PACs? In recent years, there has been much attention focused on the detection of silent AF. Prolonged rhythm monitoring with implanted loop recorders or 30-day event monitors detects undiagnosed AF in 10% of patients presenting with stroke initially categorized as cryptogenic. Some patients with PACs sufficiently frequent to be detected on a 15 s ECG will be found to have AF on further evaluation (patients with a history of AF at their initial evaluation were excluded from this study). Monitoring to detect asymptomatic AF seems reasonable, particularly in patients with additional risk factors for AF, although the therapeutic implications, particularly for short episodes of arrhythmia, may not be clear.

In the ASSERT study, AF detected by an implanted device and lasting for >6 min was associated with a 2.5-fold increase in stroke risk in hypertensive patients 65 years or older. However, it is unclear whether anticoagulation reduces this risk. A recent study designed to address the question of anticoagulation, based on device-detected AF through remote monitoring vs. a strategy of conventional office visits, was prematurely discontinued for projected futility in meeting endpoints. The AF burden beyond which benefits of anticoagulation outweigh bleeding risks remains obscure. Furthermore, it is not always possible to distinguish rapid atrial tachycardias from AF and atrial flutter. Sustained atrial flutter is felt to carry a similar risk to AF, probably because these rhythms frequently transition from one to the other. Whether a short run of atrial tachycardia carries the same risk is unknown. Current guidelines require a clear diagnosis of AF before commencing anticoagulation for stroke prevention.

Predictions are meaningful if one has the power to shape the future. Whether additional evaluation and therapy based on the considerations discussed above translates into improved outcomes in patients found to have frequent atrial ectopic activity is unknown. Nevertheless, epidemiological studies such as the study by Murakoshi et al., linking PACs to AF and worse long-term outcomes, support an initial evaluation with appropriate follow-up and interventions for modifiable risk factors in patients with this traditionally benign arrhythmia.

**Conflict of interest:** R.M.J. has received modest honoraria for educational lectures from St. Jude Medical, Inc., Medtronic, Inc., and Boston Scientific, Inc. W.G.S. is the holder of a patent for an intramural ablation needle consigned to the Brigham and Women’s Hospital, Boston, MA, USA.

**References**


