Are Premature Ventricular Complexes a New Risk Factor for Stroke?

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Premature ventricular complexes (PVCs) are easily recognized abnormalities on a 12-lead electrocardiogram or rhythm strip. During medical school and residency, it was a surprise and disappointment to learn that such an obvious abnormality was dismissed as a benign rhythm disturbance and was not indicative of serious disease.

In this issue of Stroke, Agarwal and colleagues1 report that PVCs seen on a single baseline 2-minute rhythm strip were associated with an increased risk of incident stroke. These findings are reported in a large cohort (>14,000) of middle-aged (45 to 64 years) American men and women followed for 15 to 17 years in the Atherosclerosis Risk in Communities (ARIC) study. In the 6.1% with PVCs, the adjusted hazard ratio for stroke was 1.4 (95% CI, 1.08 to 1.80) and the adjusted hazard ratio for a combined end point of stroke and death was 1.62 (95% CI, 1.44 to 1.83). Increased stroke risk was observed irrespective of gender and race. There was a marked increase in stroke risk in those participants with ≥4 PVCs in a 2-minute recording.

PVCs are suggested to be a "culprit arrhythmia" in the development of cardiomyopathy and are reported to predict a heightened risk of new-onset atrial fibrillation (AF) and cardiovascular death.4 An association of PVCs with stroke risk has been reported in an earlier smaller study cited by the ARIC investigators. In the large ARIC study, PVCs were associated with new-onset AF and death.

Agarwal and colleagues1 identified apparent effect modification on stroke risk between established stroke risk factors and the presence of PVCs at baseline. The investigators reported a hazard ratio of 2.09 (95% CI, 1.21 to 3.58) with PVCs in a subgroup of participants without 4 traditional stroke risk factors: diabetes, hypertension, smoking history, and coronary heart disease. In those without either hypertension or diabetes, PVCs were independently associated with a stroke hazard ratio of 1.72. Surprisingly, when participants had hypertension or diabetes at baseline, the presence of PVCs did not increase the hazard ratio for stroke compared with participants without PVCs.

The ARIC study satisfies many quality criteria associated with rigorously conducted observational studies.6 It is a population-based cohort study, the most robust of epidemiological investigations, because the risk factor is established before the end point is ascertained. Interpretation of baseline electrocardiograms and rhythm strips was blinded to the study hypothesis and outcomes and several sources of outcome data were reviewed for comprehensive ascertainment of stroke and death. The investigators acknowledge that the 2-minute rhythm strip at baseline is likely to underestimate PVC prevalence. Results may have been biased by the nonparticipation in clinical assessments among community members approached by the ARIC researchers (estimated to be at least one third) and attrition of respondents for follow-up assessment (although this was only 10%). There is evidence of a "healthy volunteer effect," although this appears limited to 1 subgroup.

Apart from age, there are 4 major recognized risk factors for stroke: AF, coronary heart disease, hypertension, and congestive heart failure.7 In the ARIC study, those identified with AF at baseline were excluded. AF is often difficult to identify and therefore it is likely that some cases of AF at baseline were undetected. The study did not determine the baseline prevalence of heart failure or its contribution to observed stroke risk. At baseline, a proportion of included patients with and without PVCs were on digoxin, angiotensin-converting enzyme inhibitors, and antiarrhythmic agents, which may be telltale of baseline heart failure or cardiac arrhythmias, including AF. It is uncertain whether heart failure and undetected AF at baseline may have confounded the association between PVCs and incident stroke risk at follow-up.

Continuous variables such as blood pressure and blood sugar levels are often categorized using clinically defensible thresholds such as 140/90 mm Hg for hypertension. The potential disadvantages of this approach need to be acknowledged. Dichotomization of continuous variables results in a loss of information, reduced power for statistical analysis, and may introduce bias.8,9 Risk is a continuum that extends below our thresholds for clinical diagnosis and treatment. For example, cardiovascular risk doubles for every 20/10-mm Hg increase >115/75 mm Hg.10 Morbidity is associated with impaired glucose tolerance below the thresholds for diagnosing diabetes. In ARIC, PVCs were more common in those with hypertension and diabetes, but PVCs had no apparent effect on stroke risk in the presence of these risk factors.
Instead, PVCs were associated with a higher stroke risk in those without hypertension and diabetes. It is possible that PVCs identified those at risk of stroke with blood pressure and impaired glucose tolerance on a continuum of risk below conventional diagnostic thresholds for hypertension and diabetes. The choice of cutoff points may have influenced the observed point estimates. Analyzing the effect of continuous variables instead of dichotomizing the values may be appropriate. Alternatively, sensitivity analyses could assess whether observed effects hold for different cut points when categorizing continuous variables.

The ARIC cohort is 1 of several population-based cohort studies that have included baseline electrocardiogram assessments. A quick and by no means systematic MEDLINE inquiry revealed at least 5 cohort studies. The Honolulu Heart Program, The Framingham Heart Study, and the Copenhagen City Heart Study are notable examples. None are known to have used rhythm strips to identify PVCs. At least 3 studies examined the effect of electrocardiogram findings on stroke risk, although none have reported stroke risk associated with PVCs. One found no effect of “premature beats” on stroke risk but did not specify whether the premature beats were ventricular or supraventricular. A pressing question is whether these or other population-based studies have incidentally collected sufficient data on PVCs to replicate the ARIC findings.

The intriguing results reported by Agarwal et al compel us to understand how PVCs increase or indicate stroke risk. PVCs may be a marker of underlying heart disease, which increases stroke risk. In ARIC, left ventricular hypertrophy as assessed by Cornell voltage criteria did not modify stroke risk and unfortunately, we have no echocardiography data on underlying structural heart disease. It is possible that PVCs are a “culprit arrhythmia” or an early sign of accumulating end organ damage as a result of identified or unidentified risk factors shared with stroke.

The ARIC investigators suggest that PVCs may be intimately related to the development of new-onset AF, a major risk factor for stroke. During follow-up, new-onset AF was identified in 15% of people with PVCs, accounting for 34% of stroke cases in this group. AF diagnosis can be elusive and the reported AF prevalence is likely to be an underestimate. Accordingly, AF may have accounted for an even higher proportion of the observed strokes. An association between PVCs and AF may explain the observed preponderance of “embolic stroke of noncardotic origin” in those with PVCs.

A 2-minute rhythm strip is not a routine test but it is simple and feasible in a wide range of clinical settings. As the authors discuss, PVCs detected on a rhythm strip appear to be a newly identified marker, if not risk factor, for stroke. Most importantly, PVCs may identify stroke risk in middle-aged men and women without hypertension, diabetes, and other established risk factors. If the ARIC findings are replicated with further research, a rhythm strip may be a new tool in identifying those most likely to benefit from close surveillance and further investigation as well as lifestyle and pharmacological interventions.

In conclusion, PVCs may be a new and important marker of stroke risk. This easily recognized rhythm strip abnormality may help identify those likely to benefit from stroke prevention, especially those who have flown under our radar.

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Disclosures

None.

References


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