Journal of the American Heart Association

EDITORIAL

Premature Ventricular Contractions and Atrial Fibrillation: The Reunion of Distant Relatives?

Anne-Sophie Lacharite-Roberge, MD; Kurt S. Hoffmayer, MD

The incidence and prevalence of atrial fibrillation (AF) worldwide continues to rise with aging of the population. Clinicians have been focused on prevention and identifying risk factors to better serve millions of patients affected by AF each year.[1] Another common arrhythmia sparking interest over the past decade is premature ventricular complexes (PVCs). It is now well established that a high burden of PVCs is linked to an increased risk of cardiomyopathy and that suppression of PVCs leads to improvement in left ventricular function.[2–4] Given ongoing advancements in digital health, the diagnosis of AF and the quantification of PVCs using continuous monitoring has been improved and simplified. Additionally, our heightened ability to treat both AF and PVCs safely using advanced three-dimensional mapping technologies and radiofrequency ablation has reshaped the field of electrophysiology and improved outcomes for patients with all arrhythmias. Electrophysiologists treat and view AF and PVCs as distinct entities, but could there be a hidden and still poorly understood relationship between these common diagnoses?

See Article by Lee et al.

A recent observational analysis by Kim et al published in 2021 was the first to suggest that the risk of new-onset AF was higher in patients with PVCs.[5] In this issue of the *Journal of the American Heart Association* (*JAHA*), Lee and co-authors describe a new association specifically between PVC burden and new-onset AF, irrespective of sex and underlying diseases, using a single-center, retrospective, large population-based cohort study.[6] Their work showed that a moderate to high PVC burden may be an independent risk factor for AF. A large number of patients were screened (n=25 398), with 16 030 making it to their propensity-scored matching analysis. Patients were followed for a median follow-up of 873 days. Overall, their analyses revealed that participants with moderate to high PVC burden were at higher risk of developing new AF than the low burden PVC group (5.3% versus 2.4%, $P<0.001$).

Although the authors should be commended for their work, there are some important limitations and with most studies showing intriguing results, some important hypothesis-generating questions.

The authors chose to define their PVC burden as low PVC burden as <1000/d and moderate-to-high PVC burden as >1000/d. Quantification of PVCs was evaluated with 24-hour Holter 3-channel ECG monitoring, and the indications for monitoring were report of palpitations, a clinical diagnosis of any arrhythmia, or transient loss of consciousness. First, previous literature has shown notable daily variation in PVC burden and demonstrated that up to 6 days of continuous monitoring is more accurate than the traditional

Key Words: Editorials ■ atrial fibrillation ■ catheter ablation ■ premature ventricular contraction ■ screening

Correspondence to: Kurt S. Hoffmayer, MD, University of California San Diego, 9452 Medical Center Dr, MC 7411 La Jolla, CA 92037. Email: khoffmayer@health.ucsd.edu

For Disclosures, see page 2.

JAHA is available at: www.ahajournals.org/journal/jaha

24-hour Holter monitor.[7] Additionally, continuous monitoring allows clinicians to establish the percentage of PVCs over the total sinus beats during a given timeline. Second, by dichotomizing the PVC groups, the authors categorize the moderate and high group as >1000, which correlates with ≥1% burden. In fact, the overall mean burden was 4.6% (highest seen was 11.2%) in the moderate/high burden group and almost zero PVCs in the low burden group with a range of 1 to 30 PVCs seen and a mean burden of 0.01%. This would suggest that the low group was an "extremely low-almost zero" PVCs group and the moderate to high group was a more "intermediate" group as most "high" PVCs are usually defined >15 000 to 20 000 in the literature.[8] This level of PVC burden would be much lower than the perceived risk of developing cardiomyopathy (24+%) and most falling in the <10% burden, which rarely leads to cardiomyopathy.[3,9] This would suggest that the number of PVCs needed to increase the risk of AF is a more intermediate range and needs to be prospectively validated in a new cohort. Correspondingly, alternative explanations need to be entertained regarding the potential mechanisms by which PVCs increase the risk of AF. As described in previous literature, one would not expect many patients with this PVC burden range to develop a cardiomyopathy.[9,10] Additionally, more research into the pro-arrhythmogenic retrograde activation of the atria, a phenomenon rarely discussed in electrophysiology articles, as well as confounding genetic influences leading to increased risk in both arrhythmias, is needed to better understand the mechanism between PVCs and AF.[11–13]

Perhaps more technical and hypothetical follow-up questions to the study by Lee et al are regarding specific PVC characteristics. Previous research has focused on PVC characteristics to help us differentiate high-risk features that pose a more malignant risk for cardiomyopathy including origin (epicardial), QRS width, and coupling interval.[14,15] Is there an association between a PVC anatomical location and new-onset AF? Did participants with new AF and moderate to high burden of PVCs have monomorphic, or polymorphic PVCs? May there be a similar relationship with AF incidence? Although PVC anatomical location can be a point of debate among electrophysiologists, establishing a relationship between the risk of AF and PVC anatomical location would further risk stratify patients and may support screening decisions.

The authors looked at a cohort in the highest PVC burden group (defined as >10 000 a day) that received successful catheter ablation, compared them with the index study cohort with the highest PVC burden, and found a trend in lower development of AF (not statistically significant). This raises the following important key question: Could PVCs be a modifiable risk factor for AF? The authors speculate that PVC ablation may be a possible adjuvant strategy for AF ablation, which could eliminate all potential AF triggers. Without a doubt, this statement begs further data and analysis. Yet, it may influence our use of continuous monitoring post AF ablation to screen for PVCs and may represent one missing piece of the AF ablation recurrence puzzle.

The authors also briefly discuss the risk of ischemic stroke associated with PVCs. In a previous study from Liao et al published in 2012, the authors found that among normotensive patients, the diagnosis of PVCs was associated with a 2-fold increase in the rate of incident ischemic stroke.[16] If PVCs are associated with new-onset AF, is the risk of stroke even greater when patients have both arrhythmias? Once more, although this question requires additional data, the answer would be beneficial to assist clinicians in patient counseling when discussing anticoagulation.

Current society guidelines vary in their recommendations regarding screening of AF. The American Heart Association/American College of Cardiology have not specifically addressed screening yet, and the United States Preventive Services Task Force stated in 2022 that "current evidence is insufficient to assess the balance of benefits and harms of screening for atrial fibrillation with ECG".[17,18] Clinicians use risk factor profile, in addition to symptom report, to risk stratify patients and determine appropriateness of continuous monitoring. The presence of PVCs is not an established risk factor for AF, but given these new emerging data, we may refine our initial screening strategy and pay closer attention to screening for AF in our patients with higher burden PVC. In this study, Lee et al inspire many hypotheses and raise several key questions in our quest to better understand and better serve our patients with PVCs and the associated risk of new onset AF.

ARTICLE INFORMATION

Affiliation

Division of Cardiology, Department of Medicine, Section of Cardiac Electrophysiology, University of California San Diego, San Diego, CA.

Disclosures

Kurt S. Hoffmayer completed grant support from the National Institutes of Health (F32 HL10472702 and LRP) and reports consulting for Samsung Electronics, Inc., Arga Medtech Inc, and Vektor Medical, Inc. Anne-Sophie Lacharite-Roberge has no disclosures to report.

REFERENCES

1. Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights. *Circ Res*. 2020;127:4–20. doi: 10.1161/CIRCRESAHA.120.316340
2. Duffee DF, Shen WK, Smith HC. Suppression of frequent premature ventricular contractions and improvement of left ventricular function in patients with presumed idiopathic dilated cardiomyopathy. *Mayo Clin Proc*. 1998;73:430–433. doi: 10.1016/S0025-6196(11)63724-5
3. Baman TS, Lange DC, Ilg KJ, Gupta SK, Liu TY, Alguire C, Armstrong W, Good E, Chugh A, Jongnarangsin K, et al. Relationship between

burden of premature ventricular complexes and left ventricular function. *Heart Rhythm*. 2010;7:865–869. doi: 10.1016/j.hrthm.2010.03.036
4. Albakri A. Premature ventricular complexes (PVC)-induced cardiomyopathy: a review and meta-analysis of pathophysiology, diagnosis and clinical management. *Clin Med Invest*. 2019;4:2–11. doi: 10.15761/CMI.1000192
5. Kim YG, Han KD, Choi JI, Choi YY, Choi HY, Shim J, Kim YH. Premature ventricular contraction is associated with increased risk of atrial fibrillation: a nationwide population-based study. *Sci Rep*. 2021;11:1601. doi: 10.1038/s41598-021-81229-0
6. Lee PT, Huang MH, Huang TC, Hsu C, Lin SH, Liu PY. High burden of premature ventricular complex increases the risk of new-onset atrial fibrillation. *J Am Heart Assoc*. 2023;11:e027674. doi: 10.1161/JAHA.122.027674
7. Loring Z, Hanna P, Pellegrini CN. Longer ambulatory ECG monitoring increases identification of clinically significant ectopy. *Pacing Clin Electrophysiol*. 2016;39:592–597. doi: 10.1111/pace.12852
8. Hoffmayer KS. Empiric catheter ablation of premature ventricular contractions when there is a >20% burden in an asymptomatic patient with normal left ventricular size and function-an argument for a conservative, do-less approach. *Heart Rhythm O2*. 2021;2:210–214. doi: 10.1016/j.hroo.2021.02.003
9. Bogun F, Crawford T, Reich S, Koelling TM, Armstrong W, Good E, Jongnarangsin K, Marine JE, Chugh A, Pelosi F, et al. Radiofrequency ablation of frequent, idiopathic premature ventricular complexes: comparison with a control group without intervention. *Heart Rhythm*. 2007;4:863–867.
10. Lee AKY, Andrade J, Hawkins NM, Alexander G, Bennett MT, Chakrabarti S, Laksman ZW, Krahn A, Yeung-Lai-Wah JA, Deyell MW. Outcomes of untreated frequent premature ventricular complexes with normal left ventricular function. *Heart*. 2019;105:1408–1413. doi: 10.1136/heartjnl-2019-314922
11. Peinado R, Merino JL, Gnoatto M, Arias MA. Atrial fibrillation triggered by postinfarction ventricular premature beats in a patient with Wolff-Parkinson-White syndrome. *Europace*. 2005;7:221–224. doi: 10.1016/j.eupc.2004.12.003
12. Bocchese M, Mangrolia H, Basil A, Gangireddy C, Cronin E, Yesenosky GA, Greenberg RM, Cooper JM, Whitman IR. Atrial fibrillation triggered by premature ventricular complexes: an under-recognized trigger. *JACC Case Rep*. 2020;2:2244–2248. doi: 10.1016/j.jaccas.2020.09.048
13. Schwieler JH, Zlochiver S, Pandit SV, Berenfeld O, Jalife J, Bergfeldt L. Reentry in an accessory atrioventricular pathway as a trigger for atrial fibrillation initiation in manifest Wolff-Parkinson-White syndrome: a matter of reflection? *Heart Rhythm*. 2008;5:1238–1247. doi: 10.1016/j.hrthm.2008.05.028
14. Marcus GM. Evaluation and management of premature ventricular complexes. *Circulation*. 2020;141:1404–1418. doi: 10.1161/CIRCULATIONAHA.119.042434
15. Latchamsetty R, Bogun F. Premature ventricular complexes and premature ventricular complex induced cardiomyopathy. *Curr Probl Cardiol*. 2015;40:379–422. doi: 10.1016/j.cpcardiol.2015.03.002
16. Ofoma U, He F, Shaffer ML, Naccarelli GV, Liao D. Premature cardiac contractions and risk of incident ischemic stroke. *J Am Heart Assoc*. 2012;1:e002519. doi: 10.1161/JAHA.112.002519
17. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–e151. doi: 10.1161/CIR.0000000000000665
18. US Preventive Services Task Force; Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, Doubeni CA, Epling JW Jr, Kemper AR, et al. Screening for atrial fibrillation with electrocardiography: US preventive services task force recommendation statement. *JAMA*. 2018;320:478–484. doi: 10.1001/jama.2018.10321