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EDITORIAL COMMENT

Expiration-Triggered Sinus Arrhythmia

Have We Been Waiting With Bated Breath?*

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Heart rate variability is a measure of cardiac vagal modulation and provides prognostic information and risk stratification in patients who suffered from acute myocardial infarction (AMI). Observations by Kleiger et al. (1) from almost 30 years ago demonstrated that a low standard deviation in the R-R intervals, the time elapsing between 2 consecutive R waves in the electrocardiogram (ECG), analyzed from 24-h electrocardiography conferred an increased risk of death after AMI. Subsequently, these findings were demonstrated in a number of different patient populations and in a multicenter prospective survey (2,3). Respiratory sinus arrhythmia (RSA) is a major determinant of heart rate variability and various techniques and parameters have been used for RSA quantification and risk stratification (4,5).

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In this issue of the *Journal*, Sinnecker et al. (6) make an important contribution to understanding how RSA may be used to risk stratify patients who suffered a myocardial infarction. They sought to improve the prognostic implications of RSA by measuring the amount of sinus arrhythmia with expiration, the phase of the respiratory cycle associated with vagal discharge. While the study was conducted in a relatively small number of patients and as such is exploratory and hypothesis-generating, it raises the possibility that this particular type of measurement used to evaluate sinus arrhythmia, which they termed expiration-triggered sinus arrhythmia (ETA), may be useful in risk stratification of post-MI patients.

The authors conducted a prospective study of 941 patients who suffered an AMI who underwent 30-min recordings of ECG and respiratory chest excursions within 2 weeks of their AMI. The primary outcome of the study was all-cause mortality within 5 years of the index AMI. All patients presented in sinus rhythm and did not meet criteria for implantable cardioverter-defibrillator implantation. ETA was defined as the R-R interval change associated with expiration, quantified using phase-rectified signal averaging. Raw ECG signals acquired over the 30-min recording were reviewed and processed by a technologist blinded to the clinical data, and a mathematical representation of the respiratory signal was constructed. Based on the respiratory signal data, the expiratory phase was defined as a time interval between 2 anchors, $\phi 1$ and $\phi 2$. The phase-rectified and averaged R-R intervals were collected and the average change in R-R intervals was quantified. For comparison in the study, RSA analysis assessed by 2 standard methods also was performed.

The primary endpoint, all-cause mortality, occurred in 72 patients (7.7%) after a follow-up of 5 years. In the patients who died during follow-up, ETA was significantly smaller compared to patients who survived: -0.35 (IQR: -1.33 to 0.30) ms versus 0.64 (-0.16 to 1.75) ms, meaning those patients with less ETA had worse outcomes. The area under the receiver-operating characteristic (ROC) curve for all-cause mortality prediction for ETA was 0.72 (95% confidence interval [CI]: 0.67 to 0.78). The performance of ETA was more predictive of all-cause mortality compared to standard methods of RSA assessment.

Another key finding was that in multivariable Cox analysis considering respiratory rate, left ventricular ejection fraction (LVEF), presence of diabetes, and Global Registry of Acute Coronary Events (GRACE) score, all of which were independent predictors of mortality, the association of ETA with mortality remained significant, with a hazard ratio of 0.95 (95% CI: 0.91 to 0.99). This was not the case for the standard

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measures of RSA. Using ETA as a dichotomous variable, in univariable Cox analysis, the hazard ratio for ETA ≤0.19 ms versus >0.19 ms was 5.12 (95% CI: 3.00 to 8.78). The 5-year mortality rates in patients with ETA ≤0.19 ms and ETA >0.19 were 15% and 3%, respectively. Addition of ETA to a model containing respiratory rate, LVEF, diabetes, and GRACE score increased the area under the ROC curve from 0.79 to 0.82 ($p = 0.02$).

Importantly, the authors analyzed the relationship of ETA with other criteria that could affect mortality. The majority (95.3%) of patients in this study received β-blockers, which affect sympathetic-vagal balance and reduce mortality after AMI. The 5-year all-cause mortality did not differ among those patients with and without β-blocker therapy, and in a multivariable Cox model that incorporated ETA and β-blocker use, β-blocker use was not a significant predictor of mortality, whereas ETA was a significant predictor. Thus, the authors argue that the predictive power of ETA is not a surrogate maker of effective β-blocker use. Similar analyses demonstrated that the localization of AMI (anterior vs. inferior) and the presence of heart failure (New York Heart Association functional class >II or Killip class >I) did not affect ETA as a predictor of mortality. Interestingly, respiratory rate marginally reduced the association of ETA with mortality (hazard ratio: 4.3; 95% CI: 2.5 to 7.4), although it did remain significant.

Sinnecker et al. (6) are to be congratulated on a novel and an important contribution to the existing body of data investigating the role of heart rate variability on risk prediction after AMI. The data presented in this cohort of >900 patients treated with percutaneous coronary intervention (93%) and optimal medical therapy (>90% treated with aspirin, clopidogrel, statins, β-blockers, and angiotensin-converting enzyme inhibitors) suggest that heart rate variability, as measured by ETA, is a robust prognostic factor in post-MI patients. Furthermore, the association of ETA and mortality appears to be independent of other established risk factors and the GRACE score, suggesting that the incorporation of ETA into risk stratification models may improve predictive power.

Before ETA can be applied to clinical practice, a better understanding of the link between ETA and mortality is needed. Why does ETA perform so much better in risk stratification compared to other measures of heart rate variability? Does the method described capture a signal unique in expiration that other measures of heart rate variability or vagal tone have until now been unable to identify? Answers to these questions are important to gaining a fuller understanding of the role of autonomic tone, its dysregulation, and impact on survival post-MI.

Validating ETA in a larger patient population, determining an appropriate treatment response, and assessing the cost-effectiveness of the method are required for ETA to gain acceptance in everyday clinical practice. The parameters defining the expiratory phase, $\phi 1$ and $\phi 2$, a central aspect of measuring ETA, were set after looking at the data and systematically optimizing these boundaries based on analysis of the ROC curve for 5-year all-cause mortality. While the authors argue these values were not crucial to the prognostic value of ETA, testing ETA using pre-defined $\phi 1$ and $\phi 2$ in a validation cohort is required. For ETA to be considered of widespread clinical value, effective therapeutic interventions are needed in patients who present with abnormal ETA values. Of the 72 deaths in the present study, 33 were classified as cardiac and of these 11 were sudden cardiac death. While a pairwise multivariable analysis suggested that ETA can predict sudden cardiac death, this finding needs to be recapitulated in a validation cohort. If ETA is predictive of sudden cardiac death, an appropriate therapeutic response (perhaps implantable cardioverter-defibrillator implantation in patients with abnormal ETA but otherwise low risk for sudden cardiac death by other measures) should be tested in a clinical trial.

If the previous investigations are successful, then one would turn attention to the cost effectiveness of using ETA in the post-MI population. Measuring ETA, as defined by Sinnecker et al. (6), requires a 30-min patient visit to obtain a high-resolution ECG and respiratory data. Technicians and equipment to perform the test and process data would needed, in addition to physician expertise for analysis, reporting, and quality control of the data. Finally, a cost-effective mechanism of translating the results of ETA into medical decision making would have to be developed to make this modality a viable addition to the current standard of care for post-MI patients.

In summary, Sinnecker et al. (6) provide an exciting and important contribution to the discussion on heart rate variability in patients who suffered an AMI. Unique from other studies, measurement of ETA appears to be a robust marker of mortality risk in post-infarction patients and is independent of other established risk factors. It is an enticing thought that inclusion of ETA in risk analysis post-MI may significantly improve risk assessment; however, the applicability of this method in a larger patent cohort and how it could affect therapeutic decisions remains to be seen.

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