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EDITORIAL COMMENT

Heart Rate Fragmentation and Coronary Calcification

A Neuroautonomic Connection?*

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The title of the article by Sawayama et al[1] in this issue of *JACC: Asia* will likely promptly engender 2 questions: What is "heart-rate fragmentation," and what does it have to do with the much more familiar term, "heart-rate variability"? The short answer is that both terms, abbreviated HRF and HRV, respectively, relate to measurable properties of beat-to-beat fluctuations in heart rate (HR) occurring with "normal" sinus rhythm. The word "normal" is in quotation marks because not all sinus rhythms are equivalent. Indeed, important differences (**Figure 1**) lie beneath the radar of current clinical assessments.

In healthy subjects, HR increases with inspiration and decreases with expiration, defining a "high-frequency" oscillatory pattern (~12 cycles/min) referred to as respiratory sinus arrhythmia. The physiological coupling is driven primarily by changes in vagal tone. With healthy aging, cardiorespiratory coupling degrades, leading to a decrease in the amplitude of HR fluctuations. Short-term (high-frequency) HRV metrics, such as the root mean square of successive normal-to- normal (NN) differences (rMSSD) and high-frequency (HF) power, have been used to assess these changes, under the assumption that the higher rMSSD and HF power, the higher the vagal tone modulation. Effectively, these and related indices have become surrogate measures of vagal tone modulation and, more generally, of cardiac neuroautonomic integrity.

A PubMed search for "heart rate variability" yields more than 24,000 citations (>5,000 in the last 3 years). Despite this large body of work, traditional HRV measures have failed to gain traction for diagnosis or risk stratification. One possible explanation is the increasing evidence that there are both salutary and deleterious sources of beat-to-beat fluctuations in HR, which renders the physiological interpretation of the metrics' values less reliable. The problem is particularly relevant in middle aged to older populations. As shown in **Figure 1**, with cardiovascular (CV) disease beat-to-beat changes in HR above the respiratory frequency may develop (Figure b_2). These fast fluctuations that occur within the respiratory cycle are not attributed to vagal-tone modulation but may inflate the value of traditional HRV measures.

The recognition that changes in HR above the respiratory frequency are a dynamic marker of cardioautonomic dysfunction led us to delineate the HRF construct[2-4] and the development of a set of metrics for its quantification. A visible difference between vagally and nonvagally mediated HR fluctuations is their degree of smoothness or—conversely—"fragmentation." Nonvagally mediated fluctuations are characterized by an excess of reversals in HR acceleration: that is, a higher percentage of transitions from acceleration to deceleration and vice versa, which we termed "heart rate fragmentation (HRF)."[2] The simplest measure of HRF is the percentage of inflection points (PIPs): that is, of changes in HR acceleration sign. Of key importance is fact that HRF can lead to an increase in rMSSD or HF power. Thus, there are 2 major sources of high HRV: strong vagal-tone modulation or high HRF.

In this context, what is the relevance of HRF to clinical cardiology? In the MESA (Multi-Ethnic Study of Atherosclerosis), a prospective study of middle-

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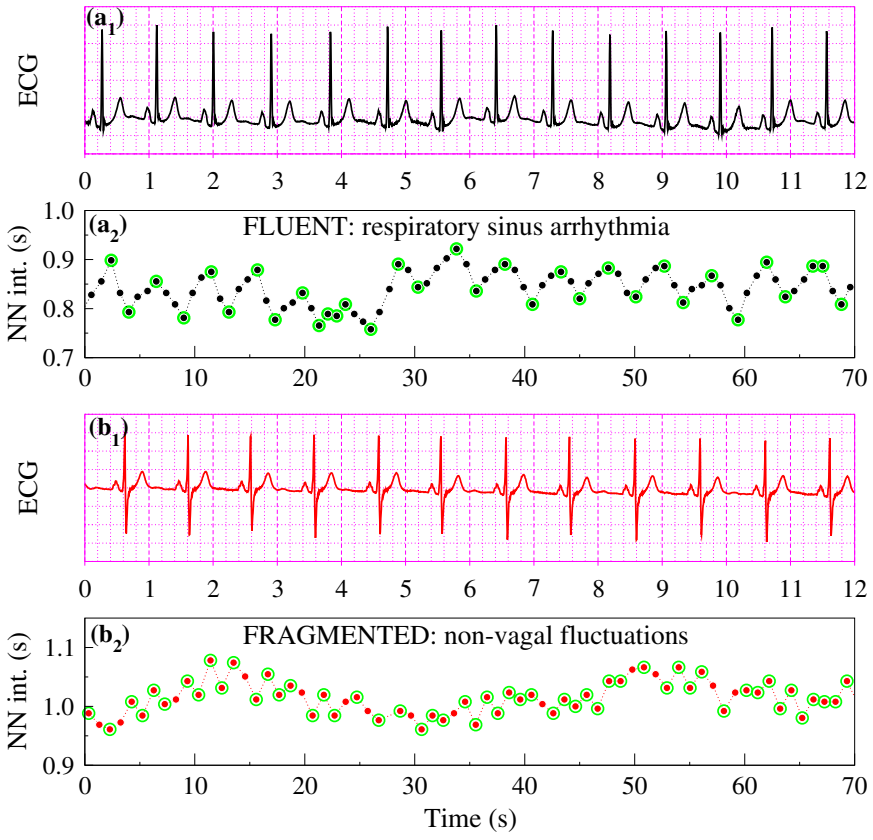
FIGURE 1 **Fragmented vs Nonfragmented Heart Rate Dynamics**



Electrocardiographic (ECG) tracings (a_1, b_1) and normal-to-normal (NN) interval time series (a_2, b_2) from 2 participants in the Multi-Ethnic Study of Atherosclerosis (MESA). The green circles in a_2 and b_2 highlight "inflection points" at which reversals in heart rate acceleration occur ($\Delta NN_i \times \Delta NN_{i-1} \leq 0$; $\Delta NN_i \neq \Delta NN_{i-1}$). Short-term heart-rate variability (HRV) values (root mean square of successive differences [rMSSD] and high-frequency [HF] power) were comparable for both participants. Participant "b," with more fragmented dynamics had higher cardiovascular risk, assessed by the Framingham index: 15.6 vs 2.4. Adapted from *Front Physiol.* 2018;9:1117.[3]

aged to older Americans, we[3,4] showed that increased HRF was independently associated with higher risk of incident major adverse CV events,[3] atrial fibrillation (AF),[4] and CV death.[3] In contrast, conventional HRV measures were not associated with these outcomes. Recently, these results have been independently confirmed in other large studies.[5,7] Of additional note was our finding that HRF added predictive value to Framingham, MESA, and CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology - Atrial Fibrillation) risk indices.

The study by Sawayama et al[1] adds support for the use of HRF metrics as independent predictors of prevalent coronary disease. Specifically, Sawayama et al[1] determined the associations of both HRF and conventional HRV metrics derived from 24-hour Holter recordings with Agatston scores. Their data were from a subcohort of the SESSA (Shiga Epidemiological Study of Subclinical Atherosclerosis), a population-based study of ostensibly healthy Japanese men. Of the 508 participants (age 67 ± 7 years) in their analytical sample, 325 (64%) had coronary artery calcium (CAC). The authors found that higher HRF was associated with greater CAC, independent of traditional risk factors. The association was slightly stronger when HRF was assessed during the sleep period and comparable in magnitude to the association between mean ambulatory systolic blood pressure and CAC. Specifically, in fully adjusted models, a 1-SD increase in sleep HRF (PIP) was associated with a 31% (5%-62%) increase in Agatston score. Analyses in which CAC was modeled as an ordinal variable yielded similar results. These findings should be confirmed in cohorts that include women.

The study by Sawayama et al[1] also clearly reveals the limitations of traditional HRV approaches. HRV metrics were not associated with CAC. In addition, HRV metrics did not significantly vary with cross-sectional age. Coronary artery disease and aging are both contexts in which vagal tone is diminished. As such, HRV metrics, interpreted as markers of vagal-tone modulation, would have been expected to be lower in those with CAC and markedly diminish with cross-sectional age.

Why would the loss of cardiorespiratory coupling and the emergence of fragmented rhythms, often so subtle that they fall under the rubric of "normal sinus rhythm" be associated with CV disease markers and adverse outcomes? The basic mechanisms underlying the dynamic patterns of HRF remain speculative.[2-4] Considering the emerging links between inflammatory diatheses and loss of vagal function,[8] and the fact that CAC is an advanced manifestation of coronary inflammation,[9] a possible mechanism underlying the association between HRF and CAC[1] is degradation of neuroautonomic function. Previous findings of significant positive associations between HRF and cross-sectional age,[2,6] higher risks of CV[2,7] and non-CV outcomes[6,10] are also consistent with this hypothesis.

The potential translational value of HRF is enhanced by the fact that HRF metrics are assessed from a continuous electrocardiogram, a readily obtainable and noninvasive signal that reflects autonomic regulation. Furthermore, HRF metrics are less affected by outliers, premature beats, noise, and trends in the data than conventional HRV measures. The reason is that HRF—unlike HRV—indices are based on the data points' rank order relative to their closest neighbors (higher/lower/equal) and not their amplitudes.

Finally, these considerations, in concert with previous findings,[2-7,10] and the work by Sawayama et al[1] align with the investigational application of vagal stimulation as a novel treatment for coronary artery disease[11] and with the possibility of using HRF to help monitor this and other interventions.

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