JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 69, NO. 3, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.11.021

EDITORIAL COMMENT

Autonomic Tone and Atrial Fibrillation

A Double-Edged Sword?*

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Atrial fibrillation (AF) is a growing epidemic with prevalence projections approaching 8 to 12 million individuals in the United States by 2050 (1). AF is associated with increased mortality as well as an increased risk for stroke and heart failure. Antiarrhythmic drug therapy to control and prevent AF has been disappointing. Furthermore, the use of catheter ablation to treat AF has limited efficacy, particularly in patients with persistent AF (2,3). These drawbacks underscore the need for major conceptual changes in our approach to AF.

One challenge to achieving such a paradigm shift is the complex nature of AF pathophysiology; importantly, multiple potential mediators may cause pathologic changes to the atrial substrate years before the development of AF. These include inflammation, oxidative stress, fibrosis, pressure overload, volume overload, and autonomic changes (4). As atrial tachyarrhythmias develop, further substrate advancement may occur as well as structural and electrical remodeling of the left atrium due to the arrhythmia itself (5). Current clinical approaches to AF are reactive, implementing treatments such as antiarrhythmic drug therapy or catheter ablation that have mediocre efficacy once the substrate is developed. An intriguing question is: Can early identification of atrial substrate abnormalities lead to early interventions that may prevent AF?

Several approaches have been considered for predicting future AF. Clinical risk scores that have been developed in large population studies (6) rely on concomitant clinical factors or entities and, therefore, do not address the atrial substrate directly. In contrast, electrical remodeling has been demonstrated before the development of AF (7,8), with prolongation of P wave duration and atrial conduction slowing. Various biomarkers also have been shown to provide incremental value in predicting AF (9). Furthermore, epicardial fat has been linked with AF and may play an independent role in the development of the substrate for AF (10). However, the early autonomic changes associated with the subsequent development of AF have not been described.

It is well known that changes in the autonomic nervous system contribute to the onset and maintenance of AF (11). Hyperadrenergic states can lead to the stimulation of atrial beta receptors, resulting in increased calcium influx; calcium overload may create action potential changes and delayed afterdepolarizations.

Interestingly, parasympathetic stimulation may also produce AF. Vagal stimulation shortens the action potential duration and atrial refractory period, facilitating AF induction and maintenance. The combined effects of sympathetic and parasympathetic stimulation have been shown to be important factors in the initiation of AF (12,13). Although the role of ablation of autonomic ganglia in the treatment of AF remains controversial at this time, the role of the autonomic nervous system in AF is well appreciated.

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With this background, it is reasonable to query whether autonomic nervous system changes may contribute to the subclinical atrial disease that ultimately leads to AF. In this issue of the *Journal*, Agarwal et al. (14) demonstrated early changes in heart rate and heart rate variability (HRV) in patients years before they developed AF. They studied short-term HRV and baseline heart rate in 11,715 middle-aged adults within the ARIC (Atherosclerosis Risk in

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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Communities) database, measuring the short-term SD of standard RR intervals as well as high-frequency (HF) (0.15 to 0.40 Hz) and low-frequency (LF) (0.04 to 0.15 Hz) variations in RR cycles. During a mean follow-up of 19.4 years, 13.5% of patients had incident AF and those who developed AF had lower baseline measures of HRV as well as lower heart rate compared with those without AF. A multivariate analysis showed higher incidence of AF in patients with heart rates of <50 beats/min (RR >1,200 ms).

Although consistent with the notion that some preclinical changes are detectable before the onset of clinically detected AF, these findings should be interpreted in the context of several important issues.

First is the important distinction between changes in autonomic tone that facilitate AF triggers or alter electrophysiological properties to support AF maintenance, and the potential role of chronic alterations in autonomic input to the atria that actually modify the atrial substrate for AF. Both "vagal" and "adrenergic" AF have been described specifically in relation to AF-inducing triggers. Similarly, experimental studies of vagal stimulation, adrenergic stimulation, and combined stimulation showed that these conditions can facilitate AF induction.

The role of isolated chronic changes in autonomic input in developing the atrial substrate that supports AF has not been delineated. The authors found an increasing risk of AF with heart rates of <50 beats/min at baseline and, based on this, concluded that increased basal parasympathetic tone is associated with AF, supported by their study demonstration that high HRV was associated with increasing risk of AF. Although only a very small subgroup fell into these groups of low heart rate and/or high HRV (<3% to 5%), it is possible that chronic parasympathetic stimulation leads to shortened atrial refractory periods in certain areas of the atrium or other undefined alterations that promote chronic changes that serve as the substrate for subsequent AF. This is consistent with the clinical observation that athletes, a group with chronically increased levels of parasympathetic tone, have an increased risk for AF (15). Finally, as the authors point out, a lower heart rate also can represent a greater use of rate-slowing drugs or the presence of sinus node dysfunction, which is certainly associated with AF; HRV parameters are not validated in the context of sinus node dysfunction. The absence of information on this small cohort precludes further extrapolation.

Furthermore, the authors found that decreased measures of HRV were associated with AF. Does the autonomic milieu a low HRV represents lead to chronic changes in the atrium that help to form the substrate for AF? Alternatively, does the early atrial disease that underlies the subsequent development of AF also affect the autonomic input to the sinus node? It cannot be overemphasized that heart rate and HRV measures define autonomic effects at the sinus node and do not necessarily represent a uniform set of autonomic changes across the atrium that would support atrial arrhythmogenesis. Overall, multiple cardiac and systemic disease states are associated with a reduced HRV, suggesting that this might better exemplify a nonspecific barometer of disease. For example, this absence of a relationship between HRV and arrhythmia risk was demonstrated in a recent meta-analysis of predictors of arrhythmic events in patients with nonischemic dilated cardiomyopathy (16).

Lower HRV in patients who subsequently developed AF might identify those who are "sicker" or have more advanced underlying atrial disease. In other words, despite multivariable adjustment, similar patients with hypertension, left ventricular hypertrophy, and other comorbidities might develop atrial disease (i.e., fibrosis) differently. Those who experience enhanced adrenergic activation might be the ones with more advanced atrial disease who are susceptible to developing AF. One of the more important final common substrates underlying the development of AF is atrial fibrosis (4). In a large study, >80% of patients with AF referred for catheter ablation had ≥10% left atrial fibrosis by cardiac magnetic resonance (17). If this is the key substrate for AF, there are no current data or paradigms that would link the moderate observed changes in HRV with fibrosis. Unless such a link is established to fibrosis or other electrophysiological remodeling, these findings are likely epiphenomena.

The technical aspects of HRV analysis and their interpretation should also be examined, given the amount of disparity in approaches, and these technical issues may decidedly influence results. Agarwal et al. (14) analyzed very short recording durations, which likely explained their stated low reliability of the LF data. Yet these data were analyzed and reported for the LF/HF ratio. The authors reported the log(LF/HF), which was not an appropriate transformation of the LF/HF ratio, because it changes this variable to be the difference in log(LF) and log(HF). It would therefore be most appropriate to discount these data completely. Additionally, we need to understand that there is not a strong, uniform relationship between HRV and autonomic (parasympathetic) tone because there is a high amount of interindividual variability in this relationship (18). Thus, population trends cannot be used to define

abnormalities for individuals and "goals" for treatment to alter HRV.

Despite its limitations, this study provided 2 key findings that should be explored further. The first relates to the very small subgroup of individuals who seemed to have enhanced parasympathetic effects on the sinus node and an increased AF risk. Whether this is a direct effect on the underlying substrate or an effect of the autonomic milieu that enhances an otherwise preexisting predisposition to AF merits more study. Similarly, identification of early risk markers that can predict subsequent AF is needed to develop better early interventions. Whether low HRV plays a pathophysiological role in developing AF or simply serves as a marker of more advanced underlying structural heart disease requires delineation. HRV abnormalities likely do not have sufficient predictive ability to alter an individual's therapy. It is too early to recommend, as the authors do, "interventions to improve autonomic tone as a potential way to reduce AF incidence or recurrence."

Further studies are needed to better understand the effect of chronic changes in autonomic control of the heart, the interaction of these changes with the anatomic substrate underlying AF development, and to what extent autonomic dysfunction directly plays a primary and/or secondary role in AF initiation/maintenance. Risk factor modification has been shown to be effective at reducing AF recurrence in groups of patients who have or have not had catheter ablation (19,20). Many of the risk factor modification interventions (weight loss, exercise, control of sleep apnea) can directly impact autonomic neural control of the heart and restore it toward normal. Thus, autonomic markers may indeed serve as a barometer for the underlying structural, metabolic, and inflammatory milieu predisposing to AF.

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KEY WORDS arrhythmia, heart rate variability, pathophysiology, substrate