Slower Heart Rates for Healthy Hearts
Time to Redefine Tachycardia?

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The management of atrial fibrillation, even in the modern era, remains complex and challenging. Preventing atrial fibrillation occurrence by identifying and favorably improving modifiable risk factors thus assumes great importance. It is well known that hypertension and resultant structural heart disease contributes significantly to the incidence of atrial fibrillation.1,2 The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study thus far has shown us that angiotensin-receptor blockade and reduction in left ventricular hypertrophy, irrespective of blood pressure-lowering, reduces the incidence of new-onset atrial fibrillation.1,3

In recent years, accumulating evidence has linked high resting sinus heart rates (HR) directly and indirectly to adverse cardiovascular outcomes.4,5 Epidemiological studies show resting HR to be an independent predictor of cardiovascular and all-cause mortality in general population as well as in hypertensive patients.6 The cardiovascular benefits offered by β-blockade in coronary artery disease and heart failure have, in part, been attributed to β-blocker-mediated HR reduction.7,8 Other studies have linked high baseline HR to the development of hypertension, to the progression of coronary artery disease, and to the trigger of myocardial infarction, ventricular dysfunction, and ventricular arrhythmias.6,9–11 In this issue of Circulation: Arrhythmia and Electrophysiology, Okin and colleagues12 examines the relationship of HR changes over time on risk of atrial fibrillation in hypertensive patients as part of the LIFE study.

In this post hoc analysis of the prospective LIFE study, 8828 hypertensive patients with left ventricular hypertrophy by ECG but without a history of atrial fibrillation were followed for a mean of 4.7±1.1 years. New onset atrial fibrillation was determined by 12-lead ECG performed on an intermittent, infrequent basis (at baseline, 6 months, and yearly thereafter). Hypertension was treated with losartan or atenolol.

Using a variety of analyses, higher in-treatment HR on serial electrocardiograms was associated with a 15% increased risk of atrial fibrillation for every 10 bpm increase in HR. Differences were substantial and independent of treatment regimen (losartan versus atenolol), reduction in blood pressure, or in-treatment regression of left ventricular hypertrophy. In-treatment persistence or development of HR ≥84 bpm was associated with a 61% higher incidence of atrial fibrillation, after adjusting for baseline variables and in-treatment changes in blood pressure and left ventricular hypertrophy.

This is an important and innovative study evaluating the impact of HR in patients with hypertension and left ventricular hypertrophy with respect to subsequent development of atrial fibrillation. Although the post hoc nature of this trial has inherent limitations, use of multiple statistical tools makes the analysis robust. A large number of patients were followed long-term. The relationship between HR and outcomes is convincing.

Mechanisms underlying this association are not immediately clear but may reflect the fact that those with faster HRs may have more comorbidities. Differences in sympathetic and parasympathetic activation reflected in the HR could also be an explanation. Sympathetic activation and simultaneous parasympathetic and sympathetic activation can initiate atrial fibrillation by shortening atrial action potential duration and effective refractory period. Higher sympathetic tone or catecholamine levels may trigger pulmonary vein ectopic activity potentially responsible for atrial fibrillation.13 The mechanisms by which hypertension leads to atrial fibrillation and the relation between atrial pressure, stretch and autonomic shifts in patients who develop atrial fibrillation remain areas of active investigation.

The data on the effect of HR alone as a mechanism contributing to atrial fibrillation are mixed. While tachycardia-induced ventricular cardiomyopathy due to rapid and persistent ventricular rates is a real and reproducible phenomenon, higher baseline HRs within the normal range (for example, 70 to 100 bpm) could result in subclinical atrial myocardial dysfunction, to create a substrate responsible for development of atrial fibrillation. The issue of whether there is an optimal HR range to reduce the risk for atrial fibrillation remains undefined.

Atrial overdrive pacing algorithms have shown mixed results in suppression of atrial fibrillation in patients with sinus node disease, with recent data showing no added benefit.15,16 Atrial overdrive pacing, however, can suppress pulmonary vein activity and has been modestly effective in preventing postoperative atrial fibrillation.17,18 Higher percentage of atrial pacing resulting from atrial suppression algorithms did not worsen heart failure–related adverse
events. Whether the neuroendocrine responses to override atrial pacing are different from sinus activity and whether bradycardia will offset the currently demonstrated advantage with slower HRs remains to be seen.

It is noteworthy that the incidence of atrial fibrillation was similar for those treated with losartan compared to those treated with atenolol. This may be due to individual differences in β-blocker requirements or that there is a disconnect between the β-blocker dosing for hypertension compared to adequate blockade of atrial myocardial β-receptors. The optimal β-blocker to treat hypertension may not eliminate enhanced sympathetic activation completely in hypertensive patients with left ventricular hypertrophy. Although it is possible that alternative β-blocker strategies may affect outcomes differently, the real reason for the lack of specific effect from atenolol remains unclear and should be explored in further studies.

In assessing the clinical implications of this study, several issues should be considered. The main concern is the ability of the infrequently performed 12-lead ECG in reflecting baseline HR. The sporadic nature of heart rhythm monitoring in this study may confound the actual risk of atrial fibrillation. The burden and impact of atrial fibrillation in this population remain unknown.

Various types of HR measurements, including resting HR from baseline ECG, mean HR for 24 hours, HR variability, HR during sleep, and recovery HR after an exercise test, have been used in assessing the prognostic value of HR. Thus, even a simple, easily accessible clinical variable like HR may not be easy to measure when you consider the best method, as well as sampling conditions, that provide the least amount of variability. Even if the best measure of HR remains unclear, no matter the type of measurement, an adequate sample size, as presented in the current study, can conceivably offset the variability among the different measures.

Partitioning HRs into 2 groups, >84 bpm and <84 bpm, may simply stratify patients into 1 group that is sicker and more prone to develop adverse cardiovascular outcomes anyway. In this setting, elevated HR may simply be a marker of poor substrate as reflected by differences in age, gender, and diabetes between the groups.

This novel work by Okin et al has the potential to influence drug therapy in hypertensive patients as part of an effort to prevent atrial fibrillation. The question, however, remains as to whether HR is really a modifiable risk factor. In the LIFE study, the incidence of atrial fibrillation was not affected by antihypertensive therapy using atenolol, which has strong negative chronotropic properties. A recent meta-analysis of randomized, controlled studies that evaluated β-blockers to treat hypertension showed that a lower HR from β-blocker use was associated with a significantly increased risk for all-cause and cardiovascular mortality. Therefore, although autonomic effects can initiate and perpetuate atrial fibrillation, it is not self-evident that upward titration of a β-blocker would necessarily prevent atrial fibrillation. Perhaps outcomes, such as mortality or atrial fibrillation, related to HR are direct and independent of autonomic influences.

This hypothesis was tested in the recently reported BEAUTIFUL (morBidity mortality EvAlUaTion of the I I inhibitor ivabradine in patients with coronary disease and left ventricUlar dysfunction) trial. Ivabradine, a specific sinus node I I current blocker, which reduces HR without affecting the autonomic tone, did not affect the primary composite end point (cardiovascular death, hospitalizations for heart failure or acute myocardial infarction) compared to placebo, in patients with coronary artery disease and left ventricular dysfunction. However, in the placebo arm, those with higher baseline HRs had adverse outcomes similar to other studies evaluating the risk of higher sinus rates.

The mechanism by which HR affects outcomes is not completely certain; it may be a direct effect or it may be a reflection of underlying autonomic tone. It may also simply be a marker of the underlying illness of the patient. This hypothesis could be tested, and would be of great interest, by assessing long-term mortality/morbidity end points in the LIFE study patients who developed atrial fibrillation and had comparably different sinus HRs at baseline. More understanding into the mechanisms behind higher HR-mediated adverse cardiovascular outcomes are needed to guide future therapies.

In summary, mounting evidence suggests that slower HRs while in sinus rhythm are associated with longevity. The present study also shows a similar association between HR and development of atrial fibrillation in a hypertensive population. It is clear that this simple vital sign needs more careful attention. As Palatini had suggested back in 1999, it may indeed be time to redefine tachycardia.

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References

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