

EDITORIAL COMMENT

Should We Be Ablating the Kidneys or the Heart to Prevent Arrhythmias?*



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Early clinical trials (1,2) and basic physiology studies (3) have shown that there can be significant benefit from renal denervation (RDN) for reducing hypertension. More recently, however, a well-controlled clinical trial (SYMPPLICITY HTN-3 [Renal Denervation in Patients With Uncontrolled Hypertension-3]) (4) suggests that this benefit may not be so clear cut. There are good reasons to question these results, but it is possible that RDN is beneficial in other important ways. It appears, from a handful of experimental studies and clinical case reports, that RDN may reduce the risk for arrhythmia independent of changes in blood pressure. However, there is very little known about the mechanism of this action, particularly for ventricular arrhythmogenesis. In this issue of *JACC: Basic to Translational Science*, Chang et al. (5) demonstrate the suppression of ventricular arrhythmias by RDN and, most importantly, a mechanism by which this can occur.

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The important role of the autonomic nervous system in determining arrhythmia risk is unquestionable yet very complex (6). Reducing sympathetic activity has long been known to be an effective approach for treating arrhythmias, as demonstrated

by the success and resiliency of beta-blockers. Specifically targeting the renal sympathetic chain by RDN can reduce norepinephrine spillover and activation of the renin-angiotensin-aldosterone system (RAAS) that is typical in patients with refractory hypertension. Theoretically, RDN should be beneficial, and this benefit can be achieved without the complications or side effects typically associated with more excessive antisymphathetic strategies (e.g., sympathectomy). Furthermore, reduction of sympathetic activity by RDN should have favorable action on ventricular arrhythmias (7,8), as demonstrated in small clinical studies (9,10) and case reports (11,12).

If the antiarrhythmic benefits of RDN hold up to clinical scrutiny, an obvious question is: why? Some mechanistic insight can be gleaned from animal models of atrial fibrillation (AF), where RDN was shown to reduce atrial nerve sprouting, fibrosis, and other electrophysiological substrates associated with AF (13). Further, results from a meta-analysis of clinical trials revealed that RDN can reduce atrial size (14), which can also prevent AF. Much of the atrial structural remodeling that is reduced by RDN could be tied to its effect on the RAAS (15). Electrophysiological (e.g., ion channel) remodeling may also be playing a role in AF prevention by RDN; however, this is less clear. Unfortunately, there is much less mechanistic insight available for ventricular arrhythmias. In pigs, it was found that RDN had a significant effect on PVCs and VF during acute ischemia; however, RDN had no effect on action potentials or on VF during reperfusion (16). In canines with acute myocardial infarction, RDN reduced VF and cardiac alternans, which was attributed to a reduction of APD restitution slope (17). These experimental studies and clinical reports mentioned above demonstrate that RDN can have favorable acute and chronic electrophysiological effects. In the study by Chang et al. (5), the authors demonstrate

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favorable ventricular electrophysiological remodeling, including preventing APD prolongation typically associated with heart failure; however, the most compelling results are related to cardiac alternans.

Cardiac alternans is a beat-to-beat oscillation of repolarization and the ECG T-wave, and it is a cause of arrhythmias (18,19). Alternans is relatively benign when spatially synchronized (concordant), because repolarization is prolonged or shortened in-phase throughout the heart. In heart disease, however, not only does alternans occur at significantly slower heart rates (20), it also can become spatially desynchronized (discordant) where repolarization is prolonged out of phase in different regions of the heart. This ultimately forms large gradients of repolarization that are sufficient to cause reentrant activity (18,21). In the present study, the authors show that RDN reduced cardiac alternans, as has been observed with antisympathetic treatment in patients with disease (22-24). The exact reason why antisympathetic treatment decreases alternans is not known, but could be related to APD restitution (25) or potentially a direct effect on Ca^{2+} cycling (26).

The most important result reported in the study by Chang et al. (5) is that RDN reduced spatially discordant alternans and the occurrence of VF, strongly suggesting a way by which RDN can suppress ventricular arrhythmias. The cellular mechanism of this action was not fully explored by the authors; however, one hypothesis is that the normalization of Ca^{2+} cycling by RDN suppressed discordant alternans (27,28). It is also important to remember that the present study is a chronic model of disease (4 weeks post-myocardial infarction) and therapy (4 weeks post-RDN), which should allow time for structural changes. It is well known that in disease, activation of the RAAS pathway promotes structural remodeling (29), and that RDN can suppress this activity (30-33). In fact, the normalization of Ca^{2+} cycling observed by Chang et al. (5) may be an indication of favorable reverse structural remodeling. The prevention of such

structural remodeling could reduce, for example, abnormal impulse conduction, which is an important substrate for VF and VT. More interestingly, it can also prevent discordant alternans, which is consistent with the results reported by Chang et al. (5). Although the mechanisms of discordant alternans are complex and not fully understood, it has been shown to significantly increase in the presence of structural barriers (34) or when cell-to-cell uncoupling is decreased (35). Therefore, it is possible that RDN mitigates structural remodeling associated with heart disease and, thus, prevents the occurrence of discordant alternans and VT/VF by this mechanism. In the present study, the authors did not assess structural remodeling and its relationship with discordant alternans, so we will not know for sure if this is the case, but it would seem worthwhile to follow-up on this possibility.

As procedures are refined and the mechanisms of action are better understood, it is possible that RDN will re-emerge as an improved therapeutic strategy for patients with heart disease that is difficult to treat. RDN may be most beneficial for patients with heart failure with recurrent, refractory arrhythmias that cannot tolerate maximal beta-blockade or complications associated with RAAS inhibition, and who are not candidates for cardiac catheter ablation. Furthermore, RDN seems to attenuate both acute and chronic arrhythmia substrates and, thus, could be developed as therapy for preventing arrhythmia associated with multiple etiologies. Clearly, further clinical and experimental studies are needed to better understand the underlying antiarrhythmic action of RDN in patients with heart disease.

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