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The “Nervous” Kidney and Ventricular Fibrillation A Possible Game Changer?

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Renal sympathetic denervation (RDN), a process intended to eradicate renal efferent and afferent sympathetic nerves, arguably reduces not only renal but also whole body sympathetic nervous activity via central control mechanisms.^{1, 2} The renal sympathetic efferent and afferent nerves that lie within and immediately adjacent to the wall of the renal artery have recently become the target for ablative therapy for drug “resistant” hypertension.^{1, 3} Interestingly, the concept of sympathetic nerve ablation for the treatment of drug resistant ventricular tachycardia (VT) was explored decades ago in humans. It was in 1961 that Estes and Izlar employed, with success, bilateral stellectomy to treat a patient with recurrent VT.⁴ Later and in 1968, Zipes and associates reported that sympathectomy successfully suppressed a drug-resistant VT in a patient.⁵ An important turning point occurred in 1970 when Moss and McDonald performed left stellectomy in a patient with idiopathic long QT syndrome refractory to medical therapy. The rationale for this pioneering intervention was to shorten the prolonged QT interval with stellectomy.⁶ With the recognition that stellate ganglion stimulation in humans increases the QT interval and promotes electrical alternans, Schwartz and Malliani performed stellectomy for the management of malignant VT in patients with the long QT syndrome with a measure of success.^{7, 8} Recently, catheter-based renal endovascular RDN therapy was used successfully in two patients for drug-resistant VT⁹ and in three patients, two with cardiomyopathy and one with coronary artery disease.¹⁰ Furthermore, catheter-based RDN also was used to control ventricular rate in patients with AF¹¹ and as an adjunct therapy to pulmonary vein isolation to mitigate AF recurrences in patients with drug-resistant paroxysmal and persistent AF.¹² The protective role of RDN, if at all, against acute ischemic VT/VF still remains undefined. Since the early experimental demonstration of reflex activation of sympathetic preganglionic nerves during acute myocardial ischemia caused by coronary artery occlusion,¹³ overwhelming experimental and clinical evidence have shown the presence of a strong association between “sympathetic hyperactivity” and acute ischemic VT/VF. It is conceivable that multiple different sources could contribute, each to a variable extent, to the overall increased sympathetic input to the ischemic heart promoting VT/VF.

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In the current issue of the *HeartRhythm*, Linz and associates¹⁴ assessed the role of the renal sympathetic nerve activity on the occurrences of ventricular premature depolarizations (“PVCs”) and VF during the first 10 min of acute ischemia caused by the occlusion of the LAD in anesthetized open-chest pigs. The role of RDN was assessed by using bilateral surgical cutting of all visible nerves in the area of the renal hilus combined with adventitial stripping (over 1 cm) and chemical ablation of the renal arteries with phenol/alcohol solution. Completeness of renal sympathetic ablation was ascertained by the suppression of renal blood flow reduction in response to apnea caused by tracheal occlusion.¹⁴ The authors observed a dramatic drop in the occurrences of VF during the first 10 min of acute ischemia in the RDN compared to sham-operated pigs (80% vs. 14%). The dramatic reduction of VF in the RDN groups occurred under controlled heart rate (i.e., pacing at 100 beats/min) and the presence of similar sized myocardial ischemia in the RDN and the sham-operated groups. While the study falls short in providing mechanistic insight, the observation made by Linz and associates is significant and may have relevance to sudden cardiac death in patients with acute ischemic VF. There appears to be no direct neural connections between the kidney and the heart as suggested by the lack of effect of RDN on the duration of the LV monophasic action potential (MAPD) prior to LAD occlusion. While only one recording site is reported in this study, clearly recording from multiple sites are needed to ascertain this point. The protective effect of RDN against ischemic VF remains elusive. It is possible that reduced norepinephrine release (“spillover”) into the body’s circulation by the renal postganglionic norepinephrine-releasing efferent nerves, as shown in human and swine studies,¹ may contribute to cardiac sympathetic hyperactivity. In contrast to ischemic VF, RDN had no protective effect against reperfusion VF as 100% of the pigs in the two groups manifested reperfusion VF after 20 min of LAD occlusion.¹⁴ The statement that “RDN did not attenuate reperfusion associated MAP shortening... which might explain the lack of inhibitory effects of RDN on reperfusion arrhythmias” needs to be qualified. Faster activation rates during reperfusion VF greatly shorten the APDs, and measurement of APD with extracellular catheters during VF is unreliable as it becomes difficult to define the beginning and the end of a severely distorted MAPs that characteristically emerge during VF.¹⁵ The lack of efficacy of RDN against reperfusion VF may well be related to other factors such as the sudden surge of reactive oxygen species that alter multiple cytoplasmic and transmembrane ionic mechanisms.¹⁶

Surprisingly the influence of RDN on the acute phase 1B arrhythmias was not reported in this study despite the availability of such data to the authors.¹⁴ The 15 to 20 min post-acute ischemic period i.e., phase 1B, (phase 1A is the first 10-15 min) engages alterations of myocardial cell couplings in the ischemic zone via altered Cx43 distribution.¹⁷ Does RDN reduce ventricular arrhythmias during phase 1B? Curiously, however, the authors do not fail to report that the beta blocker, atenolol “reduced ventricular arrhythmias during the ischemic phase induced by 20 minutes of LAD-ligation.” The proposed mechanism of delayed afterdepolarization (DAD) as a cause for PVCs based on their occurrences at long coupling intervals may not be exclusive. While animal studies showed that chemical sympathectomy with 6-hydroxy dopamine mitigates DADs induced by digitalis,¹⁸ the phenomenon of post-repolarization refractoriness may also be operative. During acute ischemia, membrane excitability is delayed beyond full repolarization causing wavefront breakup and formation

of late-coupled single or multiple reentrant PVCs.¹⁹ These comments should not detract from the importance of the observations reported here by Linz et al. The question is whether the time has come to think about “sedating the nervous kidney” as a tool to derail the trajectory of the compromised heart to fibrillatory delirium. Clearly, more work is needed to substantiate and confirm the present findings in other animal species. It also needs to be clarified if the complete surgical sympathetic nerve sectioning combined with chemical ablation used in the present pig study could be compared to the less aggressive and incomplete catheter-based endovascular renal sympathetic ablation done in humans. Finally, the long-term effectiveness of RDN also needs to be examined. The potential arrhythmic consequences of sympathetic nerve sprouting that invariably emerges in the settings of severed nerves by either myocardial ischemia^{20, 21} or myocardial damage caused by radiofrequency catheter ablation²² needs to be defined.

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