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Baroreflex stimulation vs. renal denervation for treatment of hypertension: what constitutes a logical comparison of these interventions on atrial electrophysiology?

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The autonomic nervous system is a primary modulator of blood pressure, heart rate and cardiac function, and imbalance of the parasympathetic and sympathetic arms of the autonomic nervous system underlies many forms of cardiovascular pathophysiology[1]. Heart failure and hypertension are often characterized by an excess of sympathetic nerve activity and elevated plasma catecholamine levels. Elevated catecholamines promote activation of the renin-aldosterone-angiotensin system (RAAS). Pharmacologic efforts to treat autonomic imbalance have primarily focused on the use of beta-adrenergic receptor blockers and RAAS antagonists.

In an effort to overcome the limitations of available pharmacologic agents, several novel recent interventions have focused on directly modulating the sources of autonomic imbalance. In experimental studies, direct vagal (parasympathetic) stimulation has been shown to attenuate the development of heart failure associated with rapid ventricular pacing[2]. In a first-in-human trial, heart failure patients receiving vagal stimulation had a significant increase in LV ejection fraction, 6-minute walk distance and quality of life[3, 4]. Alternative approaches that achieve a similar increase in parasympathetic activity include spinal cord stimulation and electrical stimulation of the baroreflex[5]. Electrical stimulation of the baroreflex (BRS) has been shown to have an antihypertensive effect in patients that are refractory to current antihypertensive medications[6]. An alternative to stimulating parasympathetic activity is to reduce sympathetic activity. Catheter ablation of sympathetic nerves surrounding the renal arteries has also been shown to have significant benefit in the treatment of drug-resistant hypertension[7, 8]. Thus, these interventions provide patients with new ways to reduce the burden of symptoms and improve the quality of life without the need for continuous drug therapy.

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Heart failure and hypertension are common and important risk factors for the development of atrial fibrillation (AF). Both tend to increase atrial diastolic and systolic pressures, leading to atrial dilatation, myocyte hypertrophy, electrical remodeling and interstitial fibrosis – core elements of the substrate for AF. It is thus relevant to ask how the new interventions for heart failure and hypertension affect the atria. In this issue, Linz and colleagues seek to compare the effects of renal sympathetic denervation (RDN) and baroreflex stimulation (BRS) on the atria[9]. The authors compared the effects of RDN and BRN on blood pressure, atrial effective refractory period (ERP) and inducibility of AF - using acute studies on 12 *normal*, anesthetized swine[9].

Linz, et al. found that acute (surgical) renal denervation slowed heart rate by ~18 beats per minute and decreased systolic BP by 7 mmHg. In the interest of normalizing their comparison, they titrated the degree of BRS to achieve a similar reduction in heart rate; at this level of stimulation, systolic BP was reduced by 10 mmHg. When animals were subjected to BRS following RDN, the authors found that the effects were additive, with a mean reduction in systolic BP of 19 mmHg, suggesting that the BP lowering mechanisms of BRS and RDN are independent. Under these experimental conditions, the authors report that RDN did not significantly affect the duration of atrial monophasic action potentials (MAP) or the atrial ERP. In contrast, when using a level of BRS that slowed heart rate and decreased blood pressure, they found that the atrial MAP duration and ERP was shortened. They observed a dose-dependent abbreviation of atrial ERP and slowing by varying the intensity of BRS. Under these conditions, neither RDN nor BRS affected QT interval or ventricular MAP duration. Treatment of the animals with atropine effectively suppressed the BRS-induced changes in atrial MAP duration, confirming that the primary mechanism of action of BRS was due to vagal stimulation; the lack of effect of atropine on the ventricle is consistent with the atrial and nodal, but not ventricular localization of acetylcholine-activated potassium channels (I_{KACh}) gated by M_2-muscarinic receptor activation. I_{KACh} accelerates atrial repolarization, shortens atrial action potential duration, decreases atrial ERP, and slows heart rate.

Sympathetic agonists (norepinephrine, epinephrine) activate beta-adrenergic receptors that are coupled via G_s proteins to an increase in adenylate cyclase activity, resulting in enhanced production of cAMP, activation of protein kinase A, and phosphorylation of targets including the L-type Ca^{2+} channel, phospholamban and myofilament proteins. The net impact of sympathetic activation is an increase heart rate and cardiac contractility, largely as a result of increased Ca^{2+} influx via L-type Ca^{2+} channels that are present in myocytes throughout the myocardium. In all regions of the heart, the effects of sympathetic activation are physiologically attenuated by activation of parasympathetic nerves. M_2-muscarinic receptors activated by acetylcholine are coupled to inhibitory G proteins (G_i) that attenuate adenylate cyclase activity, decreasing cAMP production and thus the entire cascade of events that are mediated by sympathetic activation.

As atrial reentry and AF inducibility are both facilitated by shortening of the atrial ERP, it is predictable that RDN, which had no impact on atrial ERP, had no impact on the inducibility of AF. In contrast, during BRS induced abbreviation of atrial ERP, AF inducibility was significantly increased, both during BRS alone and during concomitant RDN and BRS. On the basis of the experiments reported by Linz et al., the authors caution that BRS has a potential for atrial proarrhythmia at an intensity used in hypertensive patients, and note that RDN does not have this effect.

The logical inference of this presentation appears to be that RDN is a safer therapy than BRS, with less risk of AF. On the basis of blood pressure lowering and heart rate slowing in normotensive, healthy animals (or patients), this conclusion would seem to be well

supported by the results. However, caution is warranted in interpreting the results of this study. How frequently do we seek to lower blood pressure in normotensive, healthy patients? Under what conditions would we choose to do so?

Heart rate and blood pressure are determined by the balance of sympathetic and parasympathetic nerve activity. Hypertensive patients frequently have increased plasma norepinephrine levels and elevated heart rates[1]. The goal of treatment is not to drop blood pressure or heart rate in all individuals by the same amount. Rather, the goal is to bring the blood pressure of all individuals back to the normal range. Thus, one might expect that a more aggressive intervention would be needed for a patient with a blood pressure of 160/95 than for one with a blood pressure of 140/85. As acetylcholine has potent anti-adrenergic effects, the level of vagal stimulation (via BRS or direct vagal stimulation) needed to lower blood pressure in a hypertensive subject will quite likely be lower than that required to drop the blood pressure of a healthy individual – or to decrease their atrial ERP. It has long been appreciated (since ~1920) that strong vagal stimulation facilitates induction of AF that can be sustained as long as the stimulus is applied[10]. In contrast, as noted by Linz and colleagues in the current report[9], several recent studies have demonstrated beneficial effects of low level vagal stimulation in preventing atrial electrical remodeling and limiting the inducibility of AF[11-13]. In a related study, Linz and colleagues have shown that acute RDN could slow ventricular rate during AF, but that it did not prevent AF-related electrical remodeling[14]. Given the critical role of Ca^{2+} overload in atrial electrical remodeling[15], the greater impact of low-level vagal stimulation vs. RDN on atrial electrical remodeling may be due to its effects on the activity of intrinsic cardiac neurons[12].

As noted in an elegant review by Dr. Matthew Levy in 1971[16], “The neural control of the heart is extremely complex, in large part because of the dual innervation. Complicated interactions between the parasympathetic and sympathetic centers in the central nervous system, and peripheral interactions between fibers of these two divisions also take place within the tissues of the heart itself. Hence, information concerning the activity of one division or the other in isolation is certainly incomplete and may indeed be misleading.” Although this review is more than 40 years old, its wise insights remain accurate today. Efforts to compare the effects of parasympathetic stimulation (BRS) and renal sympathetic denervation require caution, as the effects observed depend strongly on the basal tone of these systems. The responses detected in healthy subjects vs. in hypertensive ones with elevated circulating catecholamines are likely quite distinct.

In conclusion, although the current study by Linz et al.[9] is provocative, studies that seek to logically compare anti-hypertensive technologies on atrial physiology and risk of AF would be better performed in a chronic hypertensive experimental model than in acute studies on healthy animals.

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