Editorial

Arterial Denervation: Clinical Implications and Future Perspectives

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The autonomic innervation of the heart has been the focus of attention for a long time, aiming at a better understanding of its physiology and its adaptation to special conditions. More recently, while the interaction of the heart muscle with other organs has been closely examined and further understood, the sympathetic system has been recognized as a target for the treatment of several disorders, including arrhythmias, idiopathic pulmonary hypertension, and resistant arterial hypertension.[1-4] In the era of evidence-based medicine, cardiac denervation has been recognized as an even earlier sign, preceding motor signs in Parkinson's disease;[5] however, the role of heart innervation in several pathological conditions is still ambiguous.

The heart is innervated by vagal and sympathetic fibers. Atrial muscle is also innervated by vagal efferents, whereas the ventricular myocardium is only sparsely innervated by vagal efferents. Sympathetic efferent nerves are present throughout the atria and ventricles, including the conduction system of the heart. Cardiac function is altered by neural activation. Sympathetic stimulation increases heart rate (positive chronotropy), inotropy and conduction velocity (positive dromotropy), whereas parasympathetic stimulation of the heart has the opposite effects. Sympathetic and parasympathetic effects on heart function are mediated by beta-adrenoceptors and muscarinic receptors, respectively. Moreover, sympathetic adrenergic nerves travel along arteries and nerves and are found in the adventitia. Activation of vascular sympathetic nerves causes vasoconstriction of arteries and veins mediated by alpha-adrenoceptors.

As previously mentioned, the dysfunction of the sympathetic system may play a significant role in several cardiac disorders. However variations of the sympathetic system activity often coexist with some cardiac disorders, rather as an adaptation mechanism than as a causative relation. Prolonged ischemia that results in myocardial infarction is known to be associated with irreversible sympathetic nerve dysfunction. The extent of denervation exceeds the infarcted area following acute myocardial infarction, as a result of downstream denervation from irreversible injury of the sympathetic nerves traversing the area of infarction. Studies by Zipes et al have shown that denervated but viable myocardium adjacent to an area of infarction may be particularly arrhythmogenic, supporting the sympathetic model of arrhythmogenesis.[6]

The sympathetic nervous system over the years has been tested as a treatment option for several heart disorders. Even before the era of less invasive, and catheter-based denervation, left cardiac sympathetic denervation was tested for the treatment of congenital long-QT syndrome.[7] Current technology, with dedicated intra-

vascular catheters, has given a boost to the field of endovascular sympathetic system modification. New approaches involving the treatment of idiopathic pulmonary artery hypertension by means of pulmonary artery denervation are being developed with promising results.[1]

Renal denervation (radiofrequency ablation, chemical denervation or barodenervation) has been used successfully as a therapeutic strategy to treat hypertension, or to modify the renal sympathetic system, in a variety of experimental models and in adults.[3,4,8-11] In humans, radical surgical methods for thoracic, abdominal, and pelvic sympathetic denervation were successfully applied as early as the 1930s to lower blood pressure in patients with malignant hypertension, but were halted by the high complication rates. More recently, local delivery of vincristine for the denervation of the sympathetic nervous system of the renal artery via a dedicated delivery catheter was tested successfully in animals and in humans.[4,10]

The sympathetic nervous system of the heart exhibits elegant properties and balances between cost and benefit, and is implicated in various conditions. It is possible that denervation of the coronary arteries in patients with resistant angina, despite optimal medical therapy, may improve the symptoms and the prognosis. Preliminary data from our experimental laboratory showed for the first time that chemical denervation and also barodenervation are two approaches with promising results, as they seem to reduce the number of nerves in the coronary arteries. Moreover, *in vivo* measurement of the coronary flow reserve was increased after these interventions. In the clinical setting, one would expect to improve the flow in ischemic areas in specific populations.[12]

Arterial denervation seems to have several implications in cardiology. In the near future, several technological advances for arterial hypertension will be tested. However, clinical trials will be needed to investigate the efficacy of this new approach.

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