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EDITORIAL

Renal sympathetic denervation: a 'remote control' for atrial fibrillation therapy

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This editorial refers to 'Effect of renal sympathetic denervation on the progression of paroxysmal atrial fibrillation in canines with long-term intermittent atrial pacing' by Wang *et al.*, doi:10.1093/europace/euu212.

Pulmonary vein isolation is a commonly used ablation approach to treat patients with paroxysmal atrial fibrillation (AF). While short-term effects after a single procedure look promising, the picture is less optimistic in the long-term, with a 5-year arrhythmia-free survival rate of ~30% after a single procedure and <40% of patients are off antiarrhythmic drugs.[1,2] Autonomic influences are prominently involved in the pathophysiology of AF.[3] Changes in the autonomic tone have been observed prior to the onset of paroxysmal AF, and both sympathetic and parasympathetic influences may act in a pro-arrhythmic fashion leading to initiation of the arrhythmia.[4,5] Cardiac structures rich in autonomic nerves such as ganglionated plexi or the ligament of Marshall represent potential targets for focal ablation during pulmonary vein isolation.[6,7] Vagal innervation from these ganglionated plexi that reside at the left atrial–pulmonary vein junction may create a milieu for AF through induction of greater heterogeneity in refractoriness. Accordingly, ablation of ganglionated plexi may add efficacy in preventing AF relapses, if performed together with circumferential ostial ablation.[8,9]

Renal sympathetic denervation is a selective way to interventionally modulate systemic sympathetic tone and has effects on atrial electrophysiology.[10] There is limited experience in man of renal sympathetic denervation in addition to pulmonary vein isolation in patients with paroxysmal or persistent AF. Two studies were performed in patients with moderate-to-severe hypertension. In a recent meta-analysis of these two small randomized trials, the beneficial effects of additional renal sympathetic denervation was most evident in patients with persistent AF and severe arterial hypertension.[11]

In this issue of EP-Europace, Wang *et al.* (*editor – please enter reference to the article by Wang et al.*) publish an elegant and comprehensive animal study trying to mimic paroxysmal AF. They detected an interesting effect of renal sympathetic denervation on atrial mechanical function, electrophysiology, and structure. In animals subjected to intermittent rapid atrial pacing, they found that animals who received bilateral renal sympathetic denervation (at the time of pacing initiation) had lesser and shorter episodes of AF than those who were not treated by denervation. The characteristic, untoward electrical consequences of rapid pacing that mimic electrophysiological changes in human AF (a shortened atrial effective refractory period and increased refractoriness heterogeneity) were largely prevented by renal sympathetic denervation. The group of animals that received denervation had, in addition to the beneficial effects on electrophysiological alterations, less remodelling in terms of left atrial size, fibrosis, connexin distribution, and ultrastructure. In summary, the authors documented a whole series of evidence that renal sympathetic denervation was able to prevent the development of a characteristic milieu for AF. If reproduced in man this could mean a significant advance in the treatment of AF.

The authors intended to mimic paroxysmal AF using their model of intermittent rapid atrial pacing. To that respect some criticism should be raised. In general, the canine rapid pacing model is well established to mimic human AF. It is commonly used to induce persistent AF in animals. The protocol applied to induce 'paroxysmal' AF in the present study is novel in this specific fashion, but it only marginally mimics human paroxysmal AF. While in human AF, pulmonary vein activity is most central, in canine models of rapid pacing one does not commonly observe this. Intermittent rapid pacing might – speculatively – lead to only a smaller amount of atrial remodelling that permanent pacing but not to a specific 'paroxysmal' substrate. Consequently, the general comparison may not necessarily be valid, but such methodological limitations are inevitable with most experimental work. It is important to keep in mind that the extrapolation needs to be done carefully.

After the publication of the results of SYMPLICITY-3 renal sympathetic denervation is currently being viewed critically for clinical application in patients with resistant hypertension.[12] Experimental studies such as the present one support its use and further scientific evaluation. Renal sympathetic denervation may potentially have beneficial implications in conditions other than hypertension that are modulated by the autonomic system such as AF. It will be interesting to learn from future human studies if renal sympathetic denervation may in fact help maintain sinus rhythm in patients with AF. With all limitations, the data from the present study look promising and give good reasons to pursue research in that direction.

The opinions expressed in this article are not necessarily those of the Editors of *Europace* or of the European Society of Cardiology.

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