



Revista Portuguesa de  
**Cardiologia**  
Portuguese Journal of **Cardiology**  
[www.revportcardiol.org](http://www.revportcardiol.org)



## EDITORIAL COMMENT

## Renal denervation in heart failure: Modulating the sympathetic nervous system



## Desnervação renal na insuficiência cardíaca: modular o sistema nervoso simpático

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Available online 13 December 2016

Heart failure (HF) is frequently the end-stage of many cardiovascular diseases and remains a major cause of morbidity and mortality, with 26 million patients now affected worldwide.<sup>1</sup> Its prevalence is around 1-2% in developed countries, rising to  $\geq 10\%$  among people over 70 years of age. The terminology of HF has recently been redefined and patients with an ejection fraction (EF) of 40-49% (the so-called 'gray area') now being classified as having 'heart failure with mid-range ejection fraction', as opposed to 'HF with reduced EF' ( $<40\%$ ) and 'HF with preserved EF' (EF  $\geq 50\%$ ).<sup>2</sup>

The pathophysiology of HF is highly complex and involves the activation of compensatory mechanisms including the renin-angiotensin-aldosterone system, the sympathetic nervous system (SNS) and arginine vasopressin release, probably as a consequence of hemodynamic changes induced by a dysfunctional myocardium.<sup>3</sup> Activation of the SNS leads to excessive release and decreased uptake of norepinephrine. This autonomic hyperactivity has long been known to be directly related to the worsening of HF, by inducing myocyte enlargement and interstitial growth and remodeling, leading to increased myocardial mass and chamber dilatation.<sup>4</sup> The SNS thus became a therapeutic target, and there is evidence that continuing pharmacological beta-blockade has favorable prognostic implications in both ischemic and non-ischemic cardiomyopathies.<sup>5</sup>

Renal denervation (RDN) is a percutaneous procedure which aims to achieve selective disruption of the sympathetic nerve endings in the renal arterial wall. It is currently under investigation as a promising technique for the treatment not only of hypertension (with varying treatment effects) but also of other clinical entities associated with an increased sympathetic drive such as advanced HF, sleep apnea and life-threatening cardiac arrhythmias.<sup>6</sup> Two pilot studies have been published that aimed to prove the effectiveness of RDN in patients with HF. The REACH-Pilot was a first-in-man study which assessed the safety of RDN in seven patients with symptomatic chronic systolic HF (New York Heart Association [NYHA] class III or IV), EF of  $45 \pm 15\%$  and without hypertension. At six months all patients were symptomatically improved, there was an increase in the six-minute walk distance ( $\Delta = 27.1 \pm 9.7$  m,  $p = 0.03$ ) and diuretics were reduced or stopped in four patients ( $p = 0.046$ ). No significant differences were observed in EF. This study had clear limitations (population and design, among others) and was underpowered for several parameters, but established the need for additional evidence.<sup>7</sup> Chen et al. conducted a randomized prospective pilot study which included 60 patients (30 in the RDN group and 30 in the optimal medical therapy group) in NYHA II-IV with EF  $\leq 40\%$ . Renal denervation was performed with a saline irrigated catheter. At six-month follow-up EF (from  $31.1 \pm 5.7\%$  to  $41.9 \pm 7.9\%$ ,  $p < 0.001$ ), the six-minute walk distance (from  $285.5 \pm 84.3$  m to  $374.9 \pm 91.9$  m,  $p = 0.043$ ), NYHA classification ( $p < 0.001$ ) and NT-pro-BNP levels ( $p < 0.001$ ) were significantly improved in the RDN group. There were no safety concerns and there was no difference in blood pressure between the groups.<sup>8</sup> Again,

DOI of original article: <http://dx.doi.org/10.1016/j.repc.2016.07.007>

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<http://dx.doi.org/10.1016/j.repc.2016.11.003>

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this study had several limitations, such as sample size, and data from two randomized trials which are currently recruiting are eagerly awaited.<sup>9,10</sup>

As the relationship between HF and the SNS is robust and the available clinical data is promising, evaluation of the effects of RDN in patients with reduced EF is appropriate. In this issue of the *Journal*, Gao et al.<sup>11</sup> present the results of a prospective, open, single-arm study which included fourteen patients with an EF below 45% (eight with ischemic cardiomyopathy), in class NYHA III or IV and on optimized medical therapy. Patients with severe renal failure (glomerular filtration rate below 30 ml/min/1.73 m<sup>2</sup>), type 1 diabetes or hypotension or in the acute phase of myocardial infarction or cerebrovascular accident were excluded. RDN was performed using a radiofrequency catheter with temperature control and 4-6 ablation points were delivered to each artery. At six-month follow-up improvements were observed in the six-minute walk distance (from 152.9±38.0 m to 334.3±94.4 m, p<0.001), EF (from 36±4.1% to 43.8±7.9%, p<0.003), NYHA functional class (p<0.001) and BNP levels (p<0.008). The recovery in EF was more significant in the group of hypertensive patients (34.5±4.3% to 52.3±6.1%, p<0.005) than in the non-hypertensive group (36.6±3.8% to 41±6.2%, p=0.07), a fact that the authors attribute to the blood-pressure lowering effect of RDN and suggesting a more beneficial effect of RDN in HF due to hypertensive disease. There were no safety issues. These results are different from those of the REACH-Pilot study in terms of change in EF, but are comparable to the results published by Chen et al., indicating a favorable effect of RDN in HF patients. However, several limitations must be taken into consideration such as the small sample size, the absence of a control group and non-randomization.

To summarize, this article highlights the role of RDN in modulating autonomic tone in specific conditions, including HF, and emphasizes the importance of further investigation in this area. The authors should be encouraged to continue their research on RDN in various clinical settings, and perhaps in the future some light will be shed on RDN's 'autonomic' significance.

## Conflicts of interest

The author has no conflicts of interest to declare.

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