The molecular basis for the neutral effect of renal denervation in patients with chronic heart failure not responding to cardiac resynchronisation therapy – a perspective

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Adv Interv Cardiol 2019; 15, 4 (58): 503–504
DOI: https://doi.org/10.5114/aic.2019.90231

In their elegant study, Drożdż *et al.* reported that renal denervation (RDN) in patients with chronic heart failure (HF) not responding to cardiac resynchronisation therapy (CRT) did not provoke any adverse effects and did not change exercise capacity and hemodynamic parameters [1]. Myocardial systolic functional impairment is related to compensatory neurohumoral overactivity to preserve cardiac output when heart function is deteriorating, a scenario characterised by increased cardiac sympathetic drive. Increased cardiac sympathetic nervous system (SNS) activity as a consequence of excitatory inputs has been described including alterations in peripheral baro- and chemo-receptor reflex responses, higher secretion of the neurotransmitters epinephrine (E) and norepinephrine (NE), as well as renin-angiotensin-aldosterone system (RAAS) activation.

SNS overactivity is characterised by augmented plasma NE and E levels, raised sympathetic discharge of the central nervous system, and enhanced NE spillover, which is increased by 50-fold in HF patients compared to healthy individuals with vigorous exercise. Patients suffering from end-stage systolic HF have reduced postsynaptic β-adrenoreceptor (AR) density, because of the exhaustion of cardiac SNS neuronal NE stores and decreased NE presynaptic reuptake secondary to NE-transporter down-regulation. After release in the heart around 70–90% of the NE released into the synaptic cleft re-enters the presynaptic nerve ending through the NE reuptake transporter (NET or uptake-1) in an energy-consuming process. However, the excess of NE in the synaptic cleft leads to toxic effects and cardiomyocyte apoptosis, as observed in the final stages of HF [2].

The SNS positron-emission-tomography (PET) imaging ^{11}C-meta-hydroxyephedrine (^{11}C-HED) in the clinical and experimental setting principally targets postsynaptic adrenergic receptor density and presynaptic neural activity (e.g., uptake-1 and metabolism). Thus far, (^{11}C-HED) has been the most significant PET radiotracer used as an NE analogue. It has a high affinity for uptake-1 without being metabolised by monoamine oxidases or catechol-O-methyl-transferase. Reduced (^{11}C-HED) uptake has been associated with autonomic dysfunction and low cardiac output in patients with HF, and it has been suggested to be a negative prognostic marker in this cohort [3].

CRT has demonstrated significant modulation of sympathovagal balance, reduced circulating NE and brain natriuretic peptide levels, and RAAS inhibition. Martignani *et al.* revealed a higher level of left ventricular (^{11}C-HED) uptake assessed by PET scans both at baseline and after resynchronisation in the CRT responders compared to non-responders, indicative of the improvement of the cardiac sympathetic nerve activity in the responders [4].

In HF patients who are non-responders to CRT, cardiac sympathetic activation is substantially deranged, thereby potentially compromising the beneficial effects of RDN mediated via afferent sensory signalling.

Conflict of interest

MGK, RC and VBM declare no conflict of interest. MPS is supported by an NHMRC Research Fellowship and has

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Received: 14.09.2019, **accepted:** 24.09.2019.

received consulting fees, and/or travel and research support from Medtronic, Abbott, Novartis, Servier, Pfizer, and Boehringer-Ingelheim.

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