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Renal denervation: expanding the indication

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Introduction

Since the introduction of the Ardian renal denervation system in California in 2008, the uptake of the technology has been overwhelming, despite a relatively scarce amount of evidence.

The benefit of renal denervation, however, may not be restricted to blood pressure lowering alone since several cardiovascular diseases are characterised by excessive central sympathetic drive[1]. An increasing body of evidence indicates that heart failure, diabetes and hyperinsulinaemia, chronic kidney disease, arrhythmias, and sleep apnoea syndrome are associated with increased sympathetic activity[2]. As renal denervation has been shown to reduce total body and muscle sympathetic nerve activity by targeting the afferent renal nerves, the expansion of the treatment indication seems intuitive.

Heart failure

Sympathetic overactivity has been documented in heart failure and appeared to be directly correlated to NYHA class[3]. In the kidney, the elevated sympathetic tone stimulates alpha- and beta-adrenergic receptors thereby increasing renin release, leading to retention of sodium and renal vasoconstriction explaining the basics of venous congestion and diuretic resistance in chronic heart failure. In order to maintain vital organ perfusion in heart failure, the body makes several neurohumoral adaptations such as activation of the RAAS system and the sympathetic nervous system in response to the low-output state[4,5]. Unfortunately, the neurohumoral activation overwhelms the vasodilatory and natriuretic effect of natriuretic peptides, nitric oxide, prostaglandins and bradykinin[6,7]. The subsequent increase in pulmonary congestion, peripheral oedema, peripheral resistance and left ventricular afterload further decreases myocardial function, catecholamine-stimulated contractility and the successive increase in heart rate can further worsen the prognosis. More specifically the sympathetic nervous system stimulates norepinephrine release and norepinephrine plasma concentrations are directly correlated with the severity of cardiac dysfunction and inversely with survival[8]. Recently, two pivotal studies demonstrated the potential benefit of sympathetic renal denervation in systolic heart failure. The REACH pilot study showed that the procedure was safe and did not lead to a significant blood pressure reduction and subsequent hypotensive or syncopal events in a population of seven patients with a mean blood pressure of 112/65 mmHg[9]. Instead, a significant increase in six-minute walk distance was noticed (+27.1±9.7 m, p=0.03). Despite these promising findings it should be noted that, although patients were requested to be in NYHA Class III of IV, mean ejection fraction was ~45%. In a recently presented randomised study by Taborsky and colleagues, renal sympathetic denervation in patients with more advanced heart failure (mean ejection fraction 25%) resulted in significant improvements over baseline in left ventricular ejection fraction, and left ventricular end-diastolic and end-systolic volumes, as well as NT-proBNP. No change in these outcome parameters was noted in patients receiving only optimal medical therapy[10]. More and larger studies are needed to confirm the preliminary findings and to see whether these structural changes will also result in a reduction of clinical adverse events.

Diabetes

In a large Spanish ambulatory blood pressure monitoring registry, the incidence of diabetes in patients with resistant hypertension proved to be over 35%[11]. While elevated sympathetic nerve activity had already been linked to hypertension earlier on, its additional detrimental effects on glucose metabolism proved to be irrespective of the presence of hypertension[12]. In line with its contribution to insulin resistance, elevated sympathetic tone has been associated

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with central obesity and the risk of developing diabetes mellitus[13]. Experimental studies demonstrated that cellular glucose uptake significantly decreased when local noradrenaline levels increased with decreased blood flow as a result[14]. A direct link appeared to exist between insulin resistance and the number of open capillaries[15].

The hypothesis that reducing the sympathetic tone may result in an improvement of glucose metabolism was already tested in 1999 when Yacubu-Madus and colleagues demonstrated that, in an animal model of type 2 diabetes, the antihypertensive agent moxonidine induced a beneficial effect on glucose metabolism and renal protein excretion[16]. These findings strengthen our belief that renal sympathetic denervation can accomplish these effects by a potential decrease in vascular alpha-adrenergic tone, leading to skeletal muscle vasodilatation, an inhibition of the renin-angiotensin system, improved glucose transport on a cellular level, an increased sensitivity to the non-esterified fatty-acid-lowering effects of insulin and a change in glucose transporters and glucagon secretion[17]. Preliminary data indicate that, aside from better blood pressure control, renal sympathetic denervation may also be associated with a reduction in fasting glucose and insulin levels. This was first tested in a substudy (n=50 patients) of the Symplicity HTN-I study, in which the incidence of diabetes was 40% (n=20)[18]. At three months, fasting glucose was reduced significantly by 10 mg/dl in the treatment arm versus no significant changes in the control group (p=0.039). A significant reduction was also noted in insulin levels and C-peptide. Furthermore, the HOMA (an index of insulin resistance) significantly decreased, indicating that some patients improved their insulin sensitivity after the procedure. Of interest, these changes were not related to the degree of blood pressure lowering. A smaller study (n=10; 40% diabetics) by Witkowski and colleagues confirmed these findings and showed that renal denervation is capable of reducing glucose and HbA1C levels during glucose tolerance testing with, however, no effect on fasting glucose levels[19]. These preliminary findings are promising but need to be tested in larger studies which are currently ongoing. Furthermore, is has to be seen whether these findings can be extended to non-resistant hypertensive diabetic patients.

Chronic kidney disease

Hypertension is present in the vast majority of patients with chronic kidney disease and has been recognised as the number one cause in the progressive deterioration of renal function and subsequent adverse cardiovascular events[20]. Even in end-stage kidney disease the unaltered elevated sympathetic drive is remarkable. More specifically, failing kidneys are able to cause persistent afferent signalling. Bilateral nephrectomy in end-stage renal disease has been shown to reduce blood pressure and normalise muscle sympathetic nerve activity[21]. Along these lines, also in patients with chronic kidney disease, increased noradrenaline plasma levels have been linked to higher rates of adverse cardiovascular events.

The effect of renal denervation in patients with moderate to severe chronic kidney disease (eGFR <45 ml/min per 1.73 m^2) has been tested in a small pilot study[22]. Fifteen patients with resistant hypertension and stage 3-4 chronic kidney disease (mean eGFR, 31 ml/min per 1.73 m^2) underwent renal denervation. In six patients, CO_2 angiography was used to minimise exposure to contrast agents. Estimated GFR remained unchanged after the procedure, irrespective of the use of CO_2 angiography. After renal denervation office systolic and diastolic blood pressure at 1, 3, 6, and 12 months were significantly reduced by 23/21, 22/21, 23/21, and 23/22 mmHg, respectively. Despite the limited sample size, the study suggests a favourable short-term safety profile and blood pressure lowering effects of catheter-based renal denervation in patients with stage 3-4 chronic kidney disease and resistant hypertension. In a second, recently published pivotal open-label single-arm study, 12 patients with uncontrolled hypertension and end-stage renal disease on haemodialysis underwent renal sympathetic denervation[23]. Although the overall blood pressure lowering effect was significant, three patients had atrophic renal arteries and were not treated. The study demonstrated for the first time that renal sympathetic denervation can be a potential therapeutic option for patients with end-stage kidney disease; however, several issues need to be resolved before a more widespread adoption of this technique in this specific setting can take place. In the pivotal study by Schlaich and colleagues, a rapid increase in temperature was noted in several cases when radiofrequency energy was applied using the Symplicity device resulting in an aborted treatment. According to the authors, this could be due to a lack of cooling consequent to reduced renal blood flow in these patients. Subsequently, the suboptimal anatomy (including higher rates of renovascular atherosclerosis and smaller diameters) in a vast proportion of patients cannot be neglected. Finally, the continuing elevated afferent activity of the remnant kidneys in combination with the detrimental effect of immunosuppressants in patients following kidney transplantation troubles the evaluation of the beneficial effect of renal sympathetic denervation in these patients.

Arrhythmias

Sympathetic nerve activity during physiologic stress has been found to have profound influences on the electrical and contractile functions of the heart. Little is still known about the temporal relationship between instantaneous autonomic nerve activity and arrhythmias[24]. Through complex feedback mechanisms the cardiac neuroaxis controls the adrenergic and cholinergic efferent neurons and ganglia in the heart. Many previous studies addressed the consequences of alterations in the cardiac sympathetic tone in arrhythmogenesis[25-28].

However, mainstream therapies for rhythm control of atrial fibrillation, such as anti-arrhythmic drugs and catheter ablation, although successful in suppressing symptoms, are not mechanism-specific and can have important side effects. It is intriguing to investigate further the potential of renal sympathetic denervation in altering the cardiac autonomous neuroaxis and potentially reducing the occurrence of tachyarrhythmias. Scrutinising the electrophysiological consequences of renal sympathetic denervation, the results of a large German registry demonstrated a significant drop in heart rate following the procedure. At six-month follow-up mean heart rate dropped 2.1±1.1 bpm (p=0.046) with a higher drop in heart rate in those with a baseline heart rate of ≥71 bpm (9.0±8.6 bpm; p<0.0001). Patients with a baseline heart rate of

<60 bpm showed a slight increase of 2.7±8.4 bpm (p=0.035). Additionally, the authors noted an increase in PR interval of 10.3±2.5 ms (p<0.0001) with a newly diagnosed first-degree AV block in 17% of the population[29]. No higher-degree AV blocks or new onset atrial fibrillation were documented. Whether the prolongation in the AV conduction is simply a benign marker of reduced sympathetic activity or the precursor of long-term adverse events remains to be studied. A subsequent animal study in 12 pigs demonstrated a drop in ventricular rate during atrial fibrillation episodes of 24% and a shorter duration of the atrial fibrillation episodes as compared to a sham procedure. In contrast, atrial fibrillation-induced atrial electrical remodelling, inducibility, and atrial fibrillation cycle length remained unchanged[30]. A second study performed by the same group in a model of sleep apnoea demonstrated a promising antiarrhythmic effect of renal denervation by reducing negative-tracheal pressure-induced atrial effective refractory period shortening and an inhibiting post-apnoeic blood-pressure rise associated with obstructive events[31].

In a recently published small randomised comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension, the combined treatment was shown to be associated with a significant reduction in atrial fibrillation recurrence (69% vs. 29% at one year)[32].

Sleep apnoea

The prevalence of obstructive sleep apnoea syndrome (OSAS) (≥15 episodes of apnoea-hypopnoea/hour) in patients with resistant hypertension is around 65-70%[33]. The pathogenesis of hypertension in OSAS seems to result from an increased upper airway resistance (potentially caused by peripharyngeal fluid accumulation) and intermittent state of hypoxia, resulting in increased vasoconstriction, vascular resistance and cardiac output along with fluid retention. Not surprisingly, elevated aldosterone levels have been found in patients with OSAS and resistant hypertension[34].

The first experience with renal sympathetic denervation in OSAS (n=10) was published in 2011[19]. A trend was noted towards a decrease in the average apnoea/hypopnoea index at six months (a reduction from 16.3 to 4.5 events per hour; p=0.059) and 8 out of 10 patients had an improvement in sleep apnoea severity. Also the oxygen desaturation index and the median Epworth sleepiness scale score were significantly lowered at six months of follow-up. Furthermore, the authors speculated on a trend towards a more pronounced benefit in those with more severe forms of OSAS (apnoea/hypopnea index >30). These findings from this single-arm open-label study are promising but should be interpreted with caution. Larger studies to confirm the role of renal denervation in patients with OSAS are ongoing.

Glimpse into the future

The above-mentioned preliminary results of studies investigating the potential therapeutic benefit of renal sympathetic denervation for novel indications are promising. However, the studies are small and the results should not be over-interpreted. Virtually all of the above-mentioned studies were performed using the same device, whilst at present there are six CE-marked devices available. However, one can speculate whether similar effects could be achieved by using differently acting devices. While the concept of direct baroreceptor stimulation had already been reported several years ago, newer and alternative options such as those using a transurethral approach are currently being explored. Similarly, we are one step further towards the potential of treating pulmonary artery hypertension with pulmonary artery denervation, a concept of whose feasibility has recently been investigated in an experimental model[35].

Conflict of interest statement

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