European Society of Hypertension Scientific Newsletter:
Update on Hypertension Management
2012; 13: No. 52

RENAL DENERVATION: AN INTERVENTIONAL THERAPY OF TREATMENT RESISTANT HYPERTENSION

Roland E. Schmieder[1], Josep Redon[2], Costas Tsioufis[3]
[1]University Hospital Erlangen, Nephrology and Hypertension, Erlangen, Germany
[2]University of Valencia, Internal Medicine, Hypertension Unit, Valencia, Spain
[3]University of Athens, First Cardiology Clinic, Hippokratio Hospital, Athens, Greece

Current status of uncontrolled hypertension

Arterial hypertension is the most important risk factor for cardiovascular morbidity and mortality worldwide. It is estimated that around 1 billion individuals currently suffer from elevated blood pressure (BP), and this figure is predicted to rise to 1.5 billion by 2025 [1]. There is a linear relationship between BP and cardiovascular risk, accounting for 1.97 million deaths due to coronary heart disease, and to 1.24 million deaths due to stroke, in Europe each year. If BP is effectively reduced, early organ damage may be prevented or at least attenuated. Most importantly, even in the later stages, even modest BP reduction is accompanied by a significant reduction of the overall cardiovascular morbidity and mortality, irrespective of starting BP levels [2].

Despite the availability of various highly-effective pharmacological agents, adequate BP control (at least < 140/90 mm Hg) is not achieved in a large number of subjects. So-called 'treatment resistant hypertension' or 'therapy resistant hypertension' is defined as BP that remains above the treatment goal despite the concurrent use of at least three antihypertensive agents in adequate doses from different drug classes, including one diuretic [3–5]. The exact prevalence of resistant hypertension is difficult to determine, but depending on the population and the hypertension centre considered, it ranges from 5% to 30% [3–7].

Several algorithms for the management of treatment-resistant hypertension have been put forward. Key elements are: reinforcement of lifestyle modification, re-evaluation and exclusion of secondary causes of hypertension, avoidance of drugs that may potentially increase BP levels along with initiation of specific attempts to improve adherence to drug therapy, and optimal drug combination [3–5]. As has been shown recently, pseudoresistance (office BP > 140/90 mm Hg with normal 24-hour ambulatory BP readings) is found to chararacterise as many as one-third of those initially diagnosed as having resistant hypertension [6].

Efforts to overcome resistance to pharmacotherapy have raised interest in the role of the sympathetic nervous system in hypertensive disease. Accordingly, it has been shown that there is a sympathetic overdrive in hypertension depending mainly on its stages and clinical forms including resistant hypertension [8]. In recent years, a novel catheter-based approach using radiofrequency energy has been developed to selectively target and disrupt the renal nerves. This approach entered clinical practice after being validated in clinical trials for the treatment of resistant hypertensive patients.

Rationale of renal denervation

Post ganglionic efferent sympathetic nerve fibres are localised in the adventitia of the renal arteries like a dense network of postganglionic neurones innervating the vasculature, the tubular cells and the juxtaglomerular apparatus. Thereby, central sympathetic activation results via the renal efferent sympathetic nerves in volume retention by tubular sodium reabsorption, reduced renal blood flow, vasoconstriction and release of renin from the juxtaglomerular apparatus [9]. Indeed, in patients with hypertension, noradrenaline spillover, a measure of efferent renal sympathetic activity, has been found to be increased in parallel with an increased sympathetic outflow to the heart [10–12]. In addition to the efferent sympathetic nerves, there are afferent sensory nerves along the renal arteries, originating mostly from the renal pelvic walls, that respond to stretch, renal ischaemia, hypoxia or other injury by increasing renal afferent activity [9, 13]. This increased renal sensory afferent signalling directly influences sympathetic outflow and is not restricted to the kidneys but also affects other highly innervated organs such as the heart, renal gland and peripheral blood vessels [13].

Several experimental studies have clearly documented that bilateral renal denervation prevented the rise in BP and thereby hypertensive disease. With the background of this experimental data, in the 1920s and 1930s, splanchnicectomy and radical sympathetictomy with radical surgery techniques were used to treat severely hypertensive patients, at a time when medical therapy consisted of low salt and diet only. In a large series of surgical interventions in more than 1,000 hypertensive patients, a significant reduction in BP was achieved accompanied by a decrease of target organ damage in retinal arteries, cardiac and renal impairments [14]. Not surprisingly, periprocedural complication rates were high, and such surgical interventions were abolished with the advent of effective pharmacological agents in the 1950s. Now, renal ablation of the sympathetic nerves has become available as an interventional procedure offering an innovative approach to treat arterial hypertension in those patients whose BP could not be controlled otherwise.

Catheter-based renal denervation

Procedural methodology

In a minimally invasive percutaneous approach, the specially designed radiofrequency ablation catheter engages the ostium of the renal artery and the tip is positioned proximal to the bifurcation. Before initiation of the renal denervation, patients are preferably given intravenous analgesic and anxiolytic/sedative medications to decrease the pain during the radiofrequency delivery, ensuring comfort. The site of initial ablation is chosen, the impedance as well as the temperature and resistance are measured, and radiofrequency energy is delivered according to the pre-specified protocol. Then the catheter is withdrawn proximally and the remaining successive discrete ablations (4–8 totally) separated both longitudinally and rotationally within the artery are applied in order to achieve circumferential nerve ablation. The ablation is performed in a similar fashion to both renal arteries, and when the procedure is completed the catheter is removed, with the time from the first to the last radiofrequency ablation being typically 40––60 minutes. Any signs of renal artery abnormalities should be inspected after non-ionic contrast injection. Minor irregularities at the treatment sites, due mainly to intimal oedema and spasm, are regularly dissolved by the end of the procedure without any additional action by the operators being required. Finally, the sheath is removed according to the interventional centre's standard of care. After the procedure, the patient is transferred to a recovery unit for monitoring until discharge after 24 hours. Appropriate hydration for intravascular volume substitution prior to and post renal denervation is recommended. This minimally invasive, non-surgical percutaneous procedure should be carried out in highly experienced hospital centres that have been specifically trained for this procedure and have previously performed other percutaneous interventional procedures such as angioplasty and stenting of renal or coronary arteries [15].

Clinical studies

Two major clinical studies on catheter-based renal sympathetic denervation in resistant hypertension, Simplicity HTN-1 with extended follow-up and Simplicity HTN-2, have been reported [16–18]. The first proof of concept study included 50 patients with severe treatment-resistant hypertension (office systolic BP ≥ 160 mm Hg) with mean office BP of 177/101 mm Hg who were on an average of 4.5 antihypertensive drugs. Office BP was reduced by –14/–10, –21/–10, –22/–11, –24/–11, and –24/–17 mm Hg at one, three, six, nine, and 12 months respectively [16]. Ten out of 49 patients who underwent renal denervation had drug reduction prior to 6 months follow-up, but only three out of 51 controls ($p = 0.04$). In an extended long-term follow-up over 24 months, 153 subjects were followed up in a non-randomised manner. Office BP fell from 176/92 mm Hg (treated with an average of 5.1 antihypertensive medications) by 20/10, 24/11, 25/11, 23/11, 26/11 and 32/15 mm Hg at one, three, six, 12, 18 and 24 months, respectively [17]. These findings suggest that BP reduction is sustained after renal denervation, at least up to two years. Thus, at least throughout the duration of this follow-

up period, no signs of re-inervation could be detected. Interestingly, as part of the proof of concept study, renal noradrenalin spillover, a measure of sympathetic activity to the kidneys, was found to be reduced by 47%. In summary, this first in man study indicated that renal denervation is an effective treatment strategy in severe therapy-resistant hypertensive patients otherwise uncontrolled [16, 17].

The Simplicity HTN-2 study was a multicentre prospective randomised clinical trial, again including patients with treatment-resistant hypertension (office BP > 160 mm Hg, or ≥ 150 mm Hg in patients with type 2 diabetes) [18]. Patients were either randomly assigned to an immediate renal denervation or to a control group with a maintenance of the antihypertensive medication without any change. Systolic BP after six months, the primary end-point, decreased by 32/12 mm Hg (baseline 178/96 mm Hg, $p < 0.001$) in the group with renal denervation (n = 52), whereas no change in the control group (n = 54) occurred. Differences in office BP between the two groups at six months were 33/11 mm Hg ($p < 0.001$), and when censored for increase in medication, the difference was 31/11 mm Hg ($p < 0.001$). Home BP recording confirmed the observed office BP changes, with a reduction in home BP by 20/12 mm Hg after renal denervation and a rise of 2/0 mm Hg in the control group ($p < 0.001$). Control rate of office BP defined as systolic BP < 140 mm Hg was obtained in 39% of patients and < 160 mm Hg in 82%, respectively. Interestingly, 20% of the patients who underwent renal denervation had drug reduction, compared to only 6% in the control group ($p = 0.04$).

The safety of catheter-based renal denervation has been carefully monitored [16–18]. In the Simplicity HTN-1 study, four acute procedure complications (three groin pseudoaneurysms and one renal artery dissection prior to application of radiofrequency energy) were managed without long term consequences. In one patient, an existing low-grade stenosis showed progression (with successful stenting), but no energy was delivered to the area of the stenosis. In the Simplicity HTN-2 study, periprocedural adverse events occurred: one femoral artery pseudoaneurysm, one post-procedural drop in BP, one urinary tract infection, one extended hospital admission for assessment of paraesthesis, and one case of back pain. In both Simplicity studies, renal function, irrespective of whether assessed by serum creatinine, estimated glomerular filtration rate or cystatin C levels, was unchanged. In both studies, six months renal imaging did not identify the development of renal artery stenosis in the areas where radio-frequency energy had been applied. This clinical safety data accords with experimental data that also has not shown any development of renal artery stenosis after radiofrequency energy delivery.

Eligibility criteria

First of all, the patients should be selected for catheter-based renal denervation only in hypertension excellence centres such as ESH Excellence Centres. 24-hour ambulatory blood pressure monitoring is essential to confirm treatment resistance, and specific attention should be paid to adherence to drug therapy, exclusion of secondary causes (including drug-induced hypertension), reinforcement of lifestyle changes, and optimisation of drug therapy (specific care to underdosed diuretic medication).

If treatment-resistant hypertension is confirmed, patients with systolic office BP ≥ 160 mm Hg (≥ 150 mm Hg in type 2 diabetes) despite treatment with ≥ 3 antihypertensive drugs of different types in adequate doses (including one diuretic) are considered to be candidates for renal denervation. The following exclusion criteria should be respected in order to safely perform renal denervation: previous renal artery interventions (balloon angioplasty or stenting), evidence of renal artery stenosis (> 50 %), the presence of multiple main renal arteries in the kidneys or main renal arteries of less than 4 mm in diameter or less than 20 mm in length, and estimated glomerular filtration rate < 45 ml/min/1.73 m^2. Furthermore, patients should be in a clinically stable condition (renal denervation is not an emergency treatment), thus ruling out patients with recent myocardial infarction, unstable angina pectoris, or a cerebrovascular accident within the last 3–6 months.

Controversy exists as to whether the use of aldosterone antagonists is a prerequisite for eligibility. BP reduction up to 25 mm Hg systolic has been reported with aldosterone antagonists, but not all patients have such a response. In the first double blind randomised trial, the fall in BP with spironolactone was rather modest and long-term safety remains a matter of concern [19]. Moreover, patients with treatment-resistant hypertension have been exposed to a variety of antihypertensive medications and many of these patients do not tolerate some drugs. The challenge of the hypertension specialist is to diagnose true drug intolerance (e.g. by re-exposition to the intolerant drug), because only in such a case does renal denervation appear to be further justified.

Perspective

Due to the fact that renal denervation leads to a significant reduction of the central sympathetic activity to all organs, this method may have beneficial effects also in conditions with increased central sympathetic activity. Pilot studies and small clinical studies have shown that renal denervation preserves cardiorespiratory response to exercise (with significant BP reduction and a maintained heart rate response), improves insulin sensitivity and apnoea/hypopnoea index in obstructive sleep apnoea, whereas clinical trials are currently being conducted to analyse the use of renal denervation in patients with chronic renal and heart failure. Conversely, several needs remain to be met, such as immediate evaluation of successful renal denervation, long-term efficacy, predictors of BP response to the procedure, and whether cardiovascular end-points are prevented and mortality reduced.-Experimental studies with other techniques (e.g. local delivery of neurotoxic drugs, cryocoagulation, ultrasound induced denervation and other types of radiofrequency catheters) are currently being undertaken.

Conclusions

Percutaneous catheter-based transluminal renal sympathetic denervation by delivery of radiofrequency energy is emerging as a viable and safe approach to achieve BP reduction in patients with resistant hypertension. Within the last few years, the innovative method of renal denervation has entered clinical practice and should currently be used in patients with treatment-resistant hypertension who fulfil the above-reported established criteria, and after careful selection in hypertension excellence centres, such as the ESH Excellence Centres. Finally, renal denervation should be performed in very experienced hospital centres by experienced interventionalists who have been trained in this specific intervention, and who are qualified to manage potential complications such as dissection of the renal artery.

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