Clinical experience with renal denervation for proven resistant hypertension

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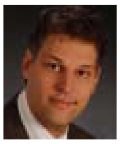

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Introduction

Arterial hypertension represents a major risk factor for cardiovascular morbidity. The incidence of arterial hypertension in Europe is about 45%, although the number of unreported cases is thought to be even higher.[1] Despite optimal medical treatment, 5–15% of patients have therapy resistant arterial hypertension.[2] Hypertension is classified as resistant if there is an insufficient reduction in systolic and diastolic blood pressure, despite the intake of at least three antihypertensive drugs of different classes (including a diuretic), at maximum permissible doses alongside lifestyle changes.[3,4] Importantly, secondary hypertension must be excluded.

The persistence of hypertension is partly regulated by the renal sympathetic nervous system.[5,6] Renal sympathetic efferent and afferent nerves (Th–10L1) within and surrounding the wall of the renal arteries are decisive for arterial hypertension.[7-10] The afferent sympathetic system is activated by rising adenosine levels and affects regulation of the neuro-humoral axis by the central nervous system. In contrast, renin release, juxtaglomerular function and renal blood flow are regulated by the efferent sympathetic nervous system. In addition, sympathetic activity modulates glucose metabolism and insulin sensitivity.[11] Modulation of the sympathetic system has been examined using a radical surgical method involving thoracic, abdominal and pelvic sympathetic nerve denervation in a trial of 50 patients. Although successful in lowering blood pressure, this method was associated with high peri-operative morbidity, vertiginous, and bowel, bladder and erectile dysfunction.[12]

Percutaneous renal sympathetic denervation represents an alternative interventional treatment option for patients with resistant arterial hypertension.[13] This treatment involves modulation of the sympathetic nervous system by selective denervation through radiofrequency (RF) ablation.[12, 14] Prior to the procedure it is essential to exclude arterial hypertension due to a secondary origin. The most prevalent origins of secondary hypertension are stenosis of the renal arteries, primary hyperaldosteronism and obstructive sleep syndrome. Therefore, imaging of the renal arteries, to exclude haemodynamic stenosis or abnormal anatomy, should be performed. In addition, hormonal diagnostics are necessary to detect primary hyperaldosteronism, pheochromocytoma and Cushing syndrome. An ambulatory blood pressure measurement is also recommended to rule out pseudo-resistance.[13]

Procedure for renal denervation

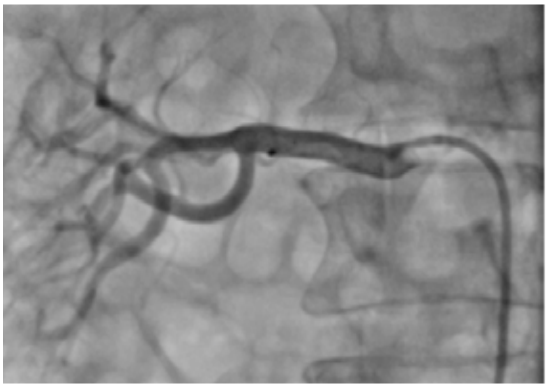
Percutaneous sympathetic renal denervation is performed by a transfemoral approach using a 6F sheath via the femoral artery. The catheter is introduced into the arterial system and advanced to the renal arteries. A specific Symplicity Catheter (Symplicity Catheter System, Ardian, Medtronic, Inc. USA) is used for the procedure, which includes an electrode on the catheter tip for ablation (fig.1). The catheter is connected to a radiofrequency generator. In terms of anatomical conditions, the renal artery should have a diameter of at least 4 mm to tolerate the temperature rise and avoid spasm. In addition, the artery should have a length of at least 20 mm to the first significant bifurcation in order to allow several ablations to be

fig. 1

The Symplicity Catheter, including an electrode on the catheter tip for energy delivery.

(Symplicity Catheter System, Ardian, Medtronic, Inc. USA) fig. 2

Angiographical image presenting the ablation catheter inside the right renal artery. The catheter was advanced to renal artery via a transfemoral approach using a 6F sheath



performed. The first RF ablation point should be placed proximal to the first bifurcation of the renal arteries. The catheter is retracted by approximately 5 mm and the single ablation points are set in a circumferential formation. In total, depending on the anatomical conditions, RF ablation is performed 4–6 times within each renal artery, in anterior, superior, posterior and inferior positions across the full circumference (fig. 2). The power delivery is controlled by a connected generator and limited to a maximum of 8 watts and to a temperature of 40–70°C. Energy delivery time is limited to two minutes. Systemic anticoagulation is necessary during the procedure; antiplatelet treatment (acetylsalicylic acid [100 mg]) is required for a total of three months following intervention. A 24-hour ambulatory blood pressure measurement should be performed to measure treatment efficacy.

Experience from clinical trials

Effects on blood pressure

The effectiveness and feasibility of catheter-based sympathetic renal denervation has been shown in international multicentre studies. These studies enrolled patients with a systolic blood pressure >160 mmHg (>150 mmHg for patients with type 2 diabetes mellitus) despite taking at least three antihypertensive drugs (including diuretics) at maximum tolerable doses.[15] At 12 months following renal denervation, results showed a notable reduction in systolic blood pressure, with an average reduction of 27 [± 12] mmHg (fig. 3), with no serious complications having occurred. Post-procedural renal imaging showed no evidence of renal artery stenosis, aneurismal dilatation or damage in these patients. In addition, no changes in renal function were measured, supporting the safety of this procedure, potentially including those patients with moderately reduced renal function. Sympathetic outflow increased in patients with essential hypertension, suggesting that renal denervation selectively reduces efferent sympathetic activity. This was confirmed by a reduction of the noradrenaline levels in the spillover measurement. Hence, both renal blood flow and renin plasma levels are decreased.[15] Given the regrowth of sympathetic nerve fibres, long-term data on the persistence of the blood pressure lowering effect are of particular interest.[13] Results showed that the blood pressure reduction was sustained for an observation period of 24 months (fig. 4), suggesting that effects of nerve fibre regrowth are not clinically relevant. Furthermore, no major complications, including stenosis, aneurysm and cholesterol emboli, were reported during a post-interventional time period of two years. However, a progression of a pre-interventional existing stenosis was observed in one patient.[15]

The therapeutic response, defined as a systolic blood pressure reduction of >10 mmHg, after renal denervation, was 84–92%. Intake of central sympatholytic medications, low heart rate, and an increased systolic blood pressure before renal denervation were shown to be predictors for a significant blood pressure reduction; predictors for non-responders are yet to be evaluated.[15]

From our own observations, the efficacy in blood pressure reductions after treatment could be broadly assigned into three groups. One group (20–25%) showed a prompt blood pressure reduction within the first few days following denervation. This reduction was maintained at a lower level in follow-up measurements. The second group (65%) did not show any significant changes in blood pressure during the early period after treatment, but did show a notable reduction in blood pressure after 3–6 months. Finally, consistent with data from other trials,[12] some patients did not show a significant reduction in blood pressure either during the early period, or after three or six months.

Effects on glucose metabolism

Resistant arterial hypertension is associated with comorbid metabolic anomalies, as a result of insulin resistance and dysregulation of the glucose metabolism caused by sympathetic overactivity. Findings demonstrated that lower levels of sympathetic activity alongside reduced

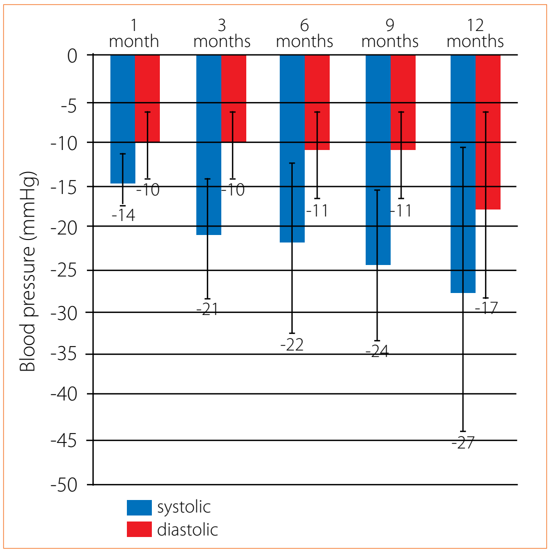


fig. 3

Blood pressure reduction at 1, 3, 6, 9 and 12 months after renal denervation

(modified from Krum et al. 2009[12])

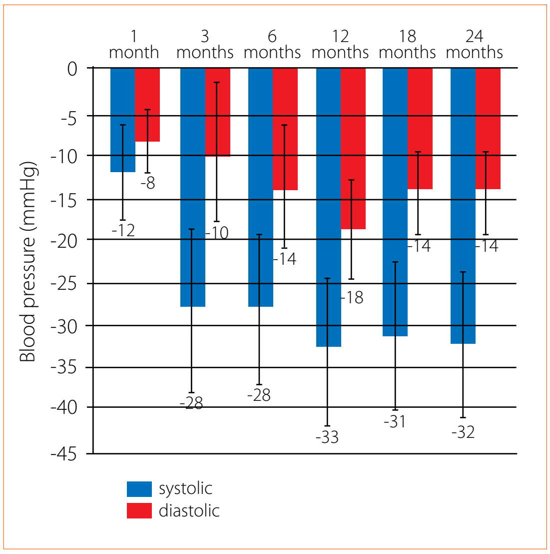


fig. 4

Systolic and diastolic blood pressure reduction after renal denervation up to 24 months follow-up

(modified from Symplicity HTN-1 Investigators 2011[15])

blood pressure following renal denervation was associated with a positive effect on glucose metabolism, such as insulin production.[11]

Effects on renal function

To date, renal denervation studies have excluded patients with progressive chronic kidney disease (estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m^2) due to potential kidney damage after ablation.[13] However, from own experience there is a trend for increased eGFR following renal denervation, although it is unclear whether this was due to the reduction in blood pressure or a direct effect of the reduced sympathetic nervous activity in the kidneys. Cholesterol emboli or thermal damage were not observed or were not described in previous studies.[13] Severe resistant hypertension is common in end-stage renal disease and a high degree of sympathetic nervous activation is observed in such patients.[16] In some patients with post-transplantation hypertension, bilateral nephrectomy is done to manage the severe hypertension present.[17] This population may experience considerable benefit from catheter-based renal denervation procedures.

Effects on sleep apnoea

Obstructive sleep apnoea syndrome is associated with cardiovascular risk factors, such as resistant hypertension, insulin resistance and metabolic syndrome, as well as with cardiovascular diseases. It was considered that obstructive sleep apnoea syndrome could be both a reason for, as well a consequence of, increased sympathetic activity.[18] Obstructive sleep apnoea syndrome is common in those with resistant hypertension having been described in up to 80% of these patients.[19-21] A recent study showed a relationship between reduced blood pressure levels and improvements in sleep apnoea.[18] Whilst the association and mechanism of the interaction between catheter-based blood pressure reduction and improvement in sleep apnoea has yet to be evaluated, it has been suggested that the reduced fluid retention after renal denervation may play a major role in this process.[18] Given the link between sympathetic nervous activity and insulin resistance, blood pressure and sleep apnoea, it is apparent that renal denervation could offer a clinical benefit in some patients with these disorders.[18]

Effect on the cardiorespiratory response

It was recently demonstrated that a reduction in peak systolic blood pressure occurs during exercise following renal denervation.[20] Moreover, the heart rate recovery was improved compared with baseline. Dysregulation of blood pressure or heart rate did not occur at the cost of blood pressure adaption. Despite a slight improvement of the maximum work rate, the oxygen consumption (VO_2 peak) was not significantly altered. Furthermore, there were no changes regarding the minute ventilation or ventilatory efficiency after renal denervation.[22]

Conclusion

Renal denervation, through selective ablation of the renal sympathetic efferent and afferent nervous system, represents a new treatment option for patients with resistant arterial hypertension. In addition to the reduction in blood pressure, the reduced sympathetic activity also has a positive effect on glucose metabolism, including increased insulin production, as well as on sleep apnoea. Persistence of the reduction in blood pressure was demonstrated by sustained effects over an observation period of 24 months. No major complications, including stenosis, aneurysm of the renal arteries and cholesterol emboli, were described. However, for a small proportion of patients (8–16%), no effects were achieved with this new therapy option. However, recent data presented at the 2012 American College of Cardiology Annual Meeting demonstrate that in patients followed for 36 months (n=24), there was a 100% response rate, as defined by an office blood pressure reduction ≥10 mmHg. Similar results were seen at 3 years even amongst non-responders at 1 month (n=8), with 100% of these patients also achieving ≥10 mmHg reduction in blood pressure.[23] Predicting parameters for non-responders have yet to be described and it is still unclear which parameters or biomarkers can identify patients who will benefit from renal denervation. A better understanding of these issues requires further clinical trials in a large number of patients.

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