

## Case Report

# Chemical Denervation of the Renal Artery with Vincristine for the Treatment of Resistant Arterial Hypertension: First-in-Man Application

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Renal artery denervation has recently emerged as a novel therapy for patients with resistant hypertension. Clinical results from renal sympathetic denervation support the safety and efficacy of this method over a period of 18 months. However, several limitations have been reported. Previous studies have shown that chemical denervation by vincristine is safe and effective in an experimental model. We describe the first-in-man application of chemical denervation with vincristine in a 74-year-old male patient with resistant arterial hypertension.

**T**he treatment of resistant hypertension has recently focused on the development of endovascular therapies that cause denervation of the sympathetic nervous system of the renal artery.<sup>1-5</sup> Radiofrequency energy can be used for the selective renal sympathetic denervation (RSD) of the kidney, by targeting the sympathetic nerve fibers that lie in the adventitia of the renal artery. The immediate and long term results of this approach are encouraging, although its efficacy in everyday clinical practice has been challenged.<sup>6-8</sup> Clinical results support the safety and efficacy of this method over a period of 18 months. However, the lack of any long-term data, together with the possible regeneration properties of the renal afferent sensory nerves and the possible complications of the method, have led to the development of alternative methods of renal denervation. Previous studies from our institution have shown that chemical denervation by vincristine is safe and effective in an experimental model.<sup>5,9</sup>

Here we report the first-in-man application of chemical denervation with vincristine, in a patient with resistant hypertension.

## Case presentation

A 74-year-old male patient was referred to our department because of uncontrolled arterial hypertension. The patient also complained of dyspnea on exertion. His office blood pressure was 174/104 mmHg under treatment with valsartan 320 mg, amlodipine 10 mg and HCTZ 25 mg as a fixed combination and bisoprolol 10 mg. His electrocardiogram (ECG) was compatible with left ventricular hypertrophy and sinus bradycardia. Echocardiography revealed concentric hypertrophy, left atrial dilatation, diastolic dysfunction with a prolonged relaxation pattern, ascending aorta dilatation, and a globally, mildly reduced ejection fraction (50%). He was a former smoker with hyperlipidemia under treatment with atorvastatin 20 mg.

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The patient underwent full laboratory examinations, ambulatory blood pressure monitoring, and further evaluation to rule out secondary hypertension. Because of the impaired left ventricular function, coronary angiography was also scheduled. The kidney function was normal (creatinine 0.9 mg/dl, estimated glomerular filtration rate 83 ml/min/1.73 m<sup>2</sup>) without electrolyte disturbances. There were no signs of hepatic dysfunction, glucose intolerance or an inflammatory state. The adrenal computed tomography scan was negative for adenomas or hyperplasia. A kidney ultrasound and duplex ultrasonography of the renal arteries were also negative for renal parenchymal disease and renal artery stenosis, respectively.

Ambulatory blood pressure monitoring (ABPM) confirmed the presence of uncontrolled hypertension: average systolic blood pressure (SBP) during the day was 146 mmHg and average diastolic blood pressure (DBP) was 85 mmHg, whereas no significant reduction in SBP or DBP was observed during the night (average SBP/DBP 139/81 mmHg).

Coronary angiography was negative for coronary artery disease. Left ventriculography confirmed the impaired left ventricular function.

The patient was diagnosed with resistant hypertension. Given that he was taking four classes of antihypertensive drugs, including a diuretic, at optimal doses, and after confirming the patient's compliance with pharmaceutical treatment, we decided to proceed to the interventional approach of renal denervation with chemical ablation, after obtaining informed consent from the patient and approval from the hospital's ethics committee.

The procedure of denervation was performed under local anesthesia via an 8 French introducing sheath that was inserted into the right femoral artery using a standard technique. An 8 French guiding catheter (Renal long, Boston Scientific, Natick, MA, USA) was inserted and advanced until it was engaged in the ostium of the left renal artery. An initial angiogram of the renal artery was performed in order to assess the anatomy and to select the segment for the chemical denervation (Figure 1). Then a guidewire (0.014", BMW, Abbott, IL, USA) was advanced to the distal segment of the renal artery and a delivery balloon-catheter (5 mm in diameter, 15 mm in length) that was developed as previously described, was advanced into the main branch of the renal artery.<sup>5</sup> Briefly, the delivery balloon-catheter consists of 6 sideholes 25 µm in diameter, at fixed intervals of



Figure 1. Baseline left renal artery angiogram.

60°, circumferentially around a non-compliant balloon. A heparin bolus of 5000 units was administered intravenously.

The proximal segment of the renal artery was selected for the chemical denervation, and after quantitative angiography the diameter of the balloon was selected in order to achieve a 1.2 balloon/artery ratio. The dedicated balloon was inflated at 20 atm, using a mixture containing vincristine and contrast, as previously described. The inflation was interrupted when a total of 4 ml of the mixture (containing 0.1 mg of vincristine) was delivered (Figure 2). A final angiogram of the renal artery was performed to confirm the safety of the procedure (Figure 3). No signs of renal artery abnormalities (vasospasm, stenosis or dissection) were present after the final angiography. The same procedure was performed for chemical denervation of the right renal artery.

After the completion of the procedure, the patient was transferred to the intensive care unit for close monitoring of his vital signs and for sheath removal. He was discharged the following day with no complications and under the same medications.

Blood sampling and 24-h ambulatory BP monitoring were scheduled after 4 weeks. At the 4-week follow up, the office BP was 132/80 mmHg. The well-controlled BP was confirmed by the ABPM measurements, where the average SBP/DBP was 123/72 mmHg and 124/73 mmHg during the wake and sleep



**Figure 2.** Fluoroscopic view showing the advance of the delivery balloon catheter in the proximal segment of the left renal artery.



**Figure 3.** Final angiography revealed no complications in the renal artery.

periods, respectively. Importantly, due to the progressively decreased BP at 2 weeks after the procedure, the dose of HTCZ was reduced to 12.5 mg and the dose of bisoprolol to 5 mg. Kidney function was intact at follow up.

## Discussion

The identification of the renal sympathetic system as a major contributor to the complex pathophysiology of hypertension has highlighted the potential for endovascular RSD for the treatment of resistant arterial hypertension. In the first decade of the 2000s, endovascular RSD was established as a safe and effective treatment for resistant hypertension, with results that are supported by large and in some cases randomized trials, while recently, a catheter-based method to induce RSD has been introduced into daily practice.<sup>3,4,10,11</sup> Limitations of this method include the possible side effects of the procedure,<sup>12</sup> the degenerative properties of the afferent sensory fibers of the renal artery,<sup>13</sup> and the possibility of causing renal artery stenosis.<sup>14</sup>

In order to overcome these limitations, other endovascular techniques aiming at the same target have been developed more recently. The RSD has been proposed to be effective when it is performed by ultrasonic ablation technology<sup>15</sup> or by tissue-directed pharmacological ablation technology.<sup>2,5,9,16</sup>

Chemical denervation of the sympathetic nervous system of the renal artery with vincristine has emerged as an alternative to RSD for the treatment of resistant hypertension. Recent studies have shown that local administration of low doses of vincristine, an anti-neoplastic drug with a broad spectrum of activity against hematological malignancies, that is well known to cause long-term neurotoxicity and secondary demyelination of the peripheral nerves, is safe and results in the denervation of the sympathetic system of the renal artery.<sup>2,5,9</sup> Moreover, in a normotensive experimental model, local administration of vincristine resulted in a significant decrease in the subjects' systolic blood pressure.<sup>5</sup>

These findings justified the first-in-man application of chemical denervation by the local delivery of vincristine in a patient with well documented resistant hypertension. The procedure was safe, without any complication, and resulted in a significant decrease in blood pressure as assessed by ABPM 4 weeks later. Further, large-scale studies are necessary to establish the long-term safety and efficacy of this novel technique.

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