Case Report
Sympathetic renal denervation in hypertension with chronic kidney disease: a case report and review of literature

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Abstract: Resistant hypertension is defined as systolic blood pressure that is higher than 140 mmHg even though they consume three maximally tolerated anti-hypertensive medication class, including diuretics at an appropriate dose [1]. There are many complications of resistant hypertension such as left ventricular hypertrophy, increased incidence of retinal hemorrhage and kidney damages [2]. A novel catheter-based technique for renal denervation (RDN) as a new therapeutic avenue has great promise for the treatment of refractory hypertension. Despite the fast pace of development in RDN therapies, only initial and very limited clinical data are available. Here, we present the effects of RDN on perivascular nerves of the renal arteries in a 62-year-old male patient. And large gaps in knowledge concerning the long-term effects and consequences of RDN still exist, and solid, randomized data are warranted.

Keywords: Renal denervation, resistant hypertension, chronic kidney disease, renal sympathetic nervous system

Introduction

Hypertension is a major global public health concern despite the recent advances and proven benefit of pharmacological therapy. A certain subset of patients have hypertension resistant to maximal medical therapy and appropriate lifestyle measures. Meanwhile, chronic kidney disease (CKD) contributes substantially to the global burden of cardiovascular morbidity and mortality. Even a moderate reduction in GFR is predictive of an increased risk for coronary heart disease [3]. Accordingly, hypertensive patients with reduced GFR are at greater risk for cardiovascular disease than for ESRD.

Pharmacological treatment for resistant hypertension is currently available. However, the effectiveness of pharmacological treatment for resistant hypertension is low [4]. New approaches in form of therapeutic intervention like RDN may be needed. We herein report a case of RDN on perivascular nerves of the renal arteries in a 62-year-old male patient, with the literature review to understand it better.

Case presentation

Here we present a patient with resistant hypertension despite use of five different anti-hypertensive drugs. A 62-year-old male patient (BMI: 23.84 kg/m²) was admitted to our outpatient clinics with poorly controlled hypertension. With 20-year diabetes and 8-year hypertension history, he got uremia 4 years ago and since then he accepted hemodialysis 3 times a week. He presented with long-standing hypertension that was resistant to pharmacological therapy with five different anti-hypertensive drugs, namely Irbesartan 300 mg/day, Nifedipine GITS 270 mg/day, Metoprolol 50 mg/day, Compound Dihydralazine Sulfate Tablets 9 tablets/day and Nimodipine 180 mg/day. His office blood pressure was 180-210/90-120 mmHg. Echocardiography showed normal left ventricular systolic function and mild mitral insufficiency.

Due to the uncontrolled nature of the resistant hypertension, the patient was eligible for percutaneous renal denervation treatment with approval of the hospital ethical committee. This
clinical trial named Renal Sympathetic Denervation in Patients with Chronic Kidney Disease and Resistant Hypertension (RSD-4CKD) was registered in Clinical Trials.gov as number NCT01737138. Under local anesthesia, the femoral artery was accessed in standard technique and angiography was performed to visualize the renal artery (diameter >4 mm, length >20 mm, with no stenosis). RDN was performed with Cordis Catheter system (JNJ Inc., Miami, Florida, USA) and Fentanyl was used to relieve pain. Mean temperature was 45°C and 10 W radiofrequency nerve ablations lasted up to 2 minute at each point, with 8 points on the left and 9 points on the right. Radio-frequency ablation was applied to both renal arteries without apparent procedural complications and no vascular complications were observed.

The patient was discharged at the fourth day with 160/90 mmHg at office. The patient was prescribed with irbesartan 150 mg/day, Nifedipine GITS 60 mg/day, and Compound Dihydralazine Sulfate Tablets 6 tablets/day. Ambulatory blood pressure has been monitored regularly which revealed an average systolic and diastolic blood pressure of 140/70 mmHg 12 months later (Figure 1).

3 months after his first hospitalization, he was hospitalized again for parathyroidectomy. We compared clinical characteristics and heart rate variability (HRV) in the two times of hospitalization (Tables 1, 2). Our experience suggests that this technique can be safely performed in elderly patients with severely impaired renal function.

Discussion

In 2009 the first in-human proof-of-concept study (Symplicity I) evaluated 50 patients with treatment-resistant hypertension [5]. BP reduction with RDN was significant, smaller in the first month after RDN (-14/-10 mmHg), and more pronounced at 6-month and 1-year follow-up (-27/-17 mmHg). In 2010 the second study (Symplicity II) with a sample of 106 patients was randomized but not blinded [6]. BP dropped significantly in the first month in the active RDN group, but BP reduction was much greater at 6-month and 1-year follow-up (-27/-17 mmHg). In 2010 the second study (Symplicity II) with a sample of 106 patients was randomized but not blinded [6]. BP dropped significantly in the first month in the active RDN group, but BP reduction was much greater at 6-month and 1-year follow-up (-27/-17 mmHg). In 2010 the second study (Symplicity II) with a sample of 106 patients was randomized but not blinded [6]. BP dropped significantly in the first month in the active RDN group, but BP reduction was much greater at 6-month and 1-year follow-up (-27/-17 mmHg). In 2014 the result of the third study (Symplicity III) which was prospective, single-blind, randomized, and sham-controlled came out [7]. A total of 535 patients underwent randomization. The mean systolic blood pressure at 6 months was -14.13±23.93 mmHg in the denervation group as compared with -11.74±25.94 mmHg in the sham-procedure group (P<0.001 for both com-
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Table 2. Heart rate variability (HRV) of patient Liu’s two hospitalization

<table>
<thead>
<tr>
<th>Heart rate variability (HRV)</th>
<th>1*</th>
<th>2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean 24-h HR</td>
<td>76</td>
<td>87</td>
</tr>
<tr>
<td>mean NN (ms)</td>
<td>792</td>
<td>690</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>76</td>
<td>60</td>
</tr>
<tr>
<td>SDANN (ms)</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>pNN50 (ms)</td>
<td>0.40%</td>
<td>0.40%</td>
</tr>
</tbody>
</table>

*1-the first time of hospitalization is for RDN, 2-the second is 3 months later for Parathyroidectomy. Mean 24-h HR: mean heart rate over 24-h. mean NN: mean normal-to-normal R-R intervals. SDNN: standard deviation of the normal-to-normal R-R intervals. SDANN: standard deviation of 5-min average of normal R-R intervals. rMSSD: root-mean square of differences between adjacent normal R-R intervals. pNN 50%: proportion of adjacent R-R intervals differing by >50 ms over 24-h.

Comparisons of the change from baseline). There were no significant differences in safety between the two groups.

Sympathetic activity is already elevated in early phases of chronic renal failure, and the magnitude of sympathetic overdrive increases with disease progression [8]. Evidence also suggests that the afferent sensory renal nerves in response to intra-renal injury have an excitatory influence on central sympathetic outflow. Consequently, renal sympathetic efferent and afferent nerves exert a powerful influence on the initiation, development, and maintenance of elevated systemic BP commonly present in patients with renal failure.

Afferent signaling derived from the native failing kidneys plays a causal role in renal efferent sympatho-excitation and potentiates the adverse effect of chronically increased sympathetic drive. Consequently, interruption of efferent and afferent renal fibers may possibly mitigate or reverse autonomic imbalance and reduce renal sympathetic outflow and arterial BP in CKD.

Chronic kidney disease is an important cause and consequence of uncontrolled hypertension. Patients with high blood pressure, especially those who are therapy resistant, are at high risk for renal impairment and other cardiovascular complications [9]. Recent findings [10-12] summarize the clinical experience with catheter-based renal nerve ablation in high-risk patients with moderate to severe renal impairment. The main results of this pilot study are as follows: (1) selective and bilateral sympathetic renal denervation is safe and effective in patients with stage 3-4 CKD; (2) bilateral renal denervation is not associated with acute or short-term deterioration of renal function; and (3) bilateral renal nerve ablation may have beneficial effects beyond improved BP control, including a potential increase in hemoglobin concentration and reductions in proteinuria, BNP levels, and peripheral arterial stiffness index.

As reviewed above, no studies covered more than one year. The kidneys are critically injured when massive proteinuria is with malignant hypertension, leading to renal insufficiency. Therefore studies should consider long-term prognosis in patients with resistant hypertension as the end point. Besides, for the patients on dialysis, cardiac function and dry weight which correlate with BP should be into consideration.

Many issues still remain unclear despite the concept of RDN has high potential, of paramount importance are (i) proper patient selection based on the knowledge of the pathophysiology, (ii) development of a method/variable that can be used to guide the interventionist during the procedure and (iii) long-term data on safety are necessary. The concept of ‘resistant hypertension’ as selection criterion will gradually disappear, simply because it does not make sense from a pathophysiological point of view. CKD patients are especially likely to benefit from RDN, possibly over the whole range of CKD [13, 14]. Present day standard therapy in CKD patients includes RAAS inhibitors, which reduce but on average do not normalize sympathetic activity. Also, blood pressure is often not adequately controlled in CKD [15]. The beneficial effect of renal denervation may not only include a reduction in cardiovascular morbidity and mortality, but also a reduction in progression of CKD. Other potential patients groups could be heart failure and obesity/metabolic syndrome/Type II diabetes. Given the financial burden to society of the ESRD programs, any reduction of CKD progression could be very cost effective.

Conclusion

Based on the results of the initial and small clinical experience, catheter-based RDN thera-
py has great promise for the treatment of refractory hypertension. Safety and efficacy findings seem to suggest that renal sympathet-
ic denervation could be of therapeutic benefit in this patient population. Despite the fast pace of development in RDN therapies, significant gaps in knowledge still exist, especially with regards to possible nerve or vessel injury and long-term consequences. Obviously, we can only achieve the “first step” for appropriate ori-
entation in the process of further development of this new therapy, which is really a multidisci-
plinary task requiring collaboration between the device industry, interventional cardiolo-
gists, pathologists, electro-physiologists, endo-
vascular physicians, radiologists and nephrolo-
gists. Given the nature of this intervention, nephrologists should be heavily involved.

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Disclosure of conflict of interest

None.

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