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Přehledový článek | Review

Renal denervation in the treatment of resistant arterial hypertension and other perspectives

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ABSTRACT

Renal denervation (RDN) is a new perspective method for the treatment of resistant hypertension. Surgical sympathectomy has been considered as a possible treatment of hypertension for many years – long before the discovery of antihypertensive drugs. The selective percutaneous transcatheter application of radiofrequency energy in renal arteries to eliminate sympathetic nerve fibres has been used in human medicine since 2009. The recent boom of this method has been supported by published clinical studies showing efficacy of this new treatment modality. Nevertheless, RDN is still an experimental method to be used only in specialized research centers. In this review we will provide up-to-date information about the use of RDN as a novel method for the treatment of hypertension as well as discuss potential perspectives of RDN in the treatment of various medical conditions.

SOUHRN

Renální denervace (RDN) je v současnosti novou perspektivní metodou pro léčbu rezistentní hypertenze. Chirurgická sympetektomie v léčbě hypertenze je známá již z dob před objevem antihypertenziv. V humánní medicíně se používá selektivní transkatetrová perkutánní aplikace radiofrekvenční energie do renální tepny za účelem odstranění sympatických nervových vláken provázejících renální tepnu od roku 2009. Obrovský rozmach této metody v posledních dvou letech podporují publikované studie, které ukazují účinnost nové metody léčby. Přesto je dnes renální denervace v léčbě hypertenze zatím metodou výzkumnou, patřící do rukou specializovaných center. Souhrnný článek popisuje RDN nejen jako možnost léčby hypertenze, ale předkládá také potenciál RDN v dalších oblastech medicíny.

Introduction

Prevalence of hypertension is very high in the Czech Republic (47.8% of males and 36.6% of females aged 25–64 years) and it is one of the most frequent cardiovascular diseases as well [1]. Arterial hypertension, as well as smoking, diabetes mellitus and hyperlipidaemia, is an important risk factor for coronary artery disease, cerebrovascular disease and peripheral artery disease. Hypertension is also a negative predictor of early cardiovascular and cerebrovascular death.

Arterial hypertension is defined as repeated measurements of blood pressure (BP) ≥ 140/90 mmHg at least at two clinical visits [1,2]. Although there are many antihy-

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pertensive drugs available and there is a clear evidence that treatment of hypertension reduces the risk of death and complications, only half of treated patients are well compensated (blood pressure < 140/90 mmHg) [3].

Resistant hypertension is defined as the blood pressure remaining above the target level despite the treatment with a combination of 3 different, full-dose antihypertensive drugs including diuretic. This definition presumes the patient be adherent to treatment and thus resistant hypertension is not synonymous to uncontrolled hypertension. Resistant hypertension does not include patients with BP over the target level due to inadequate (under) treatment by their physician and also patients with unrecognized secondary hypertension. On the contrary, patients with well controlled BP with 4 and more antihypertensive drugs meet the definition of resistant hypertension [4]. In ALLHAT study, 8% of patients had 4 or more antihypertensive agents and estimated overall prevalence of resistant hypertension was 15% [5]. Many of these patients were not "truly" resistant as the criteria for this condition were poorly defined in this trial [2]. Small studies demonstrated the prevalence of resistant hypertension be much more than 5% but accurate estimate is not possible due to many bias [6,7]. Pikus et al. found 9.8% prevalence in the cohort of 620 patients in a specialized centre for hypertension. The definition of resistant hypertension was sufficient but patients' compliance was unclear [8]. Alternative treatment strategies have been studied for patients with resistant hypertension.

Sympathetic nervous system (SNS)

Increased sympathetic activity plays an important role in hypertensive patients. Muscle sympathetic nerve activity (MSNA) was significantly higher in patients with severe essential hypertension than in normotensive controls and correlated with mean arterial pressure [9,10]. Increased levels of catecholamines were found in internal organs (heart, kidneys) of hypertensive patients [11]. In a historical study by Peet et al., that had been performed before the era of antihypertensive drugs began, the blood pressure significantly lowered after surgical sympathectomy. Major neurological symptoms including headache and ophtalmological disturbances as well as cardiac and renal status improved. Mortality of this procedure was relatively high (more than 3%) and adverse events (orthostatic hypotension, bradycardia etc.) were also frequent [12]. Kidneys are innervated with efferent and afferent adrenergic neurons. These neurons terminate in nephrons and affect sodium reabsorption, renin secretion and renal blood flow. Sympathetic stimulation causes expansion of blood volume, vasoconstriction (vascular response to norepinephrine and angiotensine II stimulation) and increase of arterial blood pressure. The afferent neurons are linked to control centers for neuromodulation in the midbrain (mesencephalon). Renal afferent signaling is activated by renal ischemia and adenosin release, both caused by intense vasoconstriction. Mechanoreceptors in renal pelvis are also involved. Increase of afferent sympathetic traffic results in efferent sympathetic response and vice versa and this potent kidney-brain sympathetic loop may potentially become self-perpetuating [13]. Higher sympathetic activity persisted in patients with end-stage renal failure who did not undergo bilateral nephrectomy (interruption of the afferent sympathetic nerves). Having removed the diseased kidneys, normalization of pathological sympathetic overactivity was demonstrated [14]. Both afferent and efferent sympathetic fibers are noradrenergic and are situated in andventitia of renal arteries. Kidneys have an important role in the overall sympathetic tone [15].

Hypertension and renal denervation

All the knowledge about the pathophysiology of renal function and its role in sympathorenal mechanism of etiology of hypertension led to an idea of selective destruction of sympathetic fibres running along the renal arteries. Preclinical studies in juvenile swines demonstrated that a catheter based approach was safe and markedly reduced the content of norepinephrine in the treated kidney by more than 85%. No significant vascular or renal injury was observed 6 months after the procedure in these animal studies, justifying the initiation of first-in-man evaluation [16]. The radiofrequency catheter ablation (renal denervation – RDN) in human was percutaneously performed for the first time in 2009 by Schlaich. In a 59 year-old patient, he demonstrated a 42% reduction in norepinephrine spillover, sustained blood pressure decrease, normalization of muscle sympathetic nerve activity and reduction of left ventricle mass during 1-year follow-up [15].

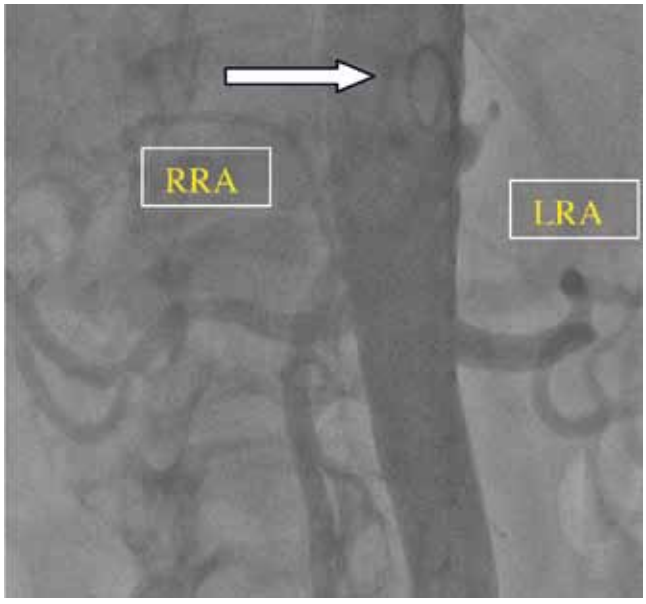

Fig. 1 – Aortography of descendent aorta and renal arteries; RRA – right renal artery, LRA – left renal artery, pigtail catheter (white arrow).

The entire procedure requires a femoral artery access with an insertion of a 6F guiding catheter. Heparin is administrated to achieve ACT (activated clotting time) ≥ 250 seconds. The RDN procedure is performed via

lumen of a renal artery. Prior aortography with the visualization of renal arteries is necessary (Fig. 1). Patients with accessory renal arteries should not be indicated for the ablation. After appropriate positioning of a specially-designed ablation catheter (Symplicity; Medtronic) in a distal part of the renal artery, having achieved a sufficient contact with the arterial wall, radiofrequency energy is delivered 5–6 times in each artery for no longer than 2 minutes per application. We start distally and pull back towards the ostium of the artery, making 5mm gaps between two spots and rotating the catheter by 90 degrees each time (Fig. 2). The last application is performed in the upper part of the renal artery right behind the ostium in order to destroy high density sympathetic nerves that are present in this location. Only mild energy (8 watts) is delivered during each application. Temperature and impedance are automatically monitored by the console (Fig. 3). After the procedure, one can see notches-like marks on ablated renal arteries (Fig. 4).

Fig. 2 – Position of denervation catheter in renal artery (reprinted with permission of Medtronic, Czech Republic).

Fig. 3 – RF generator.

One of rare adverse complications is the spasm of the renal artery which is very resistant and can persist for hours. Fortunately, in most of the cases, it remains clinically silent (Fig. 5).

As well as in clinical trials and published papers that we are now going to discuss, we use radiofrequency energy to ablate nerve fibers that are circumferentially distributed along the renal artery. The optimal energy modality for denervations is unknown. First-in-man ultrasound energy denervation results have just been announced. The advantage over the RF technology lies in its ability to denervate uniformly and circumferentially while simultaneously cooling the endothelial wall to secure safe, consistant and fast procedure. Seven patients who underwent denervation with this novel ultrasound system (PARADISE) experienced substantial systolic blood pressure reduction by 31 mmHg in 60 days [17]. Whether ultrasound energy proves to be applicable in the future will require further investigations.

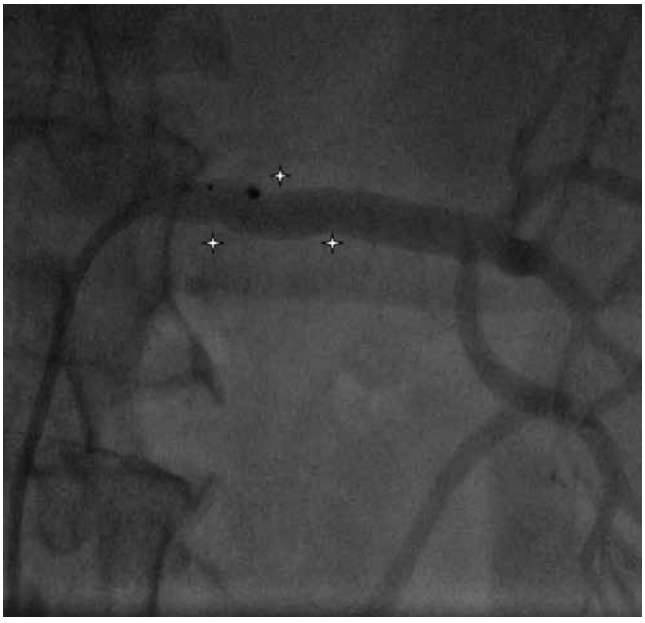

Fig. 4 – Left renal artery with "notches" (stars) after ablation.

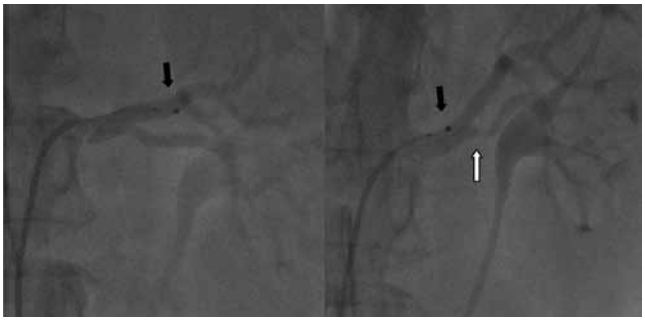

Fig. 5 – Left – artery before ablation, right – spasm of side branch (white arrow), tip of Symplicity catheter (black arrow).

Clinical trials

The safety of the procedure and efficacy in blood pressure lowering were the primary outcomes of the first trial (Symplicity HTN-1) [18]. Secondary outcomes included renal norepinephrine spillover and changes in renal function. The study was carried out at 5 centers in Australia and Europe and comprised patients treated from June 2007 to November 2008 and clinically followed for 1 year.

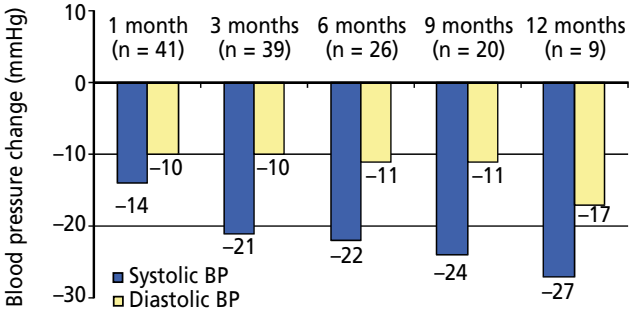

Fig. 6 – Change of office blood pressure (modified from [18]).

The inclusion criteria were office systolic blood pressure 160 mmHg and higher despite treatment with 3 or more antihypertensive drugs including diuretic or intolerance to medication. Secondary hypertension was the major exclusion criterion and also patients with renovascular disease were not enrolled. Out of 50 patients only 45 were treated, 5 patients were excluded due to anatomical criteria (accesory renal artery etc.). Repeated renal angiogram was performed after 14–30 days and magnetic resonance angiogram at 6 months. At baseline, mean blood pressure was 177/101 mmHg, average number of antihypertensive agents was 4.7, 43 patients were treated with diuretics. Average amount of energy applications was 4.2 in the right and 3.7 in the left artery. Analgetics and sedation were administered during the procedure. Concerning complications, there was one dissection of a renal artery caused by the guiding catheter and was treated with stenting and one femoral access site complication. Mean reduction of blood pressure of 14/10 mmHg at 1 month and further continuous decrease up to 27/17 mmHg at 12 months was achieved (Fig. 6). Mean reduction of norepinephrine spillover was 47%.

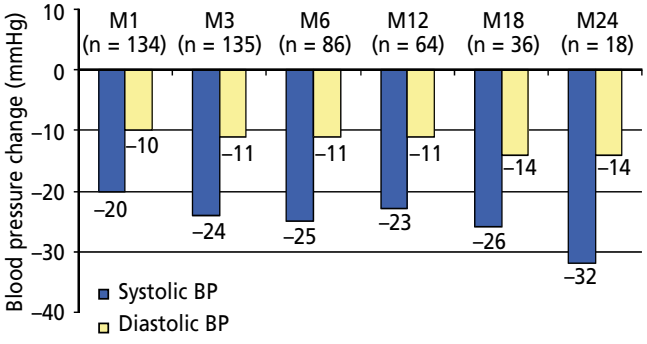

Fig. 7 – Change in office blood pressure (modified from [19]).

Thirteen patients did not respond to therapy – there was no decrease in blood pressure. In 9 patients the antihypertensive medication post procedure had to be reduced while in 4 patients increased.

The Symplicity HTN-1 trial protocol was used in a registry with 24-month follow-up and published in 2011. 153 patients were treated at 19 centers. Baseline BP was 176/98 ± 17/15 mmHg, average number of antihypertension agents was 5. Procedures were without any complications in 97% of patients, 3 patients had groin pseudoaneurysm, 1 patient had renal artery dissection. Office blood pressure post procedure was reduced by 32/14 mmHg at 24 months. The reduction of blood pressure during the follow-up period is shown in Fig. 7 [19].

The study was open-label and lasted for 4 years (from 2007 to 2010). Either 6F (55 pts) or 8F (98 pts) guiding catheters were used. It was recommended that renal arteries be minimally 4 mm wide and 2 cm long and without a significant stenosis or previous renal stenting. Bradycardia was observed during ablation in 10% of patients. Authors concluded that in patients with resistant hypertension the catheter sympathetic denervation resulted in substatial reduction of BP during 2 years of follow-up without clinically significant adverse events. But it is worthy of notice that only 18 patients completed the 24-month follow-up [19].

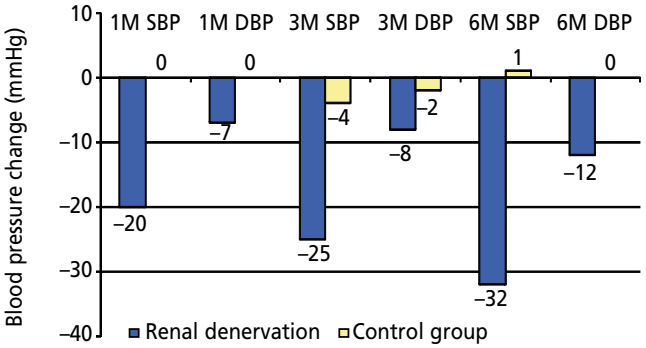

Fig. 8 – Symplicity HTN-2 – primary endpoint at 6 months (modified from [20]).

Recently published The Symplicity HTN-2 trial was already a randomized controlled study. 106 patients were allocated to renal denervation therapy (n = 52) or pharmacological therapy only (n = 54). The primary end-point was a change of seated office-based systolic BP at 6 months. Inclusion criteria were similar to those in the first trial. Baseline BP was 178/96 mmHg in the treated group and 178/97 in the control group. At 6 months, patients in the treated group achieved mean BP reduction by 32/21 mmHg while there was no change in the control group (+1/0 mmHg). The difference between the groups was statistically significant ($p < 0.0001$). The reduction of systolic BP by 10 mmHg or more was observed in 84% of patients in the treated group vs. 35% in the control group ($p < 0.0001$). No serious procedure/device-related complications occured. 3 patients in each group were lost to follow-up. Mean ambulatory 24-hour BP was reduced more in the denervation group (11/7 mmHg vs. 3/1 mmHg). Seven patients developed bradycardia during the procedure that was treated with atropine, 1 patient had groin pseudoanerysm (Fig. 8) [20].

Outcomes in The Symplicity HTN trials are very encouraging but there are several limitations to mention. Both trials were unblinded so placebo effect was possible. Patients with accessory renal arteries were not included in the trial and investigations of possible secondary etiology of hypertension were not sufficient. Reasons for nonresponding to the therapy were not explained. Moreover, both baseline and follow-up BP results were

based only on office measurements (only few patients had 24-hour BP monitoring) and white coat syndrome might have played an important role. The occurance of late renal artery stenosis was not investigated.

The Symplicity HTN-3 trial is a multi-centre, prospective, single blind, randomized controlled study of safety and efficacy of RDN. This study is currently recruiting patients, target number is over 500. Patients in the control group undergo a sham procedure in order to partially reduce the

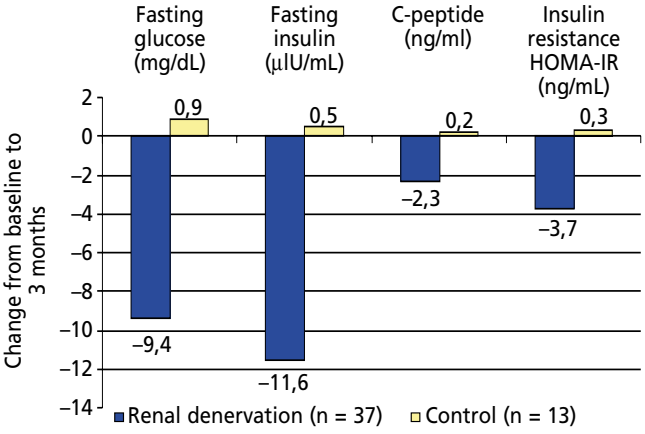

Fig. 9 – Changes of parametres associated with glucose metabolism from baseline to 3 months after renal denervation. All changes in the denervation group and the differences between RDN/control group at 3 months are statisticaly significant [24].

potential placebo effect, of course without the typical pain that is common in patients undergoing renal denervations. The primary endpoint is the change in office BP after 6 months, the secondary endpoint is the change of systolic BP during the 24-hour ambulatory monitoring [21].

RDN and other diseases

Increased renal sympathetic activity is associated with components of the metabolic syndrome [22]. There is a bidirectional relationship between sympathetic overactivity and insulin resistance and hyperinsulinemia – one can initiate another [23]. Mahfoud evaluated the role of renal denervation in glucose metabolism. 37 patients underwent renal denervation, 13 patients were in a control group. Fasting glucose was reduced from 118 ± 3.4 to 108 ± 3.8 mg/dL (p = 0.039), insulin levels decreased from 20.8 ± 3.0 to 9.3 ± 2.5 μIU/mL (p = 0.006), C-peptide levels from 5.3 ± 0.6 to 3.0 ± 0.9 ng/mL (p = 0.002) and insulin resistance from 6.0 ± 0.9 to 2.4 ± 0.8 ng/ml (p = 0.001) during 3-month follow-up. The substantial improvement in insulin sensitivity and glucose metabolism in response to RDN may be explained by reduced release of norepinephrine on regional hemodynamics and direct cellular effect (increase in norepinephrine leads to impaired ability of the cell to transport glucose across its membrane). There were no significant changes in the control group. Improvement was unrelated to changes in pharmacological treatment (Fig. 9) [24].

Witkowski at al. evaluated the effect of renal denervation in a cohort of 10 patients with refractory hypertension and sleep apnea syndrome. Denervation lowered blood pressure which was accompanied by improvement of sleeep apnea severity as evaluated by apnea-hypopnea index at 6 months (median 16.3 vs. 4.5 events per hour; p = 0.059). Significant changes were also observed in plasma glucose levels 2 hours after glucose administration (median 7.0 versus 6.4 mmol/L; p = 0.05) and in hemoglobin A1C level (median 6.1% versus 5.6%; $p < 0.05$) at 6 months. Authors concluded that denervation might be a useful option for patients with glucose intolerance, comorbid hypertension and sleep apnea syndrome [25]. Better blood pressure control leading to a reduction in fluid shifts to the neck in a lying position was suggested as a possible explanation of the positive effect of renal denervation on patients with sleep apnea syndrome [26].

Sympathetic nerve activity is increased in patients with chronic heart failure and leads to higher morbidity and mortality. In a study by Hasking at al., patients with heart failure and ejection fraction of 10% to 38% had mean plasma norepinephrine levels significantly higher compared to subjects without heart failure. Hasking also measured norepinephrine activity in individual organs. Norepinephrine spillover was increased mainly in heart and kidneys of the heart failure patients (increased by 540%, resp. 206%) but no such finding was confirmed in lungs [27]. It has also been well documented in large clinical trials that treatment with ACE inhibitors, betablockers and angiotensin II blockers in chronic heart failure patients lead to better outcomes concerning death, worsening of heart failure and hospitalizations for decompensated heart failure. Renal denervation reduces sympathetic activity and activity of renin-angiotensin-aldosteron system [28–33]. The rationale for treatment of chronic heart failure patients with renal denervation is clear and very promising. In heart failure animals after surgical renal denervation the blood flow and vascular resistance remained unchanged. Angiotensin II type 1 receptor expression is increased and type 2 decreased in heart failure condition. After renal denervation performed in animals with heart failure the abnormal expression of both receptors in kidneys almost returned to normal values [34]. Brandt et al. compared 46 patients with left ventricle (LV) hypertrophy who underwent renal denervation to 18 control subjects. Renal sympathetic denervation reduced LV filling pressure, shortened isovolumic relaxation time and increased LV ejection fraction [35]. Recently published first-in-man experience suggests that renal denervation can be successfuly used also in unstable chronic heart failure patients with electrical storm [36].

Conclusion

Over past 2 years we have learned to live with huge enthusiasm and strong belief in renal sympathetic denervation. There is a conceivable positive effect of RDN not only on blood pressure reduction in patients with resistant hypertension but RDN may also influence diseases associated with sympathetic hyperactivity like chronic heart failure, diabetes mellitus or sleep apnea syndrome.

Presently, many cardiologists consider implementation of this method into their clinical practice. But it is very important to confirm promising results in large clinical trials before we start using renal denervation as a routine intervention. Meanwhile renal denervation remains in hands of research specialists as an experimental method for further investigations. The Statement of the Czech Society of Cardiology as well as The Position Paper from the European Society of Hypertension provide practical recommendations, personnel and material requirements for performing renal denervations [37,38].

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