Expert consensus statement

Expert consensus statement of the Czech Society of Cardiology and the Czech Society of Hypertension on catheter-based sympathetic renal denervation procedures (RDN) in the Czech Republic

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ABSTRACT

The Czech Society of Cardiology and the Czech Society for Hypertension provide an expert consensus statement on the implementation of catheter-based renal denervation in the Czech Republic. Conclusion: until additional and/or larger randomized clinical trials confirm (or not) the promising results of initial studies, renal denervation can be performed exclusively as part of specific research protocols, approved by ethical committees. Renal denervation should be performed only in tertiary centers with ongoing research and publication activity to guarantee that the results will be objectively and critically evaluated. It is unethical to promote this method already today (early 2012) for routine hypertensive patients as a standard (proven) part of their treatment. Each patient must be informed, that renal denervation still is in the phase of clinical research.

1. Results of clinical trials with renal denervation

The concept of catheter-based sympathetic renal denervation (the RDN) as a method for treatment of resistant hypertension has been subjected to clinical testing in two multicentre trials—Symplicity HTN-1 (proof of concept) and Symplicity HTN-2 (randomized controlled study).

1.1. The Symplicity HTN-1 trial

This non-randomized multicentre trial [1] should assess effectiveness and safety of catheter-based renal sympathetic denervation. 50 patients at five Australian and European centers were enrolled between the year 2007 and 2008, 5 patients were than excluded for unsuitable anatomy of renal arteries. 45 patients received catheter-based renal denervation treatment with subsequent 1 year follow-up. The including criterion was systolic blood pressure ≥160 mmHg on three or more antihypertensive medications, including diuretics.
endpoints were to demonstrate blood pressure reduction and safety of the method at 1, 3, 6, 9 and 12 months after the procedure. Secondary aims were to evaluate renal functions (glomerular filtration) and noradrenaline release after renal denervation performance. Significant decrease in systolic and diastolic blood pressure of 14 mmHg and 10 mmHg in the first month after treatment and 27 mmHg and 17 mmHg in 12 months was showed. Recently published results of two years follow-up of extended group of 153 patients (decrease in blood pressure of 32 mmHg and 14 mmHg) suggest for long-term beneficial effect of treatment on blood pressure level [2]. In six of 45 patients (13%) the decrease of systolic blood pressure was less than 10 mmHg and they were identified as non-responders. In control group of five patients who did not receive renal denervation (excluded for anatomical reasons) had increase in systolic and diastolic blood pressure of +3/-2 and +26/+17 at 1 and 9 months, respectively. Postprocedural lower sympathetic activity, expressed as significant reduce of noradrenaline renal spillover of 47%, was found. Renal functions were not significantly changed. In 43 of 45 patients catheter-based renal sympathetic denervation was performed with no complications. Renal artery dissection during catheter insertion which required denervation treatment delay occurred in one patient. It was treated with stenting of renal artery with no further complications or prolonged hospitalization time. Second patient had pseudoaneurysm of femoral artery at the injection site that was successfully treated conservatively.

1.2. The Simplicity HTN-2 trial

This is multicentre, prospective, randomized trial [3] that includes 106 patients with systolic blood pressure 160 mmHg or more (150 mmHg or more for patients with type 2 diabetes mellitus) treated with combination of three or more anti-hypertensive medication, were randomly allocated in a one-to-one ratio into treated group – undergoing renal denervation (previous medical treatment was not interrupted) and control group – pharmacotherapy (maintain previous treatment). The primary endpoint was change in office-based blood pressure measurement at 6 months after randomization. Secondary endpoints were immediate and long-term safety of renal denervation defined as glomerular filtration reduce >25% or new renal artery stenosis >60% on angiography after 6 months. Other secondary endpoints were also composite cardiovascular index (myocardial infarction, sudden death, heart failure, cerebral ischemia, peripheral arteries revascularization, etc.), changes in 24-h ambulatory blood pressure measurement, incidence of decrease in blood pressure >10 mmHg, etc. 100 of 106 initially randomized patients were finally evaluated, six patients were excluded because of preterm end up with study or because they did not show up at follow-up meeting. Office-based blood pressure measurement in the renal denervation group reduced by 32/12 mmHg from initial 178/96 mmHg (pc < 0.0001 for both systolic and diastolic pressure). Whereas in control group (pharmacotherapy) the change in blood pressure was 1/0 mmHg from initial 178/97 mmHg (p = 0.77 for systolic and p = 0.83 for diastolic pressure). Similar blood pressure changes, only lower in absolute numbers, were noticed in 24-h blood pressure measurements. Reduction in systolic blood pressure more than 10 mmHg or more had 41.8% patients in treated group compared with 18.3% in control group, 19.4% patients treated with renal denervation and 3.6% patients from pharmacotherapy group achieved required systolic blood pressure level of 140 mmHg or less. There were not noted any serious complications related to catheter-based renal sympathetic denervation. As insignificant events related to catheter-based treatment were found: one pseudoaneurysm of femoral artery at the injection site, one postprocedural blood pressure drop, one urinary tract infection, one case of paraesthesia and backache. All these events were successfully treated by standard therapy and did not lead to any other complications. There were no changes in renal functions between two groups. One patient from denervation group had progression of an underlying atherosclerotic lesion in renal artery at 6 months but required no intervention. The lesion was in point of artery where the radiofrequency energy was not applied. No differences were found in composite cardiovascular events between treated and control group.

On the base of results of these trials their authors assess catheter-based renal denervation as safe method for achieving the significant lasting reduction in blood pressure at patients with resistant hypertension.

2. Clinical indications

Renal denervation still is in the late clinical research phase. What we call here “clinical indication” is based on criteria used in Symplicity HTN 1 and 2 trials [1–3] that brought the most significant findings for this type of treatment of resistant hypertension. The patient is indicated for RDN by a hypertension specialist (internist, cardiologist or nephrologist); it is optimal when the patient is indicated and long-term monitored in specialized centers for hypertension. Patient should be checked repeatedly in the same center before indication, preferably at least for six months. It is important that patient is monitored and sent by other physician than who will perform the procedure. The physician must verify patient adherence to treatment using methods that are available (counting tablets remaining from the last visit, monitoring drug levels, electronic drug use monitoring) and consider whether the patient does not commit purposeful behavior (e.g. not using medication prior to disability pension application). Patient must meet the below criteria of blood pressure (BP) while stable treated with minimal three anti-hypertensive drugs from different classes, including diuretics, in optimal doses. When measuring BP in office it should be measured 3 times in a sequence and consider the average of the second and third measurements. Patient should take his medication the days of clinical checks (morning medication using before control) and also the day of ambulatory BP monitoring. 24-h ambulatory blood pressure monitoring (ABPM) was not performed systematically in Symplicity HTN 1 and 2 trials, but we consider it necessary to exclude isolated clinical hypertension (so-called white coat hypertension) because of significantly better prognosis of this type of hypertension compared with full hypertension and that it is not clear whether such patient would benefit from RDN.
While ABPM is performed, BP is measured every 15 min in daytime and at least every 30 min during the night period.

Criteria for RDN indication are

1. good adherence to treatment,
2. hemodynamic stability during follow-up,
3. age 18–85 years,
4. office-based systolic BP ≥ 160 mmHg (average of three visits) while the average systolic BP for 24 h at ABPM is ≥ 140 mmHg when taking at least three types of antihypertensive drugs, including diuretics, in optimal doses, and
5. estimated glomerular filtration rate (MDRD) ≥ 1.0 ml/s/1.73 m².

In cases of clinical indication, the reimbursement negotiations with health care insurance payers are pending.

3. Research indications

Research indications are based on comprehensive pathophysiological perspective on the role of renal sympathetic innervation as a trigger and maintenance factor of resistant hypertension but also its influence on number of other diseases that are significantly associated with RAAS activity. For diagnosis where the indication is not yet approved and also for those using alternative technologies with absence of CE certificate renal denervation could be performed exclusively within the proper research protocol administered according to strict principles of good clinical practice. Each of these protocols must be approved by ethics committee of the department, patient must have detailed written information about the nature and risks of the research and must confirm in writing form its consent with the procedure defined in the research indication.

Currently, RDN research is focused especially on

1. resistant hypertension in patients in hemodialysis program,
2. possible influence on sleep apnea syndrome,
3. advanced heart failure with left ventricle systolic dysfunction,
4. recurrent symptomatic heart failure with preserved function of left ventricle,
5. influence on insulin resistance and atherosclerosis, and
6. resistant hypertension with office-based systolic BP ≥ 140 mmHg and average systolic BP for 24 h at ABPM ≥ 130 mmHg when taking at least three types of antihypertensive drugs.

Payment by health care insurance payers is not expected in research indications.

4. Risks and contraindications

RDN is like any other intervention performed via arterial approach associated with general risks of catheterization (access site hematoma, AV fistula, aneurysm, artery dissection, artery perforation, etc.) and also with some specific complications.

Specific risks associated with RDN are

1. renal artery perforation due to application of radiofrequency (RF) energy,
2. adrenal artery occlusion during RF application to its take-off from the renal artery,
3. stenosis/occlusion of renal artery (more likely in renal arteries with diameter < 4 mm),
4. extended spasm of renal artery,
5. pain after RF energy application, and
6. dissection of renal artery due to catheter manipulation.

Contraindications to RDN

- Secondary hypertension.
  ○ Nefrogenic hypertension.
  ○ Endocrine conditioned hypertension.
  ○ Hypertension induced by drugs that cannot be discontinued (e.g. corticosteroids).
  ○ Hypertension in untreated sleep apnea syndrome.
- History of acute coronary syndrome or stroke in last six months.
- Implantable cardioverter-defibrillator (pacemaker is relative contraindication).
- Hemodynamically significant valvular heart disease.
- Type 1 diabetes mellitus.
- Type 2 diabetes mellitus with developed organ complications such as proteinuria > 1 g/24 hod or proliferative retinopathy.
- Morbid obesity (BMI 35 kg/m² or more).
- Pregnancy (current or planned at the time within six months after the procedure).
- Other diseases that significantly affect life expectancy (life expectancy less than two years) or quality of life (in particular a significant decline in cognitive functions).
- Renal insufficiency with GFR < 1.0 ml/s/1.73 m².
- Renal arteries with unsuitable morphology (short course, massive calcification, stenosis, previous PTA) or with diameter < 4 mm.

5. Patient preparation. Renal denervation procedure

Patient who fulfills clinical indication criteria for renal denervation [4] and/or inclusion criteria for specific research project is admitted to hospital for 1–2 days. The organizational management of the hospitalization is very similar to the one of elective percutaneous coronary intervention (PCI) via femoral artery. Patient preparation for intervention is analogical, too: patient should have an empty stomach and should be well hydrated before the procedure (drinks but no food prior to intervention are allowed). Hypertension pharmacotherapy should remain unchanged before (and after) the intervention and patient should take acetylsalicylic acid prior to the procedure. At the beginning of the intervention, intraarterial bolus of 100 IU/kg of heparin is administered via catheter.

Catheter-based renal denervation (RDN) starts with introduction of catheter sheath to femoral artery (technique identical to coronary angiography or PCI). Afterwards, pigtail catheter-based angiography of the abdominal aorta aiming to depict both (and any accessory) renal arteries is performed. Angiography must confirm that renal arteries considered for denervation are at least 4 mm in diameter. Their length should at least 2 cm
and no significant stenosis or massive calcifications should be present. The type of guiding catheter is selected in accordance with the anatomy of the origin of renal arteries (the most common types of catheters are IMA, RDN1 or RDC1 with length of 45–55 cm, width of 6 F). The catheter is then introduced to the origin of renal artery (usually starting with left one).

At this moment, the sedation/analgesia should be administered. The most frequently used analgesic agent is ketamine and sedative propofol. Alternatively, combination of fentanyl and midazolam may be used. The sedation/analgesia should be performed by an anesthesiologist or an intensivist with a sufficient experience with its administration. Since the ablation itself is usually accompanied by severe pain in lumbar area, efficient sedation/analgesia is essential.

A special ablation catheter Symplix®C, connected to radiofrequency energy generator is then introduced to the femoral artery via guiding wire. This ablation catheter is currently a sole device approved for the intervention. The distal end of the catheter is introduced close to the point of renal artery branching and then bent or rotated until it touches, but not overly presses the wall of the artery. Afterwards, radiofrequency energy is applied for 120 s. During a correctly performed ablation, the temperature at the ablation spot should rise to approx. 45–65 °C (never higher than 70 °C). This can be monitored (together with the impedance changes) on the display of the ablation device. The generator switches off automatically after 120 s of ablation, or after reaching the maximal power of 8 W, respectively. It equally turns off automatically when the temperature rises insufficiently (it indicates the absence of contact between the catheter and arterial wall). This procedure is repeated 4–6 × while pulling out and rotating the ablation catheter. The ablation spots in the renal artery roughly follow a spiral contour. The distance between single “ablation spots” should be at least 5 mm. The last ablation spot (closest to the aorta) should be located on the proximal cranial wall of the renal artery, as the density of sympathetic nervous plexus is the highest there. After the last ablation and removal of the ablation catheter, selective angiography of this renal artery is performed in order to rule out possible complication [5].

The same method applies to the second renal artery (after verifying the heparinization effectiveness using the ACT—target values ≥ 250). Considering higher complications rate for renal arteries thinner than 4 mm, currently it is not recommended to target these arteries. There is so far no evidence concerning the course of action for patients with multiple renal arteries, where on every side only one has diameter of 4 mm or greater. Some workplaces do not indicate these patients for RDN at all, some perform RDN only on arteries with sufficient diameter and leave out narrower arteries. This method is safe; nevertheless, it is unknown whether it is effective.

Apart from the mentioned material there should always be renal stents of an appropriate size available (in case of dissection caused by a guiding or ablation catheter) and a super-thin (0.014 in.) guiding wire. Continuous monitoring of ECG, respiratory rate and invasively measured aortic blood pressure during the intervention should be a matter of course.

The entire intervention (from the arterial puncture until the removal of all catheters form the sheath) lasts usually 45–60 min and during its performance 60–100 ml of contrast agent is administered (volume prior to dilution). The contrast agent is diluted in saline solution 1:1.

After the procedure, the patient must be monitored until the complete retreat of sedation/analgesia. The regimen afterwards resembles to the regimen following elective PCI (care for groin puncture site and monitoring of diuresis). The patient should be followed up at the center providing the RDN and/or by a hypertension specialist who indicated the intervention. The antihypertensive medication should remain unchanged, only when there is a significant long-term drop in blood pressure after RDN, the dosing or number of antihypertensive drugs may be reduced gradually. The decrease of blood pressure never occurs immediately after the RDN (any instantaneous pressure reduction is more likely associated with the sedation/analgesia than with the effect of RDN itself); it develops weeks to months following the RDN. The follow-up on the outpatient basis should last not less than 2 years after the intervention (the blood pressure values including the ambulatory monitoring, renal functions monitoring, diabetes management), it is advisable to check the renal arteries morphology (ultrasound, computed tomography or magnetic resonance) 6–12 months after the RDN. The acetylsalicylic acid intake throughout 4 weeks following the intervention is an important preventive measure of thrombotic complications. First follow-up should occur up to one month after the procedure and besides the clinical check-up it should involve common laboratory tests such as renal markers and mineralogram. Further clinical follow-ups should be provided in minimum intervals of 6 months.

6. Qualification criteria for physicians taking part in indication process, performing RDN procedures and responsible for patients follow-up

The catheter-based renal denervation is a typical multidisciplinary procedure. Physicians experienced in diagnostics and treatment of severe arterial hypertension should take part in the indication process (preferably working at specialized hypertension centers in Czech Republic) which possesses the "Hypertension center of Excellence" certificate of the European Society of Hypertension (see www.eshonline.org), that means internists, cardiologists and nephrologists.

(a) The intervention should be carried out by a physician with the sufficient experience with the intravascular interventions and transarterial access. Interventional cardiologists are usually the most experienced in transfemoral access (license no. F010 of the Czech Medical Chamber) and this specialization is the most involved in the RDN progress worldwide. Regarding the experience in radiofrequency ablation, other group of physicians capable of this intervention are cardiologists specialized in arrhythmology (license no. F014). Naturally, the most skilled in renal arteries interventions are interventional angiologists (license no. F021) or interventional radiologists (board certification in interventional radiology). Two criteria should be taken into consideration when deciding who from these specialists would perform the intervention at the particular hospital: (1) extensive
experience with the catheter-based interventions via femoral artery, and (2) capability of systematic scientific research and critical analysis of the results including publication activity (this particular criterion should apply until the definitive establishment of RDN in the clinical practice and the intervention routine coverage by health insurance).

(b) The sedation/analgesia throughout the procedure should be administered by an experienced intensivist or anesthetist.

(c) Patients’ follow-up after the intervention should be provided by the indicating physician (internist, cardiologist, nephrologist) within hypertension centers (see above) or cardiologist at the intervening center.

7. Personnel and equipment requirements for the departments authorized to provide RDN

There are certain minimal requirements for personnel, material equipment and quantity of key interventions provided by the departments (Table 1). In general it is possible to say that the catheter-based renal denervations may be performed only at specialized tertiary cardiovascular centers (see their list in the Journal of the Czech Ministry of Health [6]). Apart from the fact that the departments providing RDN must be on this Ministry of Health list, they must fulfill following additional requirements (Table 1).

8. Conclusion

It is essential, that until additional and/or larger randomized clinical trials confirm (or not) the promising results of initial studies (and decide whether this promising method will become a standard part of the treatment strategy for severe resistant hypertension), renal denervation can be performed exclusively as part of specific research protocols, approved by ethical committees. Renal denervation should be performed only in tertiary centers with ongoing research and publication activity to guarantee, that the results will be objectively and critically evaluated. It is unethical to promote this method already today (early 2012) for routine hypertensive patients as a standard (proven) part of their treatment. Each patient must be informed, that renal denervation still is in the phase of clinical research.

REFERENCES