SPECIAL REPORT

Renal denervation for the treatment of hypertension: the Dutch consensus

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ABSTRACT

Since 2010, renal denervation (RDN) is being performed in the Netherlands. To make sure RDN is implemented with care and caution in the Netherlands, a multidisciplinary Working Group has been set up by the Dutch Society of Cardiology (NVVC). The main aim of this Working Group was to establish a consensus document that can be used as a guide for implementation of RDN in the Netherlands. This consensus document was prepared in consultation with the Dutch Association of Internal Medicine (NIV) and the Dutch Society of Radiology (NVVR).

KEYWORDS

Renal denervation

INTRODUCTION

Since 2010, renal denervation (RDN) is being performed in the Netherlands. RDN is a percutaneous catheter therapy for the treatment of resistant hypertension and is based on a promising concept. The first studies that investigated the efficacy of RDN showed impressive blood pressure reductions.[1,2] However, more recently the sham-controlled Symplicity HTN-3 trial demonstrated a less pronounced reduction of blood pressure and a relevant placebo effect.[3] To implement RDN with care and caution in the Netherlands, a multidisciplinary working group has been set up by the Dutch Society of Cardiology (NVVC). The overall consensus is that RDN seems a promising therapy to lower BP.

At present, RDN is being used in two groups of patients:

- In patients with resistant hypertension.
- In patients fulfilling the same blood pressure criteria, but without optimal pharmacological treatment due to recorded intolerance for antihypertensive drugs. These patients often pose dilemmas to the treating physician.

Resistant hypertension is defined as a blood pressure that remains above goal despite the concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic.[4] Patients whose blood pressure is controlled with four or more antihypertensive drugs are also considered to have resistant hypertension.[4] The main aim of this Working Group was to establish a consensus document that can be used as a guide for implementation of RDN in the Netherlands. This consensus document was prepared in consultation with the Dutch Association of Internal Medicine (NIV) and the Dutch Society of Radiology (NVVR). The principle is that a patient is being treated with a blocker of the renin-angiotensin system (RAS), a thiazide diuretic and a calcium antagonist in optimal dosages. In addition, it is preferable to add an aldosterone antagonist to the drug regimen. Patients should be screened first before they are treated by RDN. Screening of patients may be considered when they have an office systolic blood pressure of ≥ 160 mmHg. Subsequently a 24-hour ambulatory blood pressure

measurement should be performed while the patient is using antihypertensive drugs to exclude white coat hypertension.[5] Since 1 January 2013, there is a conditional reimbursement for RDN in the Netherlands.

Principles of the consensus document

In the future, RDN may have an important place in the treatment of patients with resistant hypertension. The indication of RDN might be expanded to milder forms of hypertension. However, further research is needed for such indications. The hospital in which RDN is performed must meet certain criteria regarding infrastructure and organisation.

When writing the present consensus document on RDN, two elements played an important role:

- In the first place: the safety of the patient.
- In second place: transparency. This transparency refers to:
  - Participation in the national registry. In this national database essential clinical data and technical aspects of the procedure are prospectively documented.
  - Reporting of clinical results.

Based on the above, the Working Group states that it is highly preferred that each patient who undergoes RDN should be treated in the context of a study or trial. At least, the patient should be included into the national registry. This is an online database operated by the Julius Center for Health Sciences and Primary Care. The Julius Center is an independent centre and will only perform analysis on the registry after written approval of the participating centres.

Standards of quality

A hospital that wants to qualify for RDN should comply with all of the following criteria to meet the optimal conditions for patient safety:

- The department of radiology or cardiology of the hospital has a catheterisation room with access to up-to-date X-ray equipment with support by experienced technicians and nurses. There is also the appropriate infrastructure to deal with any complications.
- The department of radiology or cardiology features:
  A subdivision of interventional radiology in which at least one specially designated radiologist (interventional radiologist) performs catheter-based treatments of the greater vessels on a weekly basis (> 50 annually):
  Be it a subdivision of intervention cardiology which, according to the criteria of the NVVC and in accordance with the Act on Exceptional Medical Operations (WBMV), is authorised to perform percutaneous interventions;
  Or a subdivision of clinical electrophysiology that, according to the criteria of the NVVC and in accordance with the WBMV, is authorised to perform electrophysiology catheter ablations.
- The hospital has a department of general surgery with a (sub) section on vascular surgery.
- The hospital has a vascular medicine specialist and / or a nephrologist specialised in hypertension, where patients can go for the exclusion of secondary causes of hypertension.
- Any patient who qualifies for RDN is discussed beforehand in a multidisciplinary team. This team is responsible for the exclusion of secondary causes of hypertension.
- Ambulatory blood pressure measurements, outpatient blood pressure measurements on the left and right arm, laboratory testing (serum and urine), and detailed imaging should be first performed to exclude secondary causes of hypertension. Preferably, the laboratory measurements are performed during a drug-free period to prevent the influence of the drugs on these measurements. The following measurements should be performed:
  Serum tests: Sodium, potassium, creatinine, haemoglobin, fasting glucose, fasting lipid spectrum, thyroid-stimulating hormone, plasma renin activity or plasma renin concentration and aldosterone according to the guidelines of the Endocrine Society.[6]
  24-hour urine collection: Sodium, creatinine, protein and albumin. Determination of metanephrines may be considered if there is a clinical suspicion of pheochromocytoma.
  When Cushing's disease or Cushing's syndrome is suspected, saliva cortisol or 24-hour urinary cortisol can be determined.
  When it is deemed medically unsafe to temporarily stop antihypertensive drugs, no reliable judgment can be made upon a possible primary hyperaldosteronism. In such cases the physician can consider to take the measurements under 'rescue-drugs' (diltiazem and/or doxazosin). Measurement of the aldosterone-renin ratio while using antihypertensive drugs is generally useless to diagnose primary hyperaldosteronism. A computed tomography (CT) scan may show incidentalomas, which can subsequently lead to extra diagnostics. When there is doubt about the diagnosis of primary hyperaldosteronism, a sodium-challenge test should be performed. Except for incidentalomas, the multidisciplinary team should realise that micro-adenomas can be easily missed at CT or magnetic resonance imaging (MRI).
- Secondary causes of hypertension that should first be excluded are:
  - Primary hyperaldosteronism
  - Cushing's syndrome
  - Coarctation of the aorta
  - Pheochromocytoma
  - Excessive liquorice intake
  - Thyroid disorders

The reason for exclusion is that these conditions require a distinctly different treatment. In *Appendix A* advice is given about the implementation of the various measurements.

- In the anamnesis the patient should be asked about medication compliance. In *Appendix B* the Morisky questionnaire is provided. This is a validated questionnaire that can be used to inform about medication compliance. When in doubt about compliance, this must be analysed. Documenting the impact of supervised intake of antihypertensive drugs on the blood pressure is hereby recommended. Furthermore one can determine the ACE activity in a patient who is on an ACE inhibitor.
- Lifestyle advice should be given to and implemented by the hypertensive patients before RDN is considered. This advice should include a reduced salt intake.
- To evaluate the anatomy of the renal arteries non-invasive imaging should be carried out before RDN is performed. Preferably CT angiography (CTA) or MR angiography (MRA) are used as non-invasive imaging modalities. A conventional angiography may also be considered. This (non-invasive) imaging will provide information to evaluate whether the anatomy of the patient is suitable for RDN. The following criteria should be met:
  - The renal artery has a diameter of ≥ 4 mm and a length of ≥ 20 mm.
  - No significant haemodynamic or anatomic renal artery stenosis is present.
  - One main renal artery is present on both sides with a diameter of ≥ 4 mm.

  Immediately prior to RDN a conventional angiography should be performed.
- A multidisciplinary team should be established, consisting of the physician performing RDN and a supporting specialist who has excluded secondary forms of hypertension. Each patient must be discussed in this team prior to screening for true hypertension and after the screening to reach consensus about the indication for RDN. Both eligible and non-eligible patients should be registered in a database.
- Absolute contraindications for RDN are:
  - GFR < 30 ml/min/1.73 m^2
  - A haemodynamicaly significant renal artery stenosis (> 50%)
  - Fibromuscular dysplasia of the renal artery
  - A secondary cause of hypertension
  - Nephrectomy or a mono-kidney (considering the present lack of data on the effects of the RDN procedure in these patient groups)
  - Pregnancy (considering the radiation during the procedure)
  - Incompliance for antihypertensive drug treatment
- Besides absolute contraindications, there are also relative contraindications to RDN. When one of the following is present, the physician performing RDN should be cautious about potential complications and precautions must be taken.
  - Contrast allergy
  - Atherosclerosis
  - A non-significant renal artery stenosis (< 50%)
  - Severe peripheral artery disease
  - Aortic bifurcation prosthesis
  - Coagulation disorders
- For the prevention of thrombus formation we recommend to prescribe antithrombotic therapy to the patient. Preferably aspirin 100 mg once daily is given starting three days prior to the procedure up to 30 days after the procedure.
- The team that performs RDN, consisting of the interventional cardiologist, interventional radiologist, or electrophysiologist and all relevant supporting disciplines, should have been extensively trained in the procedure. Training offered by the manufacturer, training in the skills lab or training in another centre can all be used for this purpose.
- The physician performing RDN carries out at least 20 RDN procedures annually. This number is achieved through a system of ingrowth, whereby the minimum of 20 procedures annually should be established after two years.
- The physician performing RDN has successfully completed a fellowship in interventional radiology, interventional cardiology, or clinical electrophysiology.
- In the hospital performing RDN, a protocol is present in which all steps of RDN are documented. This protocol includes the screening investigations in the outpatient clinic, the clinical aspects of the procedure itself, and the follow-up.
- The hospital has an electronic database in which relevant data on patient, procedure and complications can be registered.
- The hospital is participating in the national registration on renal denervation (operated by the Julius Center for Health Sciences and Primary Care). In this registry key demographic, clinical, and technical data and outcomes are recorded. The hospital cooperates with (ad hoc) audits and quality.
- The Working Group on RDN will report annually to the NVVC, the NIV, and the NVVR about national results of RDN procedures in the Netherlands.
- Every year, there should be a follow-up of patients who have undergone RDN. During this follow-up the 24-hour blood pressure, the number of antihypertensive drugs, and the renal function should be monitored. During the follow-up one year after treatment, we recommend to perform non-invasive

imaging of the renal arteries (the same modality as used prior to RDN). During follow-up, antihypertensive drugs should be continued. When adjustment (reduction or increase) of antihypertensive drugs is indicated, in the opinion of the treating physician, this should be done. We advise to follow the patients every six months during the first three years, and thereafter annually for up to five years after RDN. The national database will send reminders to the treating physician if the online follow-up questionnaire has not been completed. Appendix C provides an example for the follow-up.

DISCLOSURES

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APPENDIX A.

Advice from the Working Group regarding the performance of various assessments to exclude secondary hypertension.

Imaging of the renal arteries
By performing imaging of the renal arteries, renal artery stenosis can be excluded. Preferably, imaging is performed by MRA / CTA or conventional angiography.

Temporary stop of antihypertensive drugs
In order to obtain reliable results from the laboratory assessment it is strongly recommended that patients stop taking their antihypertensive drugs for at least two weeks prior to the investigations. Most antihypertensive drugs may simply be stopped at once, with the exception of beta blockers and centrally acting antihypertensives (methyldopa, clonidine, and moxonidine), which should be tapered. Stopping or tapering can be done as follows:
Four weeks prior to the investigations:
Stop: diuretics (including aldosterone antagonists) and aliskiren
Taper in two weeks, starting four weeks prior to the investigations: beta blockers and centrally acting antihypertensives according to the following scheme:

Day 1	100%	Day 6	0%	Day 11	25%
Day 2	50%	Day 7	50%	Day 12	0%
Day 3	50%	Day 8	0%	Day 13	25%
Day 4	50%	Day 9	25%	Day 14	0%
Day 5	50%	Day 10	0%		

Using this scheme, the beta blockers and centrally acting antihypertensives may be stopped two weeks prior to the investigations.
Two weeks prior to the investigations:
Stop: ACE inhibitors, calcium antagonists, alpha blockers, direct vasodilators. Also, no NSAIDs should be used in this period.

Rescue medication
If it is deemed unsafe by the treating physician to temporarily stop the antihypertensive treatment, rescue medication can be given. Examples of rescue medication are diltiazem retard (200 mg or 300 mg once daily) or doxazosin retard (4 mg or 8 mg once daily). When a patient experiences side effects from the medication stop, these rescue drugs may also be prescribed.
Next to the stopping and/or tapering of antihypertensive drugs, patients should be told that

in the 3-4 days prior to the examinations it is very important to maintain a constant daily salt intake. In daily practice this means that especially (extremely) salty meals (ready-to-eat meals, pizza, soup) should be avoided.

Interim control of potassium
In order to prevent a possible hypokalaemia from affecting the aldosterone-renin test, the potassium is determined at the end of the first medication-free interval. Hypokalaemia may lead to a false-negative outcome of the test. In the case of hypokalaemia, temporary potassium supplements are advised.

Saliva cortisol
The patient is given a salivette and instructions to collect saliva cortisol. In the second medication-free week the patient is instructed to take saliva at home at 23.00 hours. The saliva sample should be stored in the fridge and sent to the laboratory.

Blood sampling
The following measurements should be performed: Sodium, potassium, creatinine, urea, glucose, cholesterol, HDL, LDL, triglycerides. The blood can be drawn from the infusion after a dummy tube is taken to rinse off the NaCl from the infusion. After withdrawing blood the infusion should be injected with 3 ml of NaCl 0.9% to prevent clotting.
Measurement of glucose, cholesterol, HDL, LDL, and triglycerides should be performed under fasting conditions.

Aldosterone-renin ratio
The purpose of the aldosterone-renin test is to determine hyperaldosteronism. This test should be performed under the conditions prescribed in the guidelines from the Endocrine Society.[6]

24-hour urine collection
Patients are given a container to collect urine for 24 hours. From this 24-hour urine the following measurements can be done: sodium, potassium, creatinine, protein, albumin and metanephrines (the last when indicated). When indicated catecholamines or cortisol can also be determined in the 24-hour urine or in a urine sample.

APPENDIX B.

The Morisky 8-Item Medication Adherence Scale

1. Do you sometimes forget to take your high blood pressure pills?
2. Over the past two weeks, were there any days when you did not take your high blood pressure medicine?
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?
4. When you travel or leave home, do you sometimes forget to bring along your medications?
5. Did you take your high blood pressure medicine yesterday?
6. When you feel your blood pressure is under control, do you sometimes stop taking your medicine?
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment plan?
8. How often do you have difficulty remembering to take all your blood pressure medication?

Alpha reliability = 0.83
Morisky *et al*. J Clin Hypertens. 2008;10:348-54

APPENDIX C. OUTPATIENT FOLLOW-UP AFTER RENAL DENERVATION

3-6 weeks after the procedure
Control of the groin
Outpatient blood pressure measurement in both arms
Laboratory investigations (renal function, electrolytes, haemoglobin)

3 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.

6 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements may be considered

9 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.

12 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements
Laboratory investigation (renal function, electrolytes)
Non-invasive imaging of the renal arteries may be considered

18 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements

24 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements
Laboratory investigation (renal function, electrolytes)

36 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements
Laboratory investigation (renal function, electrolytes)

48 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements

60 months after RDN
Outpatient blood pressure measurement in the arm with the highest pressure.
24-hour ambulatory blood pressure measurements
Laboratory investigation (renal function, electrolytes)