Effect of renal sympathetic denervation on renal and overall sympathetic output in patients with therapy resistant hypertension

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Ethical review	-
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON37991

Source
ToetsingOnline

Brief title
Effect of renal sympathetic denervation on sympathetic nervous activity

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Vascular hypertensive disorders

Synonym
Therapy resistant hypertension ; renal sympathetic denervation

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: AMC flexible OIO grant

Intervention

Keyword: denervation, renal, sympathetic

Outcome measures

Primary outcome

Primary objectives:

To determine predictors of the BP lowering response of RSD by evaluation of:

1. Assessment of sympathetic tone by beat-to-beat analysis

2. Assessment of the effectiveness of RSD by renal MIBG-uptake

post-intervention

3. Assesment of medication adherence before and after RSD.

Secondary outcome

Secondary objectives:

To assess the auxiliary effects of RSD on:

1. Insulin sensitivity

2. Low grade inflammation

3. Central haemodynamics.

Study description

Background summary

Radiofrequency ablation of the renal sympathetic nerves has emerged as a novel minimally invasive technique to improve BP control in patients with therapy resistant hypertension. Recently a randomized controlled trial showed that, in

patients with therapy resistant hypertension, renal sympathetic denervation (RSD) resulted in a significant reduction in office BP of 32 mmHg after 6 months, compared to an increase of 1 mmHg in controls receiving conventional BP lowering therapy. Despite the general effectiveness of RSD in lowering BP in patients with therapy resistant hypertension, the magnitude of the individual BP lowering response is variable. In the recent Simplicity-2 study, the large SD of the observed BP lowering effect and the variability in BP outcome parameters suggest large differences in response to RSD. Moreover, BP failed to go down in 10% of the patients after RSD and only 39% of all patients were able to get their BP controlled (BP<140/90 mmHg). The large BP variability observed after RSD may result from several factors. First, the BP response to RSD may depend on the relative contribution of the kidneys in determining total sympathetic output. Quantifying sympathetic activity prior to RSD may predict the efficacy of RSD in lowering BP. Second, because controls received no sham treatment in the Simplicity-2 study, differences in BP may result from differences in adherence to BP lowering medication. Third, there is no certainty whether in humans afferent and efferent renal nerves are truly ablated by this novel technique. For obvious reasons, the effectiveness of ablation of renal afferent and efferent nerves has only been tested in animal studies.
Next to the BP lowering effect, RSD may also exert auxiliary benefits. It is well-established that diabetes mellitus and insulin resistance are associated with an increase in sympathetic activity. Furthermore, inhibition of sympathetic output by sympathicolytic agents such as alpha1 receptor blockers or centrally acting alpha agonists improves insulin sensitivity. It is therefore conceivable that RSD, by its decrease in total sympathetic output, may improve insulin sensitivity.
In addition the decrease in sympathetic tone may also reduce the expression of inflammatory parameters (e.g. Il-6, TNF-alpha, total WBC count), and alter central haemodynamics. We recently showed that central BP is lowered after standing. This effect may be mediated by an increase in sympathetic activity. It is conceivable that reducing sympathetic output by renal sympathetic denervation may therefore influence central BP.
Moxonidine, an I1-Imidazoline receptor agonist and centrally acting antihypertensive drug, is frequently used for the treatment of resistant hypertension and known to effectively lower sympathetic neural activity. In this study a matched Moxonidine treated group may serve as a positive control for RSD in overall sympathetic neural activity dependant outcome parameters.

Study objective

In this study our overall aim is to more precisely determine which patients will benefit most from RSD by evaluating both outcome predictors and auxiliary effects (insulin sensitivity, central haemodynamics and inflammation) of this new intervention.

Study design

Controlled experiment with measurements prior to RSD (<3 weeks) and 6 weeks after RSD with positive six-week-moxonidine-treated controls (case-control design).

Patients
Study candidates will be approached by the study physician for participation if they are referred for RSD because of therapy resistant hypertension. A maximum of 20 patients will be enrolled to undergo RSD with measurements before and after intervention. An additional 10 patients who will receive moxonidine treatment for therapy resistant hypertension will undergo the same measurements prior to and after six weeks of moxonidine. Patients will be enrolled in the age-, gender-, BMI-matched moxonidine positive control group if they are deemed unsuitable for RSD by the treating physician (e.g. inaccessible femoral artery, or accessory renal artery) and are prone to start treatment with moxonidine for therapy resistant hypertension.

Visit 1 - Screening visit
Six weeks prior to the first measurements a screening visit will be planned with the aim to assess whether patients are eligible for inclusion. During the screening visit a clinical examination will be carried out and laboratory and imaging results will be obtained to assess whether secondary causes of hypertension have been sufficiently excluded and whether renal function is intact (eGFR >45 ml/min/kg). Eligible patients will be informed about the experiments and the study burden. If patients are willing to participate they will be asked to provide written informed consent (see InformedConsentRSD). Next they will receive a questionnaire to assess medication adherence and an appointment will be made for the 24 hour ambulatory BP recording. 24-hour urine will be collected for measurement of catecholamines. After the results of the ambulatory BP measurement are obtained patients will be included in the study. The screening visit will take approximately 45 min.

Visit 2 - Measurements prior to RSD or moxonidine
Visit 2 will take place 3 weeks prior to RSD. Before the measurements patients will be asked to return the questionnaire. Thereafter office BP will be measured and pulse wave analysis will be performed followed by assessment of pulse wave velocity, central haemodynamics and sympathetic activity. Blood samples will be drawn during non-invasive assessment of central haemodynamics and after conclusion of the measurements. A catheter will be inserted to facilitate for drawing of blood samples. A total of 50ml of blood will be drawn.

Visits 3 and 4 - Measurements after RSD or moxonidine
Visit 3 will take place approximately 6 weeks after RSD. The measurements conducted during this visit are identical to the measurements conducted on

visit 2 (including 50ml of venous blood sampling). In addition a 123I-MIBG-scintigraphy, with a single oral dose of furosemide retard 60mg, will be performed after the non-invasive measurements have been conducted. The 123I-MIBG-scintigraphy includes a scintigram performed 15 minutes after tracer injection and early in the afternoon (4 hours post injection). A final scintigram will be performed at visit 4, 24 hours post MIBG tracer injection. Additionally, an appointment will be made for 24-hour ambulatory blood pressure measurement.

Additional investigations
All subjects included in this study will undergo the above mentioned measurements.
Additionally, in a subset of maximum 12 patients undergoing RSD a hyperinsulinaemic euglycaemic clamp experiment will be performed prior to RSD and after RSD. The clamping experiments will take place on two different occasions, adjacent to visit 2 and visit 3. Patients will be asked to participate in this sub-study if they have insulin-resistance, defined as a fasting blood insulin level of > 50 pmol/L. For these additional investigations a separate informed consent will be obtained (see InformedConsentRSDClamp).

Study burden and risks

RSD is a minimally invasive technique that has been shown to effectively and safely reduce BP in 90% of patient with therapy resistant hypertension. Despite its general beneficial effects on BP control, the magnitude of the BP lowering response is difficult to predict. We believe that estimates of sympathetic activity may help in selecting patients who will benefit most from this intervention. The measurements used for assessment of peripheral and central haemodynamics are all non-invasive, painless and safe. A total of 2x50ml (100ml) of venous blood will be drawn for study purposes. Subjects will have a intravenous cannula inserted on two visits to facilitate for blood drawings and 123I-MIBG injection. Included subjects in this study will be exposed to radiation as a result of the 123I-MIBG scintigraphy performed. The radiation exposure is well within the international limits as defined by the WHO (4.2mSv, ICRP category IIb). In addition, subjects who participate in the sub-study on insulin sensitivity will have additional blood drawings of 2x150ml (300ml). The hyperinsulinemic euglycemic clamp is the gold standard to measure glucose metabolism and is considered to be safe. It will be performed at the metabolic unit of the department of Endocrinology and Metabolism. The glucose tracer has no side effects and is provided by the in-house pharmacist. It will be prepared for infusion by the researcher on the day of the experiment.
The benefits related to the present study consist of the development of new methods that are able to predict the BP lowering response to this relatively new BP lowering intervention and to assess whether, apart from lowering BP, additional beneficial effects exist on insulin resistance and inflammation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients aged 40-70 years receiving RSD for therapy resistant hypertension, defined as daytime ABPM*150/100 mmHg despite the use of 3 or more anti-hypertensive drugs including or with intolerance to a diuretic.;No evidence of secondary hypertension (renal artery stenosis, pheochromocytoma, primary aldosteronism and hyper- or hypothyroidism have to be excluded prior to the intervention). ;Normal renal anatomy, single renal artery bilaterally.;Able to provide informed consent. ;Willingness to participate.

Exclusion criteria

Renal insufficiency (eGFR<45 ml/min) or proteinuria>1 gram/24 hrs.;Pacemaker or ICD device;Atrial fibrillation;Diabetes Mellitus type 1;Unstable weight 3 months prior to

inclusion;Pregnancy ;Treatment of DM type 2 with insulin, PPARγ-agonists or SU-dervatives (for clamp experiment only)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-06-2011
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	06-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL36755.018.11