Renal denervation in patients with resistant hypertension

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Cover illustration: Canine renal ganglion, non-ablated. From Hou Y et al., PLOS One 2013, with permission of the publisher.

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ABSTRACT

BACKGROUND

Catheter-based renal denervation (RDN) is a potential modality in the treatment of patients with resistant hypertension (RH). The biological effects of RDN are not fully comprehended and studies examining its impact on blood pressure (BP) and other cardiovascular surrogate markers have generated conflicting results.

AIMS

Study I aimed to assess coronary flow reserve (CFR) in patients with RH. Study II was performed in order to estimate the effect of RDN on CFR. In Study III, we examined the safety and efficacy of RDN in a real-world setting. Study IV aimed to estimate the impact of RDN on muscle sympathetic nerve activity (MSNA).

METHODS

We assessed CFR in 25 patients with RH and matched controls with controlled hypertension in Study I. In Study II, we used the same modality in 26 patients with RH, before and six months after RDN. In Study III, we used data from the Swedish Registry for Renal Denervation. In Study IV, we assessed MSNA at rest and during mental stress in patients with RH before and six months after intervention.

RESULTS

RH was associated with impaired CFR as compared to patients with controlled hypertension (I). Despite a significant reduction in BP, we did not detect any significant changes in CFR six months after RDN (II). Registry analysis showed significant reduction in office and ambulatory blood pressure six months after RDN. The procedure proved feasible and was associated with a low complication rate (III). No significant changes in MSNA at rest and mental stress were noted at six-month follow-up (IV).

CONCLUSIONS

RH is associated with an impairment of the coronary microcirculation, which may contribute to the increased risk of cardiovascular events in this patient group. RDN did not change the course of CFR, despite a significant reduction in BP. Registry data suggest a sustained reduction in both office and ambulatory BP. MSNA was unchanged at follow-up, which raises questions about the biological effects of RDN and its impact on the autonomous nervous system.

SAMMANFATTNING PÅ SVENSKA

Bakgrund och syfte

Kateterbaserad renal denervering (RDN) är en metod i behandlingen av patienter med resistent hypertoni (RH). De biologiska effekterna är inte helt kartlagda och studier avseende blodtryck har visat motstridande resultat. Avhandlingsarbetet syftar till att belysa effekten på utvalda kardiovaskulära surrogatmarkörer och närmare kartlägga mekanismen bakom RDN.

Metoder

Delarbete I beskriver hjärtats koronarflödesreserv (CFR) i patienter med RH i jämförelse med kontrollerad hypertoni. I delarbete II bestämdes CFR i patienter med RH före och sex månader efter RDN. Delarbete III är en nationell registerstudie där vi analyserade data från Svenska Registret för Renal Denervering avseende säkerhet och blodtryckseffekt. I delarbete IV användes mikroneurografi för att mäta muskelsympatisk nervaktivitet (MSNA) i patienter med RH. MSNA utfördes i vila och vid mental stress, före och sex månader efter RDN.

Resultat

RH var associerat med lägre CFR jämfört med patienter med kontrollerad hypertoni (I). RDN medförde en minskning av blodtryck men hade ingen signifikant effekt på CFR vid sex-månaders-uppföljning (II). Registeranalysen visade en ihållande minskning av både office- och 24-timmarsblodtryck. Ingreppet förefaller säkert och är associerat med ett lågt antal komplikationer (III). MSNA i vila och vid mental stress var oförändrat sex månader efter RDN (IV).

Slutsatser

RH är associerat med en nedsatt kardiell mikrocirkulation vilket kan bidra till patientgruppens höga risk för kardiovaskulära händelser (I). RDN medförde ingen effekt på CFR trots en kliniskt betydande blodtryckssänkning (II). Den första svenska registeranalysen visar en ihållande och potentiellt betydelsefull blodtrycksminskning efter RDN (III). MSNA förblev oförändrat efter RDN, både i vila och vid mental stress-provokation. Resultaten stödjer därmed inte den rådande hypotesen om verkningsmekanismen bakom RDN (IV).

LIST OF PAPERS

This thesis is based on the following studies, referred to by their Roman numerals.

I

Völz S, Svedlund D, Andersson B, Gan LM, Rundqvist B.
Coronary flow reserve in patients with resistant hypertension
Clinical Research in Cardiology 2017 Feb; 106 (2):151-157

II

Völz S, Rundqvist B, Ljungman C, Andersson B, Gan LM, Svedlund S
Effect of renal denervation coronary flow reserve in patients with resistant hypertension
Submitted

III

Völz S, Spaak J, Elf J, Jägren C, Lundin C, Stenborg A, Andersson J, Rundqvist B, Kahan T, Andersson B
Renal sympathetic denervation in Sweden: A first report from the Swedish Registry for Renal Denervation
Journal of Hypertension 2018 Jan; 36 (1):151-158

IV

Völz S, Lundblad L, Andersson B, Multing J, Rundqvist B, Elam M
Muscle sympathetic nerve acticity at rest and during mental stress in patients with resistant hypertension: before and after renal denervation
Submitted

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TABLE OF CONTENTS

ABBREVIATIONS

ABP • Ambulatory blood pressure

ACE • Angiotensin converting enzyme

ARB • Angiotension receptor blocker

Bpm • Beats per minute

BSA • Body surface area

BMI • Body mass index

CAD • Coronary artery disease

CIMT • Carotid intima media thickness

CFR • Coronary flow reserve

DBP • Diastolic blood pressure

eGFR • Estimated glomerular filtration rate

LAD • Left anterior descending artery

LVM • Left ventricular mass

LVMi • LVM index

OBP • Office blood pressure

RDN • Renal denervation

RH • Resistant hypertension

SBP • Systolic office blood pressure

INTRODUCTION

1.1 Arterial hypertension

Arterial hypertension is the leading risk factor for cardiovascular disease. It accounts for nearly 10 million deaths annually and as prevalence continues to increase, hypertension represents one of the major public health issues world-wide (1).

1.2 Resistant hypertension

Resistant hypertension (RH) is commonly defined as uncontrolled office blood pressure (BP) (>140/90 mmHg), despite treatment with three antihypertensive agents including one diuretic (2). Alternative definitions include patients with controlled BP while being treated with at least four antihypertensive drugs (3).

Prevalence

The prevalence of drug-resistant hypertension ranges from 9-15 % of all patients with hypertension, depending on the population and applied definition of RH (4-7).

Etiology

The term RH implies resistance to pharmacological treatment in the absence of secondary causes. These secondary causes include primary hyperaldosteronism, renal artery stenosis, phaechromocytoma, thyroid disease, Cushing´s syndrome, intracranial tumours and coarctation of the aorta, and these are to be excluded during clinical work-up (8).

RH can be real or merely apparent (9). Apparent forms, also labelled pseudo-resistance, may be caused by (i) poor medical adherence, (ii) white-coat hypertension, (iii) incorrect BP measurement technique, and (iv) substandard antihypertensive pharmacological treatment.

True resistant hypertension (TRH), i.e. RH after exclusion of pseudo-resistance and potential secondary causes, is commonly of multifactorial origin. As in essential hypertension, not one primary cause is found in the majority of patients. However, previous studies have identified age, obesity, chronic kidney disease,

diabetes and socioeconomic status as predictors for lack of BP-control and represent common patient features in RH (7, 10-12).

Prognosis

RH is associated with a high prevalence of left ventricular hypertrophy, chronic kidney failure (13) and an increased risk of cardiovascular morbidity and mortality when compared with controlled hypertensives (6, 14).

However, most of the above data are either observational or represent sub-group analyses of trials which were not specifically designed for RH. In order to contribute to a more profound understanding of the characteristics of RH, we performed Study I.

Conventional treatment

As RH is commonly multifactorial in origin, treatment modalities aim to cover a range of treatment aspects. In line with the recommendations for essential hypertension, lifestyle-changes including a low-salt diet, weight loss, moderated alcohol-intake and regular physical exercise are advocated. Concurrent medication that interferes with BP control and its physiological determinants, should be withdrawn (3).

The effect of pharmacological treatment in patients with RH has not been evaluated specifically in any outcome-study. However, pharmacological treatment effects are assumed to be substantial and in line with the previously published landmark trials in hypertension (15, 16).

As to the choice of drug combination, guidelines advocate a combination of drugs with complementary mechanisms of action, namely ACE-inhibitors plus calcium channel blockers and a thiazide diuretic (”A+C+D”) (17). The recently published PATHWAY-2 trial, dedicated to the comparison of additive drug treatment in diagnosed RH, has demonstrated superior complementary BP-effects of spironolactone as compared with alpha- and beta-blockers, thus supporting its use as the additional drug of choice in treatment of RH (18).

1.3 Sympathetic nerve activity and hypertension

Patients with RH are commonly characterised by a significant number of comorbidities. Associated diseases include diabetes mellitus, heart failure and chronic renal failure (7). These comorbidities are independently associated with varying degrees of sympathoexcitation (19, 20), which contributes to the chronic adrenergic burden that is considered a common trait in patients with RH (21).

Sympathetic nervous activity is integrated within the nucleus tractus solitarius, located in the brain-stem, which is cross-linked in a tight network of efferent and afferent nerve fibers leading to and from peripheral organs such as the heart, liver, blood vessels and kidneys (Fig. 1).

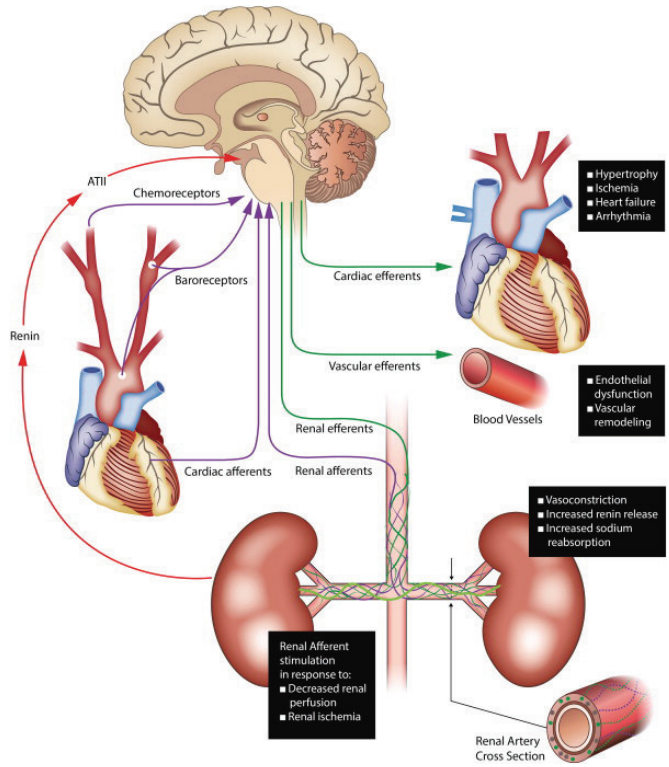

Figure 1 Interplay of key-organs contributing to blood pressure regulation by means of the autonomous nervous system. From (22) with permission of Elsevier.

The link between arterial hypertension and autonomous nervous activity has been known about since the pre-pharmacological era. In the 1930´s and 1940´s, surgical sympathectomy by means of surgical thoracolumbar splanchnicectomy constituted one of few available treatment modalities in patients with hypertension. Marked effects on BP were noted, however the invasive and non-selective nature of the method implied a significant periprocedural risk, as well as considerable side-effects (23).

In the modern era, Esler et al. were able to consolidate earlier findings and estab-

lish an important pathophysiological link between hypertension and sympathetic nerve activity by showing increased sympathoexciation in individuals with hypertension as compared to the normotensive controls (24) (Fig. 2).

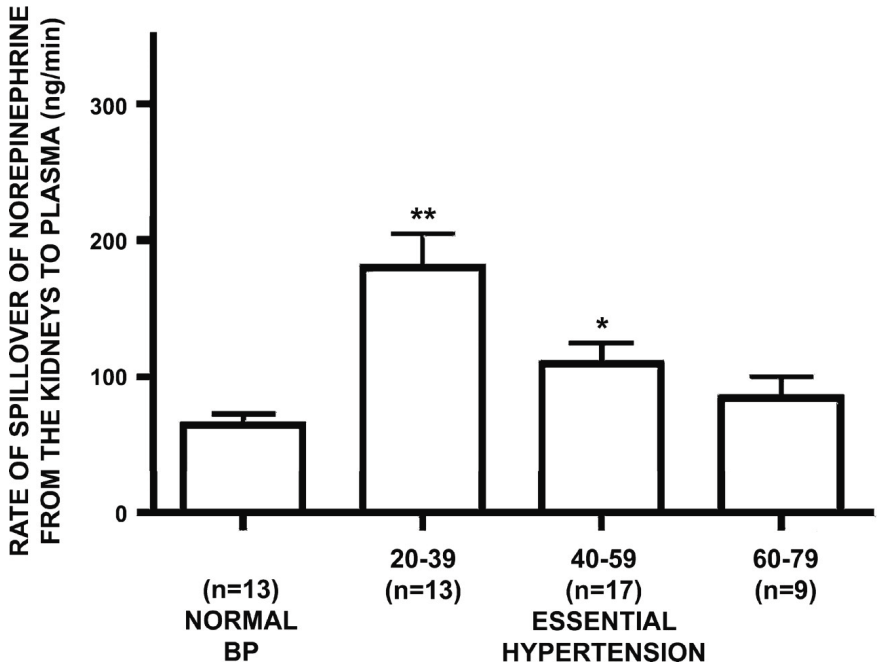

Figure 2 Renal sympathetic activity assessed by renal norepinephrine spillover measurement in patients with hypertension and normotensive controls. From (25) with permission of the American Society of Physiology.

Sympathetic nerve activity and cardiovascular reactivity

Mental stress induces transient changes in heart rate (HR) and BP, termed cardiovascular reactivity. Abnormal cardiovascular reactivity is associated with an increased risk of the development of hypertension in normotensives (26, 27) and borderline hypertensives (28, 29). Furthermore, it is considered an important aspect of essential hypertension (30) and implies an increased risk of cardiovascular events (31).

The importance of mental stress reaction in patients with advanced stages of hypertension is unclear, and this fact constituted the rationale for Study IV.

1.4 Renal sympathetic nerve activity

Renal sympathetic nerve activity is an important contributor to the development and maintenance of arterial hypertension and has been the subject of medical research since the beginnings of modern experimental physiology in the 19th century (32).

Efferent renal sympathetic nerve activity

Efferent renal sympathetic nerve fibres originate from the brain stem and travel via sympathetic ganglia along the adventitia of the renal artery to the kidney, innervating vasculature, renal tubules and the renin-containing juxtaglomerular cells (33).

Claude Bernard was the first, in 1859, to discover that cutting the greater splanchnic nerve (i.e. renal sympathetic denervation) produced ipsilateral diuresis whereas electrical stimulation of its peripheral cut end led to a marked ipsilateral antidiuresis (34). More than a century later, these findings were confirmed and further specified by DiBona et al., who demonstrated the relationship between selective renal nerve stimulation and renal blood flow, renin- and sodium-secretion- factors deemed vital for the regulation of systemic blood pressure (33) (Fig. 3).

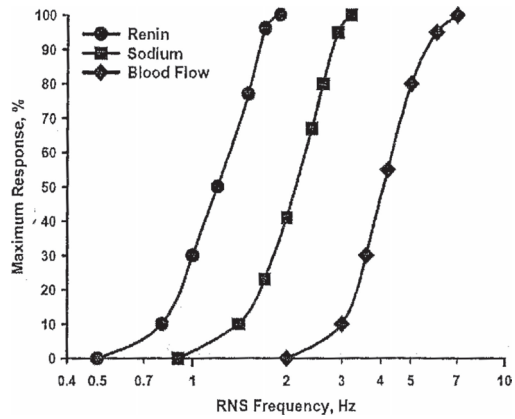

Figure 3 Relationship between renal nerve stimulation and renin secretion, sodium retention and renal blood flow. From (33) with permission of the American Physiological Society.

Afferent renal sympathetic nerve activity

Afferent sensory fibers originate from the renal pelvis and interstitium, collecting stimuli from renal mechano- and chemoreceptors. An increase in afferent renal sympathetic nerve activity is triggered by renal injury such as inflammation, ischemia, oxidative stress and acidosis (25), leading to an increase in central sympathetic nerve activity within the mechanics of a centro-renal feed-back-loop. Subsequent vasoconstriction and an increase in sodium retention then bring about an increase in arterial blood pressure. Converse et al. confirmed this concept, showing marked reductions in central sympathetic nerve activity and BP in patients after renal transplantation, including bilateral nephrectomy (i.e. renal sympathetic denervation) as compared to those after renal transplantation only (19) (Fig. 4).

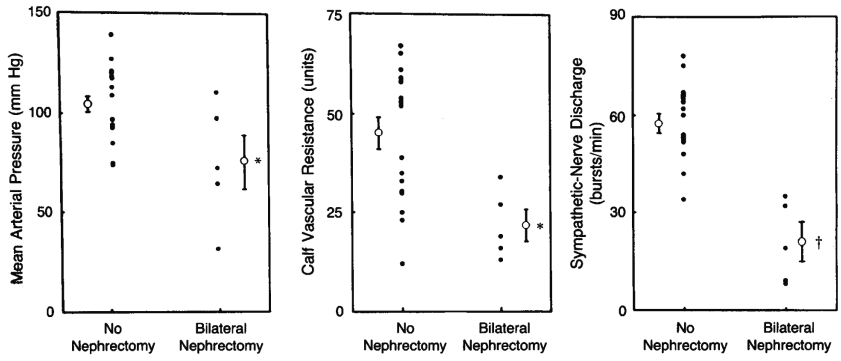

Figure 4 Comparison of mean arterial BP, vascular resistance and muscle-sympathetic nerve activity between dialysis-dependent patients with end-stage renal failure who had either undergone surgical bilateral nephrectomy or had no surgery. Reproduced with permission from (19), copyright Massachussetts Medical Society.

Consecutive studies, performed in various animal-models of hypertension, have confirmed and extended existing evidence on surgical and chemical renal sympathetic denervation and their BP-lowering properties (25) (Table 1).

Models of experimental hypertension in which renal denervation prevents or delays the development of hypertension
Spontaneously hypertensive rat
Borderline hypertensive rat
New Zealand SHR
Goldblatt 2K, 1C (rat)
Aortic coarctation (dog)
Aortic nerve transection (rat)
DOCA-NaCl (rat)
DOCA (pig)
Grollman renal wrap (rat)
Low sodium, 1K hypertension (rat)
Angiotensin II hypertension (rat)
Obesity hypertension (dog)
NaCl (baroreflex-impaired rabbit)

Table 1 Overview of models of experimental hypertension in the context of RDN. Modified from (25) with permission of the American Physiological Society.

1.5 Renal sympathetic denervation

Based on the above findings, a catheter-based, endovascular method has been developed to selectively decrease renal sympathetic nerve activity (5). Both afferent and efferent sympathetic nerves travel within the renal artery adventitia, surrounding the vessel's circumference in a net-like fashion (Fig. 5). The selective disruption of nerve fibre traffic and consecutive inhibition of renal sympathetic nerve activity constitutes the rationale behind renal denervation (RDN).

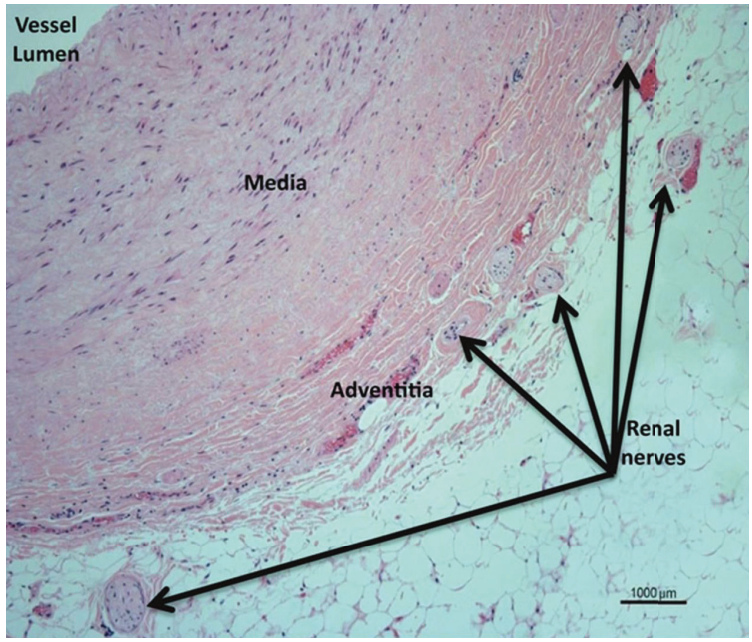

Figure 5 Sympathetic renal nerve fibers in a histological section in a swine model. With permission from Medtronic (Mountain View, CA, USA).

Renal denervation: Treatment modalities

The majority of available scientific data is based on the first generation Symplicity-Flex device (Medtronic, Mountain View, CA, USA) (Fig. 6) (35). As with most of the seven available denervation techniques, the Flex-catheter applies radiofrequency energy to directly heat contacted tissue areas, as well as induce a passive, subacute thermal conduction into deeper layers of the vessel wall (36). Other devices, using RF-energy in a modified catheter-setup, include the second generation Symplicity-Spyral (Medtronic, Mountain View, CA, USA) (37), the EnligHTN- (St. Jude Medical, St. Paul, MI, USA) (38) the One-Shot- (Covidien, Dublin, Ireland) (39), and the Vessix-system (Boston Scientific, Marlborough, MA, USA) (40). The remaining devices are based on focused high-frequency ultrasound as the energy source and include the Paradise catheter (ReCor Medical, Palo Alto, CA, USA) and the Kona Medical Surround Sound System (Kona Medical, Bellevue, Washington, USA) (41).

Head-to-head comparisons between different catheter devices regarding safety, efficacy and feasibility are not available, which is one of the reasons for the initiation of Study III.

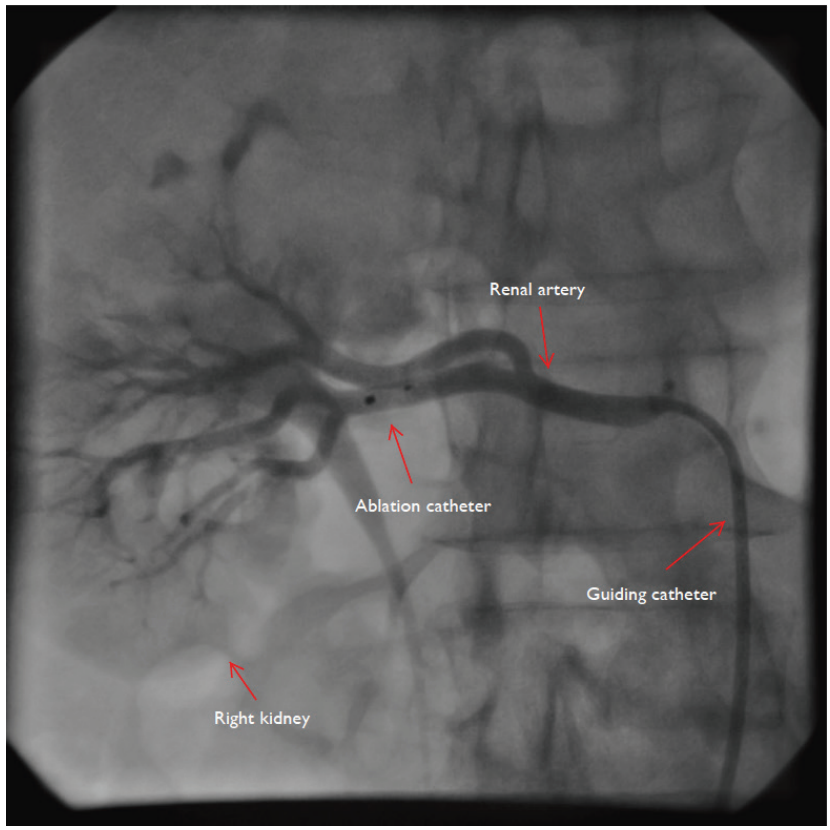

Figure 6. Renal sympathetic nerve ablation performed with the first generation Symplicity Flex-catheter.

Renal denervation: Effects on the sympathetic nervous system

There are different modalities to assess human sympathetic nerve activity. Assessment of organ-specific, renal norepinephrine spillover is a technically challenging, invasive method, which aims primarily to evaluate kidney-specific efferent sympathetic nerve activity (42). In the context of renal denervation, reductions in renal norepinephrine spillover post-intervention have been reported, but are restricted to case-based publications (35, 43).

The disruption of afferent renal nerve traffic and the consecutive resetting of central sympathetic nerve activity, constitute the major rationale for the potential BP-reducing properties of renal denervation (44). These potential changes can be evaluated by microneurographic recordings of muscle sympathetic nerve activity

(MSNA), that provides a direct measurement of efferent sympathetic activity to skin and muscle, which is considered the gold standard in the assessment of central sympathetic nerve activity (Figs. 7 and 8). MSNA has previously been investigated by several studies, generating conflicting results (45-50). Whether BP changes after RDN may be attributed to the inhibition of centrally generated sympathetic nerve activity remains a matter of debate and also motivated us to perform Study IV.

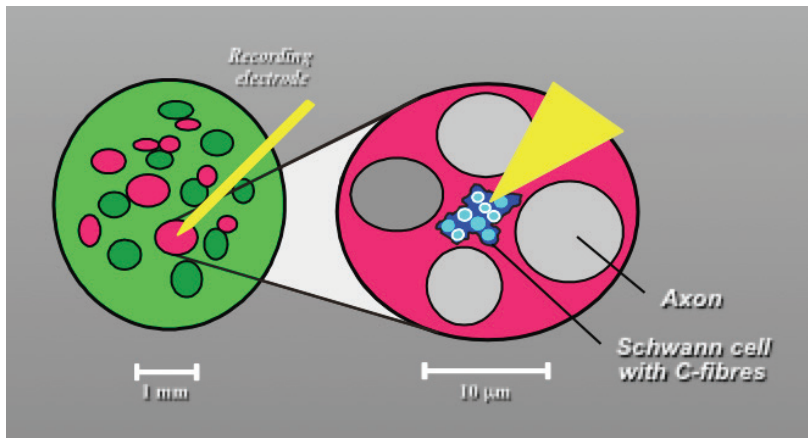

Figure 7 Microneurographic recording of sympathetic nerve firing rate. Image provided by Mikael Elam.

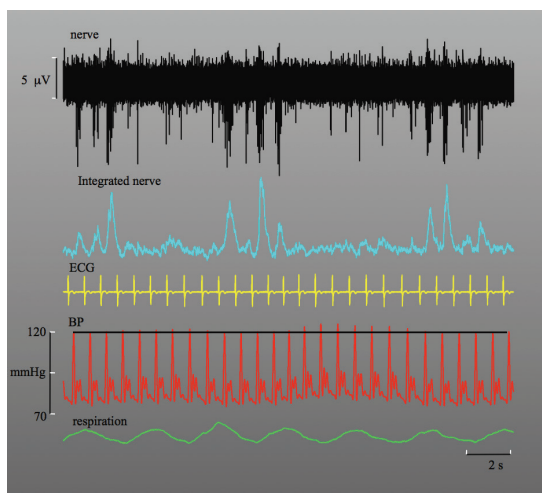

Figure 8 Example of muscle sympathetic nerve activity-output. Image provided by Mikael Elam.

Renal denervation: Effects on arterial blood pressure

Randomised controlled trials examining the impact on brachial BP in patients with RH have generated conflicting data (35, 51-54). While Dener-HTN showed a significant impact of RDN on ambulatory BP in patients with RH after having undergone a structured optimisation of antihypertensive drug therapy (51), Symplicity HTN-3, the largest randomised trial in the context of RDN, did not show any significant changes post-intervention as compared with sham-control (52). However, the results from Symplicty HTN-3 have remained a subject of debate, and the study has been criticised for suboptimal procedural precision as well as unaccounted medication changes in a significant portion of the study population (55).

Registry-based data are a valuable complement to clinical trial data adding information on the external validity of data acquired in selected trial populations (56). In the context of RDN, publications based on observational registry data have consistently shown BP reductions in patients with RH up to 12 months after RDN (57-61).

In order to contribute to these open questions in regard to the BP-lowering abilities of RDN, we established the Swedish Registry for Renal Denervation and conducted Study III.

Renal denervation: Recent developments

The discrepant BP-effects after RDN have been a matter of discussion, and potential explanatory factors include confounding factors such as lack of technical precision, varying degrees of drug adherence, the placebo and Hawthorne-effects, as well as result-distortion by regression to the mean (62). Furthermore, studies have identified certain patient attributes, that may predict response after RDN (55, 63).

As a direct result of this debate, the SPYRAL HTN Global Clinical Trial Program was designed (37), aiming to address previous trial limitations. In order to achieve this goal, the focus was shifted towards less severe forms of hypertension with less severe comorbidities and less intense comedication.

Data from the first study arm have recently been published and show promising results: The randomized, sham-controlled SPYRAL HTN-OFF MED-study showed significant BP reductions in patients with hypertension without concomitant antihypertensive medication at three-month follow-up (64). These study results thereby support the rationale for RDN and its BP-reducing properties. However, adequately powered clinical trials in patients with ongoing antihypertensive treatment are still needed to prove the clinical significance of RDN.

Renal denervation: Effects on selected cardiovascular surrogate markers

Studies on the impact of RDN on cardiovascular surrogate markers have shown a variety of beneficial effects: RDN is associated with a decrease in left ventricular mass (LVM) (65, 66), a reduction in aortic pulse-wave velocity (67) and BP variability (68, 69) as well as an increase in heart rate-recovery (70). Several of these aspects have been observed independently of office BP response, and might thus be mediated by a direct modulation of the sympathetic nervous system (65, 66).

1.6 Coronary flow reserve: A cardiovascular surrogate marker with prognostic implications

CFR describes cardiac capacity to adapt to changes in myocardial workload and reflects both macro- and microvascular coronary function (Fig. 9). It is considered a reliable surrogate marker for cardiovascular morbidity and an independent predictor for mortality in patients with diabetes (71), coronary artery disease (72), and normal and near-normal coronary angiographies (73). CFR is impaired in patients in less advanced stages of hypertension (74).

Whether CFR is impaired in patients with RH and whether RDN impacts on this prognostically significant surrogate marker constitute the main hypotheses for Studies I and II.

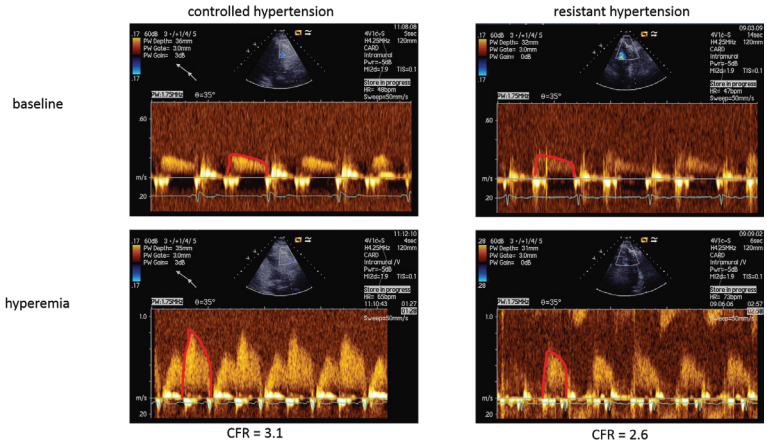

Figure 9 Transthoracic Doppler assessment of mean flow velocity in the left anterior descending artery at rest and during Adenosine infusion in two patients with varying stages of hypertension. From (75) with permission of Springer-Verlag, Berlin Heidelberg.

AIMS

Study I

To assess CFR in patients with RH. The main study hypothesis was that patients with RH would present with an impairment in CFR and that CFR would depend on the varying severity of hypertension.

Study II

To examine the effects of RDN on CFR in patients with RH and assess whether potential changes in CFR are dependent on changes in BP. The study's main hypothesis was that RDN improves CFR at follow-up.

Study III

To investigate the safety and efficacy of RDN in a real-world setting. We aimed to assess long-term BP changes, long-term safety, potential differences in regard to the effect of different ablation systems, and identify predictors for BP response after RDN.

Study IV

To explore the effect of RDN on MSNA at rest and during mental stress in patients with RH. We aimed to test whether (i) RDN decreases MSNA at rest and/or (ii) modifies MSNA- and blood pressure-responses to mental stress, and whether the inhibition of MSNA during mental stress is a rare response-profile in patients with RH (iii).

PATIENTS AND METHODS

All studies were conducted according to the Declaration of Helsinki and approved by the Regional Research Ethics committee in Gothenburg. All patients gave their informed consent to participate.

Study I

Twenty-five consecutive patients with RH scheduled for RDN, 25 matched patients with controlled hypertension and 25 healthy controls underwent CFR assessment by transthoracic Doppler echocardiography at rest and during Adenosine infusion. Mean flow velocity was assessed in the left anterior descending artery. Patients with controlled and resistant hypertension were pair-matched according to age, sex, body-mass-index (BMI), smoking status, diabetes mellitus and ischemic heart disease. Healthy controls were selected with regard to age and sex.

Study II

Twenty-six consecutive patients with RH underwent percutaneous renal sympathetic denervation. Assessment of CFR by transthoracic Doppler echocardiography was performed in accordance with Study I at baseline and at six-month follow-up.

Study III

The Swedish Registry for Renal Denervation is an investigator-inititated academic online database, developed by our group and supported by the Swedish authorities. The registry contains 130 variables summarizing baseline patient characteristics, procedural details, as well as follow-up data. The database contains patient data from the seven Swedish university hospitals that have performed RDN since 2011 exclusively, thereby providing a nation-wide data set with a follow-up of up to five years.

The study population comprised a total of 260 patients, who had undergone RDN during the period 2011 - 2015. Two hundred and fifty-seven patients underwent RDN successfully and were included in the data analysis.

Study IV

Fourteen consecutive patients with RH underwent percutaneous renal sympathetic denervation. MSNA, BP and HR at rest and during mental stress were assessed at baseline and six months after RDN.

Mental stress was induced by a three-minute protocol of forced arithmetics, initiated verbally by the experimenter and where patients were prompted to respond with the right answer in a timely fashion. HR and mean arterial BP were assessed continuously by the volume-clamp method (Finometer ®).

We acquired a complete data set for eleven patients, who were all included in the data analysis.

STATISTICS

Results are expressed as means ± SD if not marked otherwise. Statistical analysis was performed with the SPSS Statistics 24.0 (IBM, Armonk, USA) statistical program software.

Study I

The Student's t-test for paired and unpaired comparisons was applied when appropriate. A two-sided p-value of < 0.05 was considered statistically significant. Pearson's correlation coefficient was used to assess dependence between quantitative variables.

Study II

The sample size was calculated to detect a 10% difference in CFR after intervention (α-level $p = 0.05$, power 80%). The Student's t-test was applied for paired comparisons and a two-sided p-value of < 0.05 was considered as statistically significant. In order to test for possible interdependence of categorical variables, Pearson's chi-square and Fisher's exact test were performed. An analysis of dependence between quantitative variables was performed by the application of Pearson's correlation coefficient.

Study III

Results are presented as mean values ± SD or with 95 % confidence intervals, if not otherwise stated. The paired Student's t-test and repeated measures ANOVA were used for comparisons of continuous variables. The Wilcoxon signed-rank test was used when normal data distribution could not be assumed. Pearson's correlation coefficient was applied when assessing the dependence between two quantitative variables. Multiple linear regression analysis was applied in order to identify predictors of changes in BP. Analysis was performed following a forced entry algorithm including age, sex, BMI, estimated glomerular filtration (eGFR; by the MDRD formula), diabetes mellitus, obstructive sleep apnoea, heart failure, isolated systolic hypertension (ISH), number of antihypertensive drugs at baseline, treatment with mineralo-corticoid-receptor antagonists, baseline pulse pressure, baseline systolic office BP, and baseline systolic ABPM, as appropriate. A two-sided p-value of < 0.05 was considered as significant.

Study IV

The paired and unpaired Student's t-test and, when appopriate, repeated-measures-ANOVA were applied for comparisons of continuous variables. A two-sided p-value of < 0.05 was considered statistically significant. It was estimated that a total of ten patients in a paired analysis would provide a statistical power $> 80\%$ to show a clinically relevant reduction of five bursts per minute at follow-up (45).

RESULTS

The main results and conclusions for each study are summarised below. For details, see the respective manuscript at the end of the thesis.

Study I

CFR was significantly lower in patients with RH when compared with patients with controlled hypertension (Fig. 10). Also, systolic office BP was significantly higher in patients with RH. No difference was noted in regard to left ventricular mass index and baseline mean flow velocity between the two groups with hypertension.

Healthy controls presented with significantly higher CFR, lower baseline mean velocity and lower BP when compared to all individuals with hypertension.

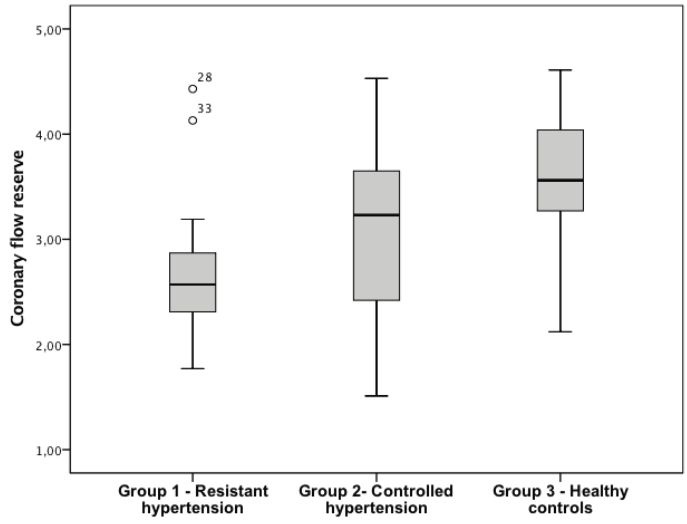

Figure 10 Distribution of coronary flow reserve in the three study groups. From (75) with permission of Springer-Verlag, Berlin Heidelberg.

Study II

Systolic office BP was significantly reduced six months after RDN. No significant changes in regard to ambulatory BP were noted at follow-up.

Despite the observed drop in BP, CFR remained unchanged six months after RDN. Baseline- and hyperaemic flow velocities did not change significantly at follow-up (Fig. 11). No correlation between change in BP and CFR was noted.

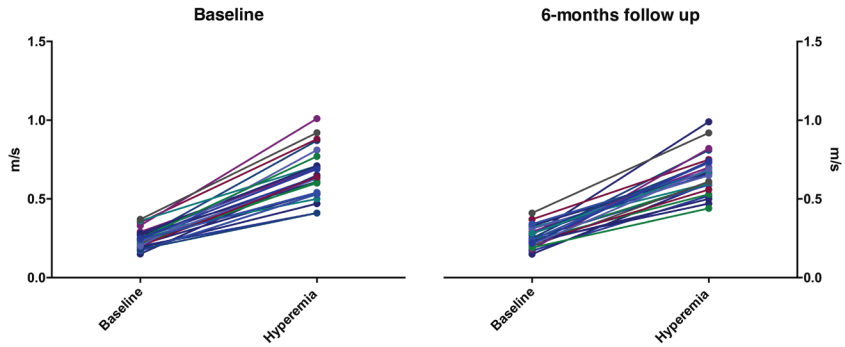

Figure 11 Individual mean flow velocities at rest and during hyperaemia, at baseline and at follow-up.

Study III

RDN was associated with sustained office and ambulatory BP reductions throughout the study period of 36 months (Fig. 12). Independent of catheter-type, the procedure was deemed safe and few short-term and no clinically relevant long-term complications were noted. The sole consistent predictor for BP-response was baseline BP. The use of mineralocorticoid receptor antagonists predicted ambulatory BP-response at 12 months.

A high degree of variation in BP change after RDN was observed: In one-third of the study population, office BP was reduced by at least 10 mmHg accompanied by ambulatory BP-reductions of at least 5 mmHg. These patients were considered true responders. Another third of the patients showed a corresponding decrease for either office or ambulatory BP, while the remaining third did not respond, either in regard to office or ambulatory BP.

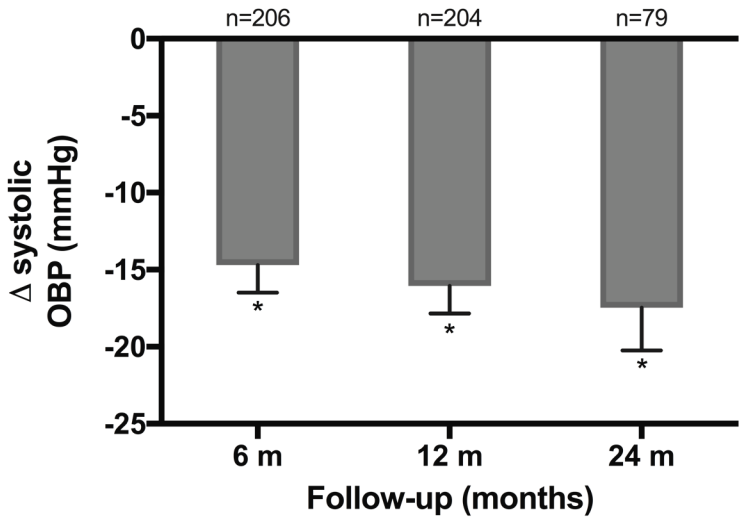

Figure 12 Systolic office BP 6, 12 and 24 months after renal denervation (* p<0.01). From (76) with permission of Wolters Kluwer, Alphen an den Rijn.

Study IV

Significant reductions for office BP six months after RDN were noted.

RDN was not associated with a reduction in resting-MSNA, nor did it change the pattern of MSNA during mental stress (Fig. 13). Mental stress induced a signficant increase in both HR and BP. The extent and pattern of this observed cardiovascular reactivity, however, remained unchanged when comparing pre- and post-RDN recordings. No correlation between BP response and change in MSNA was noted.

MSNA inhibition, i.e. a decrease in MSNA activity during mental stress, was a rare phenomenon, occurring in < 20% of all study patients (Fig. 14).

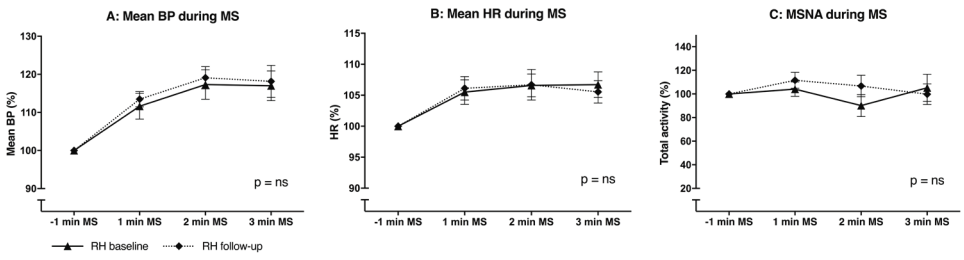

Figure 13 Mean arterial BP, HR and MSNA during mental stress before and after renal denervation.

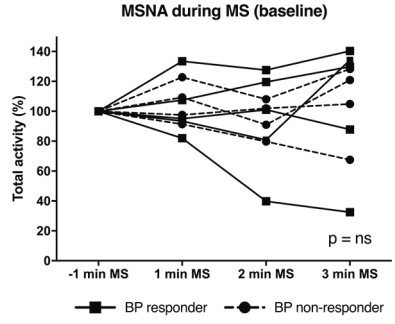

Figure 14: Mean arterial BP, HR and MSNA during mental stress before and after renal denervation.

DISCUSSION

During this thesis, we have made the attempt to further characterise the group of patients with RH (Study I), describe effects of RDN in this particular patient group (studies II and III) and finally elucidate its potential mechanisms of action (Study IV).

Coronary flow reserve is impaired in patients with resistant hypertension

Study I showed that patients with RH present with impaired CFR, which further illustrates and underlines the prognostic implications in this patient group. Interestingly, this difference was noted despite a similar distribution of left ventricular mass between the two hypertension populations, suggesting cardiac microvascular dysfunction as the primary cause of our findings.

The regulation of coronary vessel tone is the result of a multifactorial process, promoted by endothelial function (77, 78) and impacted by endothelium-independent structural changes in the cardiac microvasculature and interstitium (79, 80). Furthermore, cardiac afterload and the sympathetic tone (21, 81) are contributory elements during cardiac adjustments to changes in myocardial workload. Arterial hypertension is linked to changes in both endothelium-dependent and endothelium independent modes of vasodilation (77-80).

Our study confirms this concept and provides the background for future studies dedicated to the significance of the specific aspects of coronary microcirculation in patients with resistant hypertension.

Coronary flow reserve remains unchanged six months after renal denervation

The regulation of CFR is a multifactorial process. Factors, that predict the capacity to adapt myocardial perfusion to an increase in work-load include age, sex, smoking status, BMI (82) and comorbidities such as diabetes mellitus (71), coronary artery disease (72), left ventricular hypertrophy and the presence of arterial hypertension (74, 83).

While we aimed to assess the particular role of RH in the context of Study I, Study II was performed to measure renal denervation's impact on CFR and assess whether these potential changes correlate with changes in BP.

Despite a signficant reduction in office BP, CFR remained unchanged at follow-up. Potential explanations for this finding include: (i) Our patient population presented with a high degree of comorbidities such as obesity, coronary artery disease and diabetes mellitus. These conditions are per se linked to structural cardiac changes and an impairment in CFR, and thus may determine CFR independently of the observed moderate changes in BP. (ii) No diagnostic method is available to measure the achieved degree of sympathetic denervation after intervention. Given the relatively modest reduction in office BP and absence of signficant changes in ambulatory BP, an insufficient degree of RDN cannot be excluded entirely.

Our findings stress the complex and multifactorial regulation of human coronary flow reserve. Study II raises questions about the impact of RDN on coronary microcirculation in the context of RH.

The Swedish Registry for Renal Denervation: Renal denervation is safe and associated with sustained blood pressure reductions

The effects of RDN on BP in patients with RH have generated conflicting results (35, 51-54). Registry-data are a valuable complement to clinical trial data by testing the external validity of data acquired in selected trial populations (56).
While studies I and II were mainly dedicated to pathophysiological aspects, Study III assesses the BP effects of RDN in a clinical setting.
The observed BP reductions were in line with previous observational registry studies showing clinically potentially significant changes for both office and ambulatory BP and a good short- and long-term safety-profile (57-60).
Study III is the first published report of a comprehensive nation-wide experience with RDN, i.e. RDN has not been performed outside this network of seven Swedish university hospitals. Furthermore, our study contributes to the existing body of evidence by extending previously published observation periods and thereby providing further evidence on the long-term development of BP after RDN. Finally, we were able to provide a head-to-head comparison of the most commonly used ablation systems, which did not yield significant differences in regard to neither safety nor efficacy.

Does renal sympathetic denervation modulate afferent renal sympathetic nerve activity?

Inhibition of afferent sympathetic nerve signals and a consecutive resetting of central sympathetic nerve activity constitute the major rationale for the development of RDN (44).

These potential changes, as assessed by MSNA, have been the subject of several studies in varying settings that have generated conflicting results. While some groups have shown a significant impact of RDN on MSNA (46, 48, 50), others have not been able to reproduce these positive results (45, 47, 49). Furthermore, only a few studies have been able to show a correlation between changes in MSNA and BP (50), which is considered to be an important link in the attempt to confirm this major hypothesis.

Our findings from Study IV contribute to current knowledge in several different ways: (i) In confirmation of previous studies, we did not note significant changes in MSNA at rest after RDN, nor did we detect any correlation between changes in MSNA and BP. (ii) The assessment of MSNA during mental stress in patients with RH is a scientific novelty, and showed no detectable change in the pattern of either MSNA or cardiovascular reactivity during mental stress provocation. (iii). Finally, MSNA inhibition in patients with RH appears to be rare phenomenon. This observation evokes associations with findings from previous studies, which have demonstrated that the lack of MSNA inhibition during mental stress predicts future development of hypertension in healthy subjects (84). As this matter may touch vital aspects of the pathophysiology of essential hypertension, we have initiated a larger study to provide further evidence on the occurrence of MSNA inhibition in patients with RH.

CONCLUSIONS

Study I

RH was associated with an impairment in CFR as compared to controlled hypertensives, which may contribute to the increased risk of cardiovascular morbidity and mortality in this patient population. CFR values differed despite a similar distribution in left ventricular mass, which indicates an advance degree of microvascular dysfunction in patients with RH. Further research is warranted to differentiate and quantify the importance of the different aspects of regulation of the coronary vessel tone in patients with advanced degrees of hypertension.

Study II

Regulation of CFR is a multifactorial process. Renal sympathetic denervation and its subsequent moderate changes in BP were not associated with modifications of CFR six months after the procedure.

Study II

RDN was associated with clinically relevant BP reductions in this observational, uncontrolled patient cohort. Our study emphasises the good safety and therapeutic potential of RDN in the treatment of hypertension. Rigorously designed, randomised trials are needed to confirm and contextualise the observed treatment effect.

Study II

We conclude that the changes in BP, as noted in our study, did not seem to depend on changes in MSNA, either at rest or during mental stress. MSNA inhibition in patients with RH is a rare phenomenon, raising questions about the significance of MSNA inhibition in the pathophysiology of essential hypertension.

FUTURE PERSPECTIVE

As illustrated by the results of this thesis, there are many open questions in the field of percutaneous renal sympathetic denervation. However, besides our own findings, substantial developments have been made during the course of this thesis:

(i) Important study-design inherent confounders have been identified.

(ii) New anatomical insights have changed established strategies during renal nerve ablation and have shifted the focus to a more aggressive and distal approach.

(iii) New catheters have been developed in order to achieve a more reliable, circumferent vessel contact.

(iv) Insights from previous studies have led to the identification of patient populations prone to respond to renal denervation.

(v) Due to the abundance of confounding factors in patients with resistant hypertension, the focus has shifted towards new patient populations, including those with less advanced stages of hypertension.

Recently published and ongoing clinical trials have taken these novel insights into consideration and have generated promising data.

As hypertension remains a major global health issue, renal denervation deserves the field's continued scientific effort in order to identify its true potential.

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