

Renal sympathetic denervation in therapy resistant hypertension - pathophysiological aspects and predictors for treatment success

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: Philipp Lurz is consultant to ReCor Medical and Medtronic.

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Manuscript source: Invited manuscript

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Received: April 27, 2016

Peer-review started: April 28, 2016

First decision: June 16, 2016

Revised: June 21, 2016

Accepted: July 14, 2016

Article in press: July 18, 2016

Published online: August 26, 2016

Abstract

Many forms of human hypertension are associated with

an increased systemic sympathetic activity. Especially the renal sympathetic nervous system has been found to play a prominent role in this context. Therefore, catheter-interventional renal sympathetic denervation (RDN) has been established as a treatment for patients suffering from therapy resistant hypertension in the past decade. The initial enthusiasm for this treatment was markedly dampened by the results of the Symplicity-HTN-3 trial, although the transferability of the results into clinical practice to date appears to be questionable. In contrast to the extensive use of RDN in treating hypertensive patients within or without clinical trial settings over the past years, its effects on the complex pathophysiological mechanisms underlying therapy resistant hypertension are only partly understood and are part of ongoing research. Effects of RDN have been described on many levels in human trials: From altered systemic sympathetic activity across cardiac and metabolic alterations down to changes in renal function. Most of these changes could sustainably change long-term morbidity and mortality of the treated patients, even if blood pressure remains unchanged. Furthermore, a number of promising predictors for a successful treatment with RDN have been identified recently and further trials are ongoing. This will certainly help to improve the preselection of potential candidates for RDN and thereby optimize treatment outcomes. This review summarizes important pathophysiologic effects of renal denervation and illustrates the currently known predictors for therapy success.

Key words: Renal sympathetic denervation; Sympathetic nervous system; Predictors; Hypertension; Renal hypertension

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Core tip: The initial enthusiasm for renal sympathetic denervation (RDN) has disappeared. However, the detailed effects of RDN on the complex pathophysiological

mechanisms underlying therapy resistant hypertension are only partly understood and are part of ongoing research. Moreover, a number of promising predictors for successful RDN treatment have been identified recently which could help to improve future trial design. This review summarizes important pathophysiological effects of renal denervation and illustrates the currently known predictors for therapy success.

Fengler K, Rommel KP, Okon T, Schuler G, Lurz P. Renal sympathetic denervation in therapy resistant hypertension - pathophysiological aspects and predictors for treatment success. *World J Cardiol* 2016; 8(8): 436-446 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v8/i8/436.htm> DOI: <http://dx.doi.org/10.4330/wjc.v8.i8.436>

BACKGROUND

Many forms of human hypertension are associated with an increased systemic sympathetic activity^[1]. Especially the sympathetic nervous system of the kidney plays a key role in the pathogenesis and perpetuation of hypertension. An activation of efferent renal nerve fibers leads to salt and water retention *via* stimulation of α_{1B} -adrenoceptors, activation of the renin-angiotensin-aldosterone system *via* β_1 -adrenoceptors causing thereby an increased systemic blood pressure (BP)^[1,2]. The release of vasoactive peptides present in renal nerve fibers is also controlled by efferent sympathetic fibers^[3,4]. *Via* afferent fibers, the kidney itself affects systemic sympathetic activity^[1].

One option to reduce the systemic sympathetic activity is renal sympathetic denervation (RDN). Once introduced as a surgical treatment for hypertension in the past century^[5,6], this interesting therapeutic approach lost clinical relevance since medical antihypertensive treatment was introduced to practice. As the burden of cardiovascular diseases associated with hypertension increased over the last decades, RDN experienced a renaissance, now as a catheter-based interventional treatment option^[7]. After the first promising trial results, the initial enthusiasm for this therapy strategy was markedly dampened, when the results of the sham-controlled randomized Symplicity-HTN-3 trial did not show any significant effect on BP of RDN-treated vs sham-treated patients^[8]. The results of this particular trial are part of an ongoing debate and further trials to allow definite conclusion on the effect of RDN on BP are on the way^[9]. In contrast to the extensive use of RDN in treating hypertensive patients within or without clinical trial settings over the past years, the detailed effects of RDN on the complex pathophysiological mechanisms underlying therapy resistant hypertension are only partly understood.

In the following review we present a short overview of the manifold effects described for RDN so far (Table 1).

EFFECTS OF RDN

BP

The main indication for RDN in the past decade and in the past century has been therapy resistant hypertension. Therefore, BP as an end point has been included in nearly every single trial regarding RDN. In almost any trial, controlled, uncontrolled or sham-controlled, a significant BP reduction was found after RDN^[7,10-14] (Table 2). However, the largest randomized sham-controlled trial to date, the Symplicity-HTN-3 trial, failed to show any superiority of RDN over sham-control, mostly through an unexpected drop in BP in the sham-treated arm of the trial^[8].

Another sham-controlled randomized approach, excluding most of the confounding factors which might have blurred the results of Symplicity-HTN-3 by careful patient selection, the ongoing SPYRAL-HTN trial (NCT02439775), will hopefully give a definite answer to this issue soon.

It is of particular interest, that many of the effects attributed to RDN result in a reduced BP: A diminished systemic vascular tone leading to a reduced afterload, sympathetic mediated alterations in cardiac output, altered sodium- and volume-state or (*via* the renin-angiotensin-aldosterone axis) humoral-mediated changes. Which and how much these effects contribute to a RDN-induced BP drop and how they are counter-regulated remains an unresolved issue that needs to be clarified in future RDN-trials.

Besides other confounders, a constant observation in clinical trials is that a proportion of patients does not respond to RDN, which might in part contribute to the negative results in Symplicity-HTN3. Interestingly, the problem of non-responsiveness to renal denervation seems to be as old as the procedure itself: Even for surgical sympathectomy a high proportion of non-responders (ranging between 55% and 68%) has been described^[5,6]. Despite that, a strong positive effect on long-term mortality was found in a large series of 1200 patients^[5]. This leads to the question which other beneficial effects besides BP reduction RDN might have in humans, which might explain this discrepancy.

Renal function and sodium excretion

A potential deterioration of renal function - either by renal artery stenosis or by changes in intrarenal hemodynamics - is an often raised concern regarding RDN. On the contrary, as renal blood flow and salt/water retention is influenced by sympathetic activity^[2], RDN might have nephroprotective effects.

Two larger non-randomized analyses found glomerular filtration rates (GFR) to be unchanged after RDN^[15,16]. Interestingly, one trial could even show a decrease in albuminuria, consistent with an improvement of hypertension-induced end-organ damage^[16]. In another study, examining the effects of RDN in patients with impaired renal function, the authors were able to show that the hypertension-related deterioration of renal

Table 1 Effects of renal sympathetic denervation

Ref.	Year	n (RDN/control)	Effector	Effect	Control
Ott <i>et al</i> ^[15]	2013	19/-	Renal blood flow	None	None
Pöss <i>et al</i> ^[19]	2015	137/-	Renal sodium excretion	Increased sodium excretion, less pronounced in responders	None
Mahfoud <i>et al</i> ^[24]	2014	55/17	Left ventricular mass	Reduced left ventricular mass after RDN	Medical therapy
Doltra <i>et al</i> ^[25]	2014	5/23	Left ventricular mass		Medical therapy
McLellan <i>et al</i> ^[26]	2015	14/-			None
Lu <i>et al</i> ^[27]	2016	139/-			Meta-analysis
McLellan <i>et al</i> ^[26]	2015	14/-	Atrial conduction	Improved atrial conduction after RDN	None
Qiu <i>et al</i> ^[31]	2016	21/-	Persistent atrial fibrillation	Reduced heart rate after RDN	None
Armaganijan <i>et al</i> ^[36]	2015	10/-	Ventricular arrhythmia	Reduced frequency of ventricular arrhythmia episodes	None
Ott <i>et al</i> ^[15]	2013	19/-	Central hemodynamics	Reduced central BP and augmentation index after RDN	None
Brandt <i>et al</i> ^[38]	2012	110/10		Reduced aortic pulse pressure, pulse wave velocity and augmentation index	Medical
Mortensen <i>et al</i> ^[39]	2012	21/-		Reduced augmentation index	None
Hering <i>et al</i> ^[40]	2013	40/10			Medical
Okon <i>et al</i> ^[41]	2016	23/-		Unchanged invasive pulse wave velocity after RDN	None
Donazzan <i>et al</i> ^[51]	2015	11/-	Sympathetic activity	Reduced cardiac sympathetic activity after RDN	None
van Brussel <i>et al</i> ^[52]	2016	21/-		Unchanged cardiac sympathetic activity after RDN	None
Tsioufis <i>et al</i> ^[53]	2014	14/-		Reduced heart rate and arrhythmia burden and improved heart rate variability after RDN	None
Vink <i>et al</i> ^[55]	2014	13/-			None
Brinkmann <i>et al</i> ^[56]	2012	12/-		Unchanged muscle sympathetic nervous activity after RDN	None
Hering <i>et al</i> ^[57]	2013	10/25		Reduced muscle sympathetic nervous activity after RDN	Medical
Dörr <i>et al</i> ^[58,59]	2015	150/-		Reduced Neuropeptide Y and transiently reduced brain derived neutrophic factor after RDN	None
Dörr <i>et al</i> ^[63]	2015	100/-	Inflammation	Reduced systemic inflammation after RDN	None
Mahfoud <i>et al</i> ^[65]	2011	60/-	Insulin sensitivity	Improved insulin sensitivity after RDN	Medical
Verloop <i>et al</i> ^[66]	2015	29/-		Unchanged insulin sensitivity	None
Ewen <i>et al</i> ^[71]	2014	50/10	Exercise testing	Reduced Exercise BP after RDN	Medical
Ukena <i>et al</i> ^[69]	2011	37/9			Medical
Fengler <i>et al</i> ^[70]	2016	22/26			Sham
Lenski <i>et al</i> ^[72]	2013	36	Orthostatic reaction	None	None

BP: Blood pressure; RDN: Renal sympathetic denervation.

function could be halted with RDN over a follow up of three years^[17]. This suggests overall beneficial effects of RDN on renal function, especially in these patients who already suffer from hypertension-induced end-organ damage, which will clearly improve long-term mortality.

Despite the known vasoconstrictive effects of systemic sympathetic activity on the arterial vasculature^[2] and significant alterations in an animal study^[18], RDN does neither seem to improve nor deteriorate renal blood flow in humans^[15]. Presumably, this can be explained by the auto-regulative capacities of the renal vessels outweighing any RDN-induced changes.

The putative effect of RDN on renal sodium excretion is a promising therapeutic goal. The only human trial investigating this hard-to-assess endpoint however showed mixed results, as patients with stronger BP response after RDN showed a diminished effect on sodium excretion compared to those with less BP changes^[19]. To some extent this might be explained by a compensatory dietary sodium intake which was not assessed in the study. Therefore, this interesting aspect of RDN needs to be investigated thoroughly by additional rigorous

assessment of dietary sodium intake. An additional MRI-based quantification of tissue sodium and water might be helpful here as elevated concentrations are observed in patients with essential hypertension. Sodium and water tissue content might therefore represent an interesting diagnostic and therapeutic goal^[20,21].

Cardiac and hemodynamic changes

Left-ventricular-mass and fibrosis: An elevated left-ventricular mass is a frequent finding in hypertensive subjects^[22]. Its presence and its regression through therapeutic interventions significantly affects patients' outcomes^[22,23]. Therefore, it is a worthwhile therapeutic target in the treatment of human hypertension.

Several smaller studies and one recent meta-analysis describe a reduction of left-ventricular mass after RDN^[24-27]. In one of them an additional improvement in left-ventricular strain and ejection fraction was observed in patients with reduced values at baseline^[24]. Besides reversal of myocyte hypertrophy left-ventricular fibrosis might be altered by renal denervation, as the absolute extracellular volume was found to be reduced

Table 2 Blood pressure effects of renal sympathetic denervation

Ref.	Year	Control	n (RDN/control)	Systolic office BP (mmHg)	P-value	Systolic ambulatory BP (mmHg)	P-value
Krum <i>et al</i> ^[7]	2009	None	50	-22	< 0.001 ^a	NA	NA
Esler <i>et al</i> ^[11]	2010	RDN <i>vs</i> medical	106 (52/54)	-32 <i>vs</i> 1	< 0.00001 ^b	-11/-7 <i>vs</i> -3/-1	NA
Bhatt <i>et al</i> ^[8]	2014	RDN <i>vs</i> sham	535 (364/171)	-14 <i>vs</i> -12	0.26 ^b	-6.8 <i>vs</i> -4.8	0.98 ^b
Desch <i>et al</i> ^[10]	2015	RDN <i>vs</i> sham	71 (35/36, intention to treat) 63 (29/34, per protocol)	NA NA	NA NA	-8.5 <i>vs</i> -4.7 -8.3 <i>vs</i> -3.5	0.06 ^b 0.04 ^b
Rosa <i>et al</i> ^[13]	2015	RDN <i>vs</i> intensified medical treatment	106 (52/54)	-12 <i>vs</i> -14	< 0.001 ^a /0.60 ^b	-8.6 <i>vs</i> -8.1	< 0.001 ^a /0.87 ^b
Azizi <i>et al</i> ^[14]	2015	Stepped-care antihypertensive treatment with <i>vs</i> without RDN	106 (53/53)	-15 <i>vs</i> -9	0.15 ^b	-15.8 <i>vs</i> -9.9	0.03 ^b
Böhm <i>et al</i> ^[12]	2015	None	998	-12	< 0.00001 ^a	-6.6	< 0.00001 ^a

^aP-value for within group change; ^bP-value for between group change. BP: Blood pressure; RDN: Renal sympathetic denervation; NA: Not available.

after RDN^[25]. This finding might be supported by a reduced cellular matrix turnover assessed by collagen pro-peptides in patients after renal denervation in an upcoming laboratory study^[28].

Atrial fibrillation: Associated with BP reduction, RDN has been shown to improve atrial conduction^[26]. This might allow a look-out on renal denervation as an alternative or additional option for the treatment of symptomatic atrial fibrillation. This concept is supported by two recent animal studies in dogs, where RDN could impede the induction of atrial fibrillation^[29,30]. Also, for persistent atrial fibrillation, RDN was found to reduce the heart rate in a small case-series of symptomatic patients^[31]. Beyond this, several in-human trials regarding this issue are currently ongoing which will certainly help to improve our understanding of the intra-cardiac effects of RDN (NCT01635998, NCT01990911, NCT02064764).

Ventricular arrhythmia: As ventricular arrhythmias are more likely to occur under an elevated sympathetic activity, using RDN as a treatment for refractory ventricular arrhythmia seems a reasonable endeavor^[32]. Animal studies show promising effects for RDN in ischemia-induced arrhythmias when compared to a sham procedure^[33,34], while inducibility of ventricular arrhythmias cannot be prevented by RDN in healthy animals^[35]. Also a first in-man cohort of 10 patients with mainly non-ischemic cardiomyopathies reveals a dramatic drop in arrhythmia burden after RDN^[36]. Nonetheless, further prospective, randomized trials are needed to confirm this scope of application for RDN.

Hemodynamics and volume changes: Since the effects of RDN on renal water/sodium excretion and systemic vasculature are likely to be associated with changes in systemic volume status, it would be interesting to assess changes in intra-cardiac pressure and pressure-volume relations. Also, changes in central and peripheral hemodynamics in patients undergoing

RDN are of particular interest, as they determine the incidence of heart failure and potentially the course of cardiovascular remodeling^[37].

Several trials investigated central hemodynamics using non-invasive methods^[15,38-40]. Herein, alterations of cardiac afterload, namely a significant reduction in central pulse pressure and aortic augmentation index after RDN could be demonstrated. Also, a reduction of non-invasively assessed pulse-wave velocity, indicating decreased arterial stiffness after RDN, was observed, even if this is conflicting with the results of a smaller cohort with unchanged invasively acquired pulse-wave-velocity 6 mo after RDN^[41]. As arterial stiffness is - to some extent - a BP-dependent parameter, any changes observed after RDN have to be interpreted with caution.

An explicit effect of RDN on cardiac hemodynamics, including changes in preload, filling and contractility, has - to the present date - not been described. Assessment of hemodynamic changes can be achieved *via* echocardiography, which was part of virtually all protocols of bigger studies examining treatment effects of RDN. The paucity of published data regarding echocardiographically assessed hemodynamic changes in patients treated with RDN might imply negative findings (assuming a publication bias), might be a consequence of the limited sensitivity of echocardiography in detecting cardiac filling pressures or might just have been neglected so far. Therefore - besides invasive measurements - other non-invasive methods like MRI-based analyses (e.g., the left atrial transit time) could provide additional information here^[42].

Furthermore, given the described impact of RDN on the LV musculature and the arterial system, an improvement of ventricular-atrial coupling could be assumed after treatment.

However, as cardiac loading underlies marked intra-individual changes, reliable assessment of changes in central hemodynamics depend on testing of patients instantaneously under different physiologic conditions (such as rest and exercise) or under longitudinal observational trial settings.

Central and peripheral nervous changes

As illustrated above, mediated through afferent central nervous fibers RDN also affects the central nervous system. Interestingly, overall successful treatment of essential hypertension is associated with improved neuropsychological performance and to some extent with alterations in regional cerebral blood flow response to working memory tasks at short-term follow up^[43]. To date, this has not been assessed for patients undergoing RDN but might be a promising task for future trials, especially since uncontrolled hypertension is a well-known risk factor for cerebrovascular diseases and might contribute to cognitive decline^[44].

The link between central-nervous and peripheral sympathetic-nervous alterations in hypertensive patients could further be investigated in assessing to which extent central nervous changes are mediated indirectly by BP alterations or by increased sympathetic overdrive and afferent signaling itself.

The role of a potential sympathetic re-innervation after RDN^[45,46] warrants further investigation as it might partly explain non-responsiveness and lead to negative trial results. However, BP reductions in response to effective RDN seems to be long-lasting in the data published so far^[47-49].

Systemic sympathetic activity

Direct measurement of the systemic sympathetic activity is difficult to perform and is therefore underrepresented in clinical trials of RDN^[50]. Indirect assessment, however, is feasible with different techniques and has been used in various trials.

Cardiac scintigraphy: Two small trials (including only 23 and 11 patients) examined alterations in the cardiac sympathetic nervous system activity after RDN using scintigraphy^[51,52]. Their results were conflicting, as in one trial with only a non-significant BP drop in ambulatory BP-measurements in the RDN patients, no significant alterations in cardiac sympathetic activity were found. The other trial found a remarkable impact of RDN on ambulatory measured BP and also found a strong reduction in cardiac sympathetic activity. Since the results are inconclusive at present, further evaluation in larger, adequately powered cohorts is necessary.

Heart rate variability: Another way to measure systemic sympathetic activity is assessing heart rate variability (HRV). In a small case series, Tsioufis and coworkers were able to show RDN achieved a significant reduction in patient's HRV and arrhythmia burden, suggesting a reduced systemic sympathetic activity in the treated patients^[53].

Muscle sympathetic nerve activity: Muscle sympathetic nerve activity is known to be elevated in hypertensive subjects^[54], indicating a direct link to systemic sympathetic activity. Hence, direct intraneural

recordings could be considered as a good marker for treatment success after RDN. So far this hypothesis has been investigated in two smaller case series which failed to show any alterations through RDN^[55,56]. In contrast, a prospective controlled trial in 35 patients found significant alterations in single- and multi-unit muscle sympathetic nerve activity^[57]. Despite the latter results, overall the role of muscle sympathetic activity as an outcome marker in RDN trials is not fully determined and warrants further research.

Laboratory markers: Dörr *et al.*^[58] investigated the role of Neuropeptide Y, a neurotransmitter that is co-released with norepinephrine and up-regulated during sympathetic activity. They were able to show a significant drop of Neuropeptide Y after RDN which can be interpreted as an expression of a reduced systemic sympathetic activity.

Successful RDN also leads to a transient down-regulation of serum brain-derived neurotrophic factor immediately after denervation^[59]. Since brain-derived neurotrophic factor is a neuronal growth factor, this adds further evidence for true downregulation of the sympathetic nervous system on a neuronal base through RDN.

Overall, despite the lack of data for a direct assessment of systemic sympathetic activity in RDN-trials, indirect markers strongly indicate that RDN results in significant changes of systemic sympathetic activity.

Inflammation

Arterial hypertension is associated with chronic vascular inflammation and remodeling^[60-62]. In a prospective analysis of 60 patients undergoing RDN, a significant reduction of pro-inflammatory cytokine interleukine-6 and high-sensitive C-reactive protein was achieved^[63]. This is in particular encouraging, as it might be related to beneficial long-term effects of RDN. It has however to be debated, if the observed changes are rather related to the BP lowering effects of RDN, which might attenuate the pathologic immune response, rather than to RDN itself.

Metabolic effects

Insulin sensitivity: An elevated sympathetic activity seems to be associated with an altered insulin sensitivity^[64]. Therefore, RDN might help to improve the glucose metabolism in patients with a high sympathetic overdrive. The first trial to investigate this relation, a pilot-study in 50 patients, found a significant change in glucose metabolism and insulin sensitivity^[65]. Notably, only 40% of these patients were diagnosed with diabetes mellitus and only 36% had an impaired glucose tolerance at baseline. In contrast, a smaller, uncontrolled prospective trial did not find any changes in insulin sensitivity after a follow up of 12 mo in 29 patients with metabolic syndrome^[66]. Therefore, the role of RDN for improvement of insulin sensitivity remains equivocal.

However, if an effect of RDN on this very relevant end point could be proven, it could tremendously affect patients' long-term prognosis.

Exercise testing: Exercise BP, an important risk factor for future cardiovascular events^[67,68], was found to be reduced after RDN in two non-randomized studies and one sham-controlled trial^[69-71]. Also beneficial effects for exercise capacity and duration are described for RDN without affecting chronotropic competence in treated patients^[69,71].

Orthostatic effects: Safety concerns regarding potential unfavorable orthostatic effects of RDN can largely be ruled out due to the lack of the occurrence of orthostatic side effects in the large RDN treatment trials and a smaller trial which did not find any pathologic alterations in tilt table testing for RDN-treated patients^[72].

Conclusion

Beyond the still debated effects of RDN on BP in hypertensive patients, a wide range of promising effects has been shown. Most of these changes could importantly change long-term morbidity and mortality of the treated subjects, even if their BP remained unchanged. To determine the value of non-BP effects of RDN for clinical practice, further long-term data with multiple cardiovascular endpoints is needed.

Until then, it seems prudent to optimize BP outcome in RDN trials through the identification of predictors for treatment success. In the following we will give a brief overview of such predictors that have been identified so far.

PREDICTORS FOR SUCCESSFUL RDN

Baseline BP

High BP prior to renal denervation has most frequently been described as the strongest predictor of BP reduction after RDN^[12,73]. However, whether this is related to a higher sympathetic activity in patients with higher baseline BP or a manifestation of the regression to mean phenomenon remains controversial and is an unresolved issue to date^[74]. Thus, other predictors for treatment success in RDN are needed.

Anatomy and technological aspects

Anatomy: The anatomy of the renal arteries seems to have considerable influence on the BP response to RDN. Importantly, the anatomy of human renal vessels shows a high variability^[75]. Accessory renal arteries or an early bifurcation occurs in approximately one of three patients^[75]. This is important, as the presence of accessory or early bifurcated vessels seems to influence outcome negatively^[76]. In principle it seems prudent to exclude these patients from renal denervation. Nevertheless, in the ongoing SPYRAL-HTN trial (NCT02439775) denervation of accessories with a diameter above or equal 3 mm is

planned. This will hopefully clarify the role of accessory arteries and early bifurcations soon.

As the sympathetic nerve fibers are closer to the lumen in the distal part of the renal vessel^[77], ablation of the distal main artery or even the side branches are also thought to improve outcome^[78,79].

Technological aspects: One of the major shortcoming of RDN is the lack of a direct feedback mechanism during intervention^[50]. Despite many promising approaches, including direct intravascular and (sub-)cutaneous measurements of renal sympathetic activity, the challenging task of a direct *in-vivo* feedback for renal denervation success is still far away from clinical practice. Nevertheless, once a direct assessment method for renal sympathetic activity is established this will be a milestone in improving renal denervation success^[50].

Another technological aspect for future trial designs is that denervation success seems to be dependent of the number of ablation points as well as the experience of the interventional physician^[73]. Therefore, RDN should only be performed by trained interventionalists and as many ablations as possible should be delivered to optimize BP outcome.

Most clinical trials regarding RDN were carried out using radiofrequency based catheters. The role of other devices, like ultrasound-based^[80-82] or chemical approaches^[83,84], remain uncertain, as head-to-head comparisons of different techniques are lacking. Nevertheless, ultrasound treatment appears to be a promising treatment option, as recent work from our group suggests: Treatment of 24 non-responders to radiofrequency based RDN with an ultrasound denervation system significantly improved BP^[85].

Obesity

Obesity seems to be associated with an elevated sympathetic activity, even in normotensive subjects^[86]. Therefore, it might be a good predictor for BP responsiveness to RDN. In contrast, according to one singular study^[87] obesity seems to be a predictor for non-responsiveness to RDN. The results of this trial are however somewhat questionable, as this constellation was neither found in any other trial^[8,73] nor in the even large multicenter Global Simplicity Registry^[12]. Moreover, in two smaller trials a higher body mass index was found to be a predictor for responsiveness to RDN^[47,88]. To date, obesity should not be considered to have any predictive value for RDN success until reevaluation in larger, adequately powered cohorts has been performed.

Gender

So far the effect of RDN seems to be independent of gender. Nevertheless, due to the higher incidence of hypertension and therapy resistant hypertension in men, women are strongly underrepresented in any clinical trial regarding RDN. The percentage of women included in trials of renal denervation ranges between 23 and

Table 3 Predictors for blood pressure change after renal sympathetic denervation

Ref.	Year	Patients	Predictor
Böhm <i>et al</i> ^[12]	2015	998	Higher baseline BP predicts better BP response to RDN
Kandzari <i>et al</i> ^[73]	2015	364	
Id <i>et al</i> ^[76]	2013	74	Less BP response to RDN if accessories are present
Ewen <i>et al</i> ^[89]	2015	126	Better BP response in patients with combined vs isolated systolic hypertension
Okon <i>et al</i> ^[41]	2016	58	Lower pulse wave velocity predicts BP response
Zuern <i>et al</i> ^[88]	2013	40	Better BP response in patients with impaired baroreflex sensitivity

BP: Blood pressure; RDN: Renal sympathetic denervation.

41^[8,10,13,14,47]. Realizing a meta-analysis of prospective trials could clarify the role of gender for RDN success.

Age

The age of the treated patients itself was not found to have a good predictive value for the success of RDN^[73]. In contrast, considerable evidence was found for vascular aging and stiffening as a predictor for renal denervation over the last years^[41,89].

Vascular aging and stiffness

Arterial stiffening is associated with a high cardiovascular mortality in hypertensive patients^[90,91]. It also can be regarded as a cause for essential hypertension^[92,93]. Ewen *et al*^[89] found, that the presence of isolated systolic hypertension - characterized by increased aortic stiffness - is associated with a diminished response to RDN. In line with these data, our group also found an increased aortic stiffness, assessed by invasive pulse wave velocity, to be an independent predictor for poor BP response to renal denervation^[41]. This is a promising finding, as isolated systolic hypertension and pulse wave velocity, among other markers of vascular aging and aortic stiffness, can easily be assessed non-invasively and thereby could help improving the preselection of patients available for renal denervation. To some extent, this might also explain why a trial by Vink *et al*^[94] found the presence of cardiovascular diseases (a composite of stroke, transient ischemic attack and coronary artery disease), which are associated with increased vascular stiffness, to be a predictor for BP response to RDN.

Baroreflex

An impaired cardiac baroreflex occurs frequently in hypertensive subjects^[95]. This might be explained by sympathetic overactivity^[88]. Therefore, the presence of an impaired cardiac baroreflex as an indicator for high sympathetic overdrive could be a good predictor for renal denervation success. This hypothesis was already confirmed by a trial in 50 patients^[88], but has not been applied in other prospective trials to date.

Renal function

Patients with renal diseases have often been excluded from clinical trials for safety reasons. Despite these considerations, patients with impaired renal function

show an elevated sympathetic activity^[96,97], and therefore might be good candidates for RDN. Consequently, Vink *et al*^[94] found an inverse relation between the estimated GFR and the change in BP after RDN in a hypertensive population off antihypertensive medication. However, when analyzing patients on antihypertensive medication, no significant predictive value for estimated GFR was observed. These interesting findings warrant further investigation, as - besides enlightening the predictive role of renal function - they might partly explain why and how antihypertensive drugs interact with the effectiveness of RDN. Several trials investigating the effect of renal denervation in chronic kidney disease are currently recruiting patients (*e.g.*, NCT02002585, NCT01442883).

Conclusion

Despite the disappointing results of the SYMPPLICITY-HTN3 trial, the canon of published data identifies RDN as a promising therapeutic option for hypertensive patients. Besides direct BP-lowering effects RDN has been shown to affect a broad range of pathophysiological mechanisms and might even be a viable treatment option for patients with other conditions such as heart failure or arrhythmias.

Although various predictors for the success of RDN have been identified (Table 3), an optimization for the prediction of RDN response is highly desired and several trials are ongoing which hopefully will improve treatment success and future RDN-trial design.

Verification of specific treatment effects of RDN in carefully and well-designed trials bare the hope to secure the role for RDN in treating arterial hypertension and ideally in reducing cardiovascular morbidity and mortality in the future.

REFERENCES

- 1 **Krum H**, Sobotka P, Mahfoud F, Böhm M, Esler M, Schlaich M. Device-based antihypertensive therapy: therapeutic modulation of the autonomic nervous system. *Circulation* 2011; **123**: 209-215 [PMID: 21242507 DOI: 10.1161/CIRCULATIONAHA.110.971580]
- 2 **DiBona GF**. Physiology in perspective: The Wisdom of the Body. Neural control of the kidney. *Am J Physiol Regul Integr Comp Physiol* 2005; **289**: R633-R641 [PMID: 16105818 DOI: 10.1152/ajpregu.00258.2005]
- 3 **Reinecke M**, Forssmann WG. Neuropeptide (neuropeptide Y, neurotensin, vasoactive intestinal polypeptide, substance P, calcitonin gene-related peptide, somatostatin) immunohistochemistry and

- ultrastructure of renal nerves. *Histochemistry* 1988; **89**: 1-9 [PMID: 2452814]
- 4 **Mione MC**, Ralevic V, Burnstock G. Peptides and vasomotor mechanisms. *Pharmacol Ther* 1990; **46**: 429-468 [PMID: 2188271]
 - 5 **Smithwick RH**, Thompson JE. Splanchnicectomy for essential hypertension; results in 1,266 cases. *J Am Med Assoc* 1953; **152**: 1501-1504 [PMID: 13061307]
 - 6 **Parkes WE**. Thoracolumbar sympathectomy in hypertension. *Br Heart J* 1958; **20**: 249-252 [PMID: 13523020]
 - 7 **Krum H**, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**: 1275-1281 [PMID: 19332353 DOI: 10.1016/S0140-6736(09)60566-3]
 - 8 **Bhatt DL**, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; **370**: 1393-1401 [PMID: 24678939 DOI: 10.1056/NEJMoa1402670]
 - 9 **Kandzari DE**, Kario K, Mahfoud F, Cohen SA, Pilcher G, Pocock S, Townsend R, Weber MA, Böhm M. The SPYRAL HTN Global Clinical Trial Program: Rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications. *Am Heart J* 2016; **171**: 82-91 [PMID: 26699604 DOI: 10.1016/j.ahj.2015.08.021]
 - 10 **Desch S**, Okon T, Heinemann D, Kulle K, Röhnert K, Sonnabend M, Petzold M, Müller U, Schuler G, Eitel I, Thiele H, Lurz P. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. *Hypertension* 2015; **65**: 1202-1208 [PMID: 25824248 DOI: 10.1161/HYPERTENSIONAHA.115.05283]
 - 11 **Esler MD**, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; **376**: 1903-1909 [PMID: 21093036 DOI: 10.1016/S0140-6736(10)62039-9]
 - 12 **Böhm M**, Mahfoud F, Ukena C, Hoppe UC, Narkiewicz K, Negoita M, Ruilope L, Schlaich MP, Schmieder RE, Whitbourn R, Williams B, Zeymer U, Zirlik A, Mancía G. First report of the Global SYMPPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. *Hypertension* 2015; **65**: 766-774 [PMID: 25691618 DOI: 10.1161/HYPERTENSIONAHA.114.05010]
 - 13 **Rosa J**, Widimský P, Toušek P, Petrák O, Čurila K, Waldauf P, Bednář F, Zelinka T, Holaj R, Štrauch B, Šomlůvová Z, Táborský M, Václavík J, Kociánová E, Branny M, Nykl I, Jiravský O, Widimský J. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension* 2015; **65**: 407-413 [PMID: 25421981 DOI: 10.1161/HYPERTENSIONAHA.114.04019]
 - 14 **Azizi M**, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, Midulla M, Mounier-Véhier C, Courand PY, Lantelme P, Denolle T, Dourmap-Collas C, Trillaud H, Pereira H, Plouin PF, Chatellier G. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015; **385**: 1957-1965 [PMID: 25631070 DOI: 10.1016/S0140-6736(14)61942-5]
 - 15 **Ott C**, Janka R, Schmid A, Titze S, Ditting T, Sobotka PA, Veelken R, Uder M, Schmieder RE. Vascular and renal hemodynamic changes after renal denervation. *Clin J Am Soc Nephrol* 2013; **8**: 1195-1201 [PMID: 23559677 DOI: 10.2215/CJN.08500812]
 - 16 **Ott C**, Mahfoud F, Schmid A, Ditting T, Veelken R, Ewen S, Ukena C, Uder M, Böhm M, Schmieder RE. Improvement of albuminuria after renal denervation. *Int J Cardiol* 2014; **173**: 311-315 [PMID: 24681017 DOI: 10.1016/j.ijcard.2014.03.017]
 - 17 **Ott C**, Mahfoud F, Schmid A, Toennes SW, Ewen S, Ditting T, Veelken R, Ukena C, Uder M, Böhm M, Schmieder RE. Renal denervation preserves renal function in patients with chronic kidney disease and resistant hypertension. *J Hypertens* 2015; **33**: 1261-1266 [PMID: 25923731 DOI: 10.1097/HJH.0000000000000556]
 - 18 **DiBona GF**, Sawin LL. Effect of renal denervation on dynamic autoregulation of renal blood flow. *Am J Physiol Renal Physiol* 2004; **286**: F1209-F1218 [PMID: 14969998 DOI: 10.1152/ajprenal.00010.2004]
 - 19 **Pöss J**, Ewen S, Schmieder RE, Muhler S, Vonend O, Ott C, Linz D, Geisel J, Rump LC, Schlaich M, Böhm M, Mahfoud F. Effects of renal sympathetic denervation on urinary sodium excretion in patients with resistant hypertension. *Clin Res Cardiol* 2015; **104**: 672-678 [PMID: 25715938 DOI: 10.1007/s00392-015-0832-5]
 - 20 **Kopp C**, Linz P, Dahlmann A, Hammon M, Jantsch J, Müller DN, Schmieder RE, Cavallaro A, Eckardt KU, Uder M, Luft FC, Titze J. ²³Na magnetic resonance imaging-determined tissue sodium in healthy subjects and hypertensive patients. *Hypertension* 2013; **61**: 635-640 [PMID: 23339169 DOI: 10.1161/HYPERTENSIONAHA.111.005666]
 - 21 **Kopp C**, Linz P, Wachsmuth L, Dahlmann A, Horbach T, Schöfl C, Renz W, Santoro D, Niendorf T, Müller DN, Neining M, Cavallaro A, Eckardt KU, Schmieder RE, Luft FC, Uder M, Titze J. ²³Na magnetic resonance imaging of tissue sodium. *Hypertension* 2012; **59**: 167-172 [PMID: 22146510 DOI: 10.1161/HYPERTENSIONAHA.111.183517]
 - 22 **Levy D**, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996; **275**: 1557-1562 [PMID: 8622246]
 - 23 **Okin PM**, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, Snapinn S, Harris KE, Aurup P, Edelman JM, Wedel H, Lindholm LH, Dahlöf B. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004; **292**: 2343-2349 [PMID: 15547161 DOI: 10.1001/jama.292.19.2343]
 - 24 **Mahfoud F**, Urban D, Teller D, Linz D, Stawowy P, Hassel JH, Fries P, Dreyse S, Wellnhofer E, Schneider G, Buecker A, Schneeweis C, Doltra A, Schlaich MP, Esler MD, Fleck E, Böhm M, Kelle S. Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multicentre cardiovascular magnetic resonance imaging trial. *Eur Heart J* 2014; **35**: 2224-231b [PMID: 24603307 DOI: 10.1093/eurheartj/ehu093]
 - 25 **Doltra A**, Messroghli D, Stawowy P, Hassel JH, Gebker R, Leppänen O, Gräfe M, Schneeweis C, Schnackenburg B, Fleck E, Kelle S. Potential reduction of interstitial myocardial fibrosis with renal denervation. *J Am Heart Assoc* 2014; **3**: e001353 [PMID: 25516438 DOI: 10.1161/JAHA.114.001353]
 - 26 **McLellan AJ**, Schlaich MP, Taylor AJ, Prabhu S, Hering D, Hammond L, Marusic P, Duval J, Sata Y, Ellims A, Esler M, Peter K, Shaw J, Walton A, Kalman JM, Kistler PM. Reverse cardiac remodeling after renal denervation: Atrial electrophysiologic and structural changes associated with blood pressure lowering. *Heart Rhythm* 2015; **12**: 982-990 [PMID: 25638699 DOI: 10.1016/j.hrthm.2015.01.039]
 - 27 **Lu D**, Wang K, Liu Q, Wang S, Zhang Q, Shan Q. Reductions of left ventricular mass and atrial size following renal denervation: a meta-analysis. *Clin Res Cardiol* 2016; **105**: 648-656 [PMID: 26838292 DOI: 10.1007/s00392-016-0964-2]
 - 28 **Dörr O**, Liebetrau C, Möllmann H, Gaede L, Troidl C, Morczek K, Wiebe J, Hoffmann J, Voss S, Bauer T, Hamm C, Nef H. Influence of Renal Sympathetic Denervation on Cardiac Extracellular Matrix Turnover and Cardiac Fibrosis. *Am J Hypertens* 2015; **28**: 1285-1292 [PMID: 25767136 DOI: 10.1093/ajh/hpv020]
 - 29 **Zhou Q**, Zhou X, TuEr-Hong ZL, Wang H, Yin T, Li Y, Zhang L, Lu Y, Xing Q, Zhang J, Yang Y, Tang B. Renal sympathetic denervation suppresses atrial fibrillation induced by acute atrial ischemia/infarction through inhibition of cardiac sympathetic activity. *Int J Cardiol* 2016; **203**: 187-195 [PMID: 26512836 DOI: 10.1016/j.ijcard.2015.10.120]
 - 30 **Hou Y**, Hu J, Po SS, Wang H, Zhang L, Zhang F, Wang K, Zhou Q.

- Catheter-based renal sympathetic denervation significantly inhibits atrial fibrillation induced by electrical stimulation of the left stellate ganglion and rapid atrial pacing. *PLoS One* 2013; **8**: e78218 [PMID: 24223140 DOI: 10.1371/journal.pone.0078218]
- 31 **Qiu M**, Shan Q, Chen C, Geng J, Guo J, Zhou X, Qian W, Tang L, Yin Y. Renal sympathetic denervation improves rate control in patients with symptomatic persistent atrial fibrillation and hypertension. *Acta Cardiol* 2016; **71**: 67-73 [PMID: 26853256 DOI: 10.2143/AC.71.1.3132100]
 - 32 **Kosiuk J**, Hilbert S, Pokushalov E, Hindricks G, Steinberg JS, Bollmann A. Renal denervation for treatment of cardiac arrhythmias: state of the art and future directions. *J Cardiovasc Electrophysiol* 2015; **26**: 233-238 [PMID: 25231911 DOI: 10.1111/jce.12553]
 - 33 **Linz D**, Wirth K, Ukena C, Mahfoud F, Pöss J, Linz B, Böhm M, Neuberger HR. Renal denervation suppresses ventricular arrhythmias during acute ventricular ischemia in pigs. *Heart Rhythm* 2013; **10**: 1525-1530 [PMID: 23851058 DOI: 10.1016/j.hrthm.2013.07.015]
 - 34 **Huang B**, Yu L, He B, Lu Z, Wang S, He W, Yang K, Liao K, Zhang L, Jiang H. Renal sympathetic denervation modulates ventricular electrophysiology and has a protective effect on ischaemia-induced ventricular arrhythmia. *Exp Physiol* 2014; **99**: 1467-1477 [PMID: 25172887 DOI: 10.1113/expphysiol.2014.082057]
 - 35 **Lubanda JC**, Kudlicka J, Mlcek M, Chochola M, Neuzil P, Linhart A, Kittnar O. Renal denervation decreases effective refractory period but not inducibility of ventricular fibrillation in a healthy porcine biomodel: a case control study. *J Transl Med* 2015; **13**: 4 [PMID: 25591755 DOI: 10.1186/s12967-014-0367-y]
 - 36 **Armaganijan LV**, Staico R, Moreira DA, Lopes RD, Medeiros PT, Habib R, Melo Neto J, Katz M, Armaganijan D, Sousa AG, Mahfoud F, Abizaïd A. 6-Month Outcomes in Patients With Implantable Cardioverter-Defibrillators Undergoing Renal Sympathetic Denervation for the Treatment of Refractory Ventricular Arrhythmias. *JACC Cardiovasc Interv* 2015; **8**: 984-990 [PMID: 26088516 DOI: 10.1016/j.jcin.2015.03.012]
 - 37 **Chirinos JA**, Kips JG, Jacobs DR, Brumback L, Duprez DA, Kronmal R, Bluemke DA, Townsend RR, Vermeersch S, Segers P. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2012; **60**: 2170-2177 [PMID: 23103044 DOI: 10.1016/j.jacc.2012.07.054]
 - 38 **Brandt MC**, Reda S, Mahfoud F, Lenski M, Böhm M, Hoppe UC. Effects of renal sympathetic denervation on arterial stiffness and central hemodynamics in patients with resistant hypertension. *J Am Coll Cardiol* 2012; **60**: 1956-1965 [PMID: 23062529 DOI: 10.1016/j.jacc.2012.08.959]
 - 39 **Mortensen K**, Franzen K, Himmel F, Bode F, Schunkert H, Weil J, Reppel M. Catheter-based renal sympathetic denervation improves central hemodynamics and arterial stiffness: a pilot study. *J Clin Hypertens* (Greenwich) 2012; **14**: 861-870 [PMID: 23205753 DOI: 10.1111/j.1751-7176.2012.00704.x]
 - 40 **Hering D**, Lambert EA, Marusic P, Ika-Sari C, Walton AS, Krum H, Sobotka PA, Mahfoud F, Böhm M, Lambert GW, Esler MD, Schlaich MP. Renal nerve ablation reduces augmentation index in patients with resistant hypertension. *J Hypertens* 2013; **31**: 1893-1900 [PMID: 23697964 DOI: 10.1097/HJH.0b013e3283622e58]
 - 41 **Okon T**, Röhnert K, Stiermaier T, Rommel KP, Müller U, Fengler K, Schuler G, Desch S, Lurz P. Invasive Aortic Pulse Wave Velocity as a Marker for Arterial Stiffness Predicts Outcome of Renal Sympathetic Denervation. *EuroIntervention* 2016; In press
 - 42 **Cao JJ**, Wang Y, McLaughlin J, Haag E, Rhee P, Passick M, Toole R, Cheng J, Berke AD, Lachman J, Reichel N. Left ventricular filling pressure assessment using left atrial transit time by cardiac magnetic resonance imaging. *Circ Cardiovasc Imaging* 2011; **4**: 130-138 [PMID: 21262980 DOI: 10.1161/CIRCIMAGING.110.959569]
 - 43 **Richard Jennings J**, Christie IC, Muldoon MF, Ryan CM, Price JC, Meltzer CC. Brain function, cognition, and the blood pressure response to pharmacological treatment. *Psychosom Med* 2010; **72**: 702-711 [PMID: 20639391 DOI: 10.1097/PSY.0b013e3181e7c1a2]
 - 44 **Gąsecki D**, Kwarciany M, Nyka W, Narkiewicz K. Hypertension, brain damage and cognitive decline. *Curr Hypertens Rep* 2013; **15**: 547-558 [PMID: 24146223 DOI: 10.1007/s11906-013-0398-4]
 - 45 **Booth LC**, Nishi EE, Yao ST, Ramchandra R, Lambert GW, Schlaich MP, May CN. Reinnervation of renal afferent and efferent nerves at 5.5 and 11 months after catheter-based radiofrequency renal denervation in sheep. *Hypertension* 2015; **65**: 393-400 [PMID: 25403610 DOI: 10.1161/HYPERTENSIONAHA.114.04176]
 - 46 **Rodionova K**, Fiedler C, Guenther F, Grouzmann E, Neuberger W, Fischer MJ, Ott C, Linz P, Freisinger W, Heinlein S, Schmidt ST, Schmieder RE, Amann K, Scrogin K, Veelken R, Ditting T. Complex reinnervation pattern after unilateral renal denervation in rats. *Am J Physiol Regul Integr Comp Physiol* 2016; **310**: R806-R818 [PMID: 26911463 DOI: 10.1152/ajpregu.00227.2014]
 - 47 **Tsioufis CP**, Papademetriou V, Dimitriadis KS, Kasiakogias A, Tsiachris D, Worthley MI, Sinhal AR, Chew DP, Meredith IT, Malaïapan Y, Thomopoulos C, Kallikazaros I, Tousoulis D, Worthley SG. Catheter-based renal denervation for resistant hypertension: Twenty-four month results of the EnLIGHTN I first-in-human study using a multi-electrode ablation system. *Int J Cardiol* 2015; **201**: 345-350 [PMID: 26301677 DOI: 10.1016/j.ijcard.2015.08.069]
 - 48 **Mancia G**, Mahfoud F, Narkiewicz K, Ruilope LM, Schlaich MP, Schmieder RE, Williams B, Böhm M. 4A.01: long-term effects of renal artery denervation in real world patients with uncontrolled hypertension from the global simplicity registry. *J Hypertens* 2015; **33** Suppl 1: e49 [PMID: 26102834 DOI: 10.1097/01.hjh.0000467475.67073.7e]
 - 49 **Hering D**, Marusic P, Walton AS, Lambert EA, Krum H, Narkiewicz K, Lambert GW, Esler MD, Schlaich MP. Sustained sympathetic and blood pressure reduction 1 year after renal denervation in patients with resistant hypertension. *Hypertension* 2014; **64**: 118-124 [PMID: 24732891 DOI: 10.1161/HYPERTENSIONAHA.113.03098]
 - 50 **Nair GK**, Massé S, Asta J, Sevaptisidis E, Azam MA, Lai PF, Veluppillaim A, Magtibay K, Jackson N, Nanthakumar K. The need for and the challenges of measuring renal sympathetic nerve activity. *Heart Rhythm* 2016; **13**: 1166-1171 [PMID: 26806582 DOI: 10.1016/j.hrthm.2016.01.018]
 - 51 **Donazzan L**, Mahfoud F, Ewen S, Ukena C, Cremers B, Kirsch CM, Hellwig D, Eweïwi T, Ezziddin S, Esler M, Böhm M. Effects of catheter-based renal denervation on cardiac sympathetic activity and innervation in patients with resistant hypertension. *Clin Res Cardiol* 2016; **105**: 364-371 [PMID: 26493305 DOI: 10.1007/s00392-015-0930-4]
 - 52 **van Brussel PM**, Eeftinck Schattenkerk DW, Dobrowolski LC, de Winter RJ, Reekers JA, Verberne HJ, Vogt L, van den Born BJ. Effects of renal sympathetic denervation on cardiac sympathetic activity and function in patients with therapy resistant hypertension. *Int J Cardiol* 2016; **202**: 609-614 [PMID: 26447672 DOI: 10.1016/j.ijcard.2015.09.025]
 - 53 **Tsioufis C**, Papademetriou V, Tsiachris D, Dimitriadis K, Kasiakogias A, Kordalis A, Antonakis V, Kefala A, Thomopoulos C, Kallikazaros I, Lau EO, Stefanadis C. Drug-resistant hypertensive patients responding to multielectrode renal denervation exhibit improved heart rate dynamics and reduced arrhythmia burden. *J Hum Hypertens* 2014; **28**: 587-593 [PMID: 24621623 DOI: 10.1038/jhh.2014.14]
 - 54 **Anderson EA**, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. *Hypertension* 1989; **14**: 177-183 [PMID: 2759678]
 - 55 **Vink EE**, Verloop WL, Siddiqi L, van Schelven LJ, Liam Oey P, Blankestijn PJ. The effect of percutaneous renal denervation on muscle sympathetic nerve activity in hypertensive patients. *Int J Cardiol* 2014; **176**: 8-12 [PMID: 25027168 DOI: 10.1016/j.ijcard.2014.06.021]
 - 56 **Brinkmann J**, Heusser K, Schmidt BM, Menne J, Klein G, Bauersachs J, Haller H, Sweep FC, Diedrich A, Jordan J, Tank J. Catheter-based renal nerve ablation and centrally generated sympathetic activity in difficult-to-control hypertensive patients:

- prospective case series. *Hypertension* 2012; **60**: 1485-1490 [PMID: 23045466 DOI: 10.1161/HYPERTENSIONAHA.112.201186]
- 57 **Hering D**, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, Esler MD, Schlaich MP. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. *Hypertension* 2013; **61**: 457-464 [PMID: 23172929 DOI: 10.1161/HYPERTENSIONAHA.111.00194]
- 58 **Dörr O**, Ewen S, Liebetrau C, Möllmann H, Gaede L, Linz D, Hohl M, Troidl C, Bauer T, Böhm M, Hamm C, Mahfoud F, Nef H. Neuropeptide Y as an indicator of successful alterations in sympathetic nervous activity after renal sympathetic denervation. *Clin Res Cardiol* 2015; **104**: 1064-1071 [PMID: 26008896 DOI: 10.1007/s00392-015-0874-8]
- 59 **Dörr O**, Liebetrau C, Möllmann H, Gaede L, Troidl C, Haidner V, Wiebe J, Voss S, Bauer T, Hamm C, Nef H. Brain-derived neurotrophic factor as a marker for immediate assessment of the success of renal sympathetic denervation. *J Am Coll Cardiol* 2015; **65**: 1151-1153 [PMID: 25790889 DOI: 10.1016/j.jacc.2014.11.071]
- 60 **Virdis A**, Dell'Agnello U, Taddei S. Impact of inflammation on vascular disease in hypertension. *Maturitas* 2014; **78**: 179-183 [PMID: 24846805 DOI: 10.1016/j.maturitas.2014.04.012]
- 61 **Mendall MA**, Patel P, Asante M, Ballam L, Morris J, Strachan DP, Camm AJ, Northfield TC. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart* 1997; **78**: 273-277 [PMID: 9391290]
- 62 **Furumoto T**, Saito N, Dong J, Mikami T, Fujii S, Kitabatake A. Association of cardiovascular risk factors and endothelial dysfunction in Japanese hypertensive patients: implications for early atherosclerosis. *Hypertens Res* 2002; **25**: 475-480 [PMID: 12135329]
- 63 **Dörr O**, Liebetrau C, Möllmann H, Mahfoud F, Ewen S, Gaede L, Troidl C, Hoffmann J, Busch N, Laux G, Wiebe J, Bauer T, Hamm C, Nef H. Beneficial effects of renal sympathetic denervation on cardiovascular inflammation and remodeling in essential hypertension. *Clin Res Cardiol* 2015; **104**: 175-184 [PMID: 25326158 DOI: 10.1007/s00392-014-0773-4]
- 64 **Masuo K**, Mikami H, Ogihara T, Tuck ML. Sympathetic nerve hyperactivity precedes hyperinsulinemia and blood pressure elevation in a young, nonobese Japanese population. *Am J Hypertens* 1997; **10**: 77-83 [PMID: 9008251]
- 65 **Mahfoud F**, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, Hoppe UC, Vonend O, Rump LC, Sobotka PA, Krum H, Esler M, Böhm M. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation* 2011; **123**: 1940-1946 [PMID: 21518978 DOI: 10.1161/CIRCULATIONAHA.110.991869]
- 66 **Verloop WL**, Spiering W, Vink EE, Beeftink MM, Blankestijn PJ, Doevendans PA, Voskuil M. Denervation of the renal arteries in metabolic syndrome: the DREAMS-study. *Hypertension* 2015; **65**: 751-757 [PMID: 25646297 DOI: 10.1161/HYPERTENSIONAHA.114.04798]
- 67 **Mundal R**, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Exercise blood pressure predicts cardiovascular mortality in middle-aged men. *Hypertension* 1994; **24**: 56-62 [PMID: 8021008]
- 68 **Fagard R**, Staessen J, Thijs L, Amery A. Prognostic significance of exercise versus resting blood pressure in hypertensive men. *Hypertension* 1991; **17**: 574-578 [PMID: 2013484]
- 69 **Ukena C**, Mahfoud F, Kindermann I, Barth C, Lenski M, Kindermann M, Brandt MC, Hoppe UC, Krum H, Esler M, Sobotka PA, Böhm M. Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol* 2011; **58**: 1176-1182 [PMID: 21884958 DOI: 10.1016/j.jacc.2011.05.036]
- 70 **Fengler K**, Heinemann D, Okon T, Rohnert K, Stiermaier T, von Roder M, Besler C, Müller U, Hollriegel R, Schuler G, Desch S, Lurz P. Renal denervation improves exercise blood pressure: insights from a randomized, sham-controlled trial. *Clin Res Cardiol* 2016 [PMID: 26728060 DOI: 10.1007/s00392-015-0955-8]
- 71 **Ewen S**, Mahfoud F, Linz D, Pöss J, Cremers B, Kindermann I, Laufs U, Ukena C, Böhm M. Effects of renal sympathetic denervation on exercise blood pressure, heart rate, and capacity in patients with resistant hypertension. *Hypertension* 2014; **63**: 839-845 [PMID: 24420550 DOI: 10.1161/HYPERTENSIONAHA.113.01985]
- 72 **Lenski M**, Mahfoud F, Razouk A, Ukena C, Lenski D, Barth C, Linz D, Laufs U, Kindermann I, Böhm M. Orthostatic function after renal sympathetic denervation in patients with resistant hypertension. *Int J Cardiol* 2013; **169**: 418-424 [PMID: 24157238 DOI: 10.1016/j.ijcard.2013.10.017]
- 73 **Kandzari DE**, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, Flack JM, Katzen BT, Lea J, Lee DP, Leon MB, Ma A, Massaro J, Mauri L, Oparil S, O'Neill WW, Patel MR, Rocha-Singh K, Sobotka PA, Svetkey L, Townsend RR, Bakris GL. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 2015; **36**: 219-227 [PMID: 25400162 DOI: 10.1093/eurheartj/ehu441]
- 74 **Howard JP**, Shun-Shin MJ, Hartley A, Bhatt DL, Krum H, Francis DP. Quantifying the 3 Biases That Lead to Unintentional Overestimation of the Blood Pressure-Lowering Effect of Renal Denervation. *Circ Cardiovasc Qual Outcomes* 2016; **9**: 14-22 [PMID: 26758193 DOI: 10.1161/CIRCOUTCOMES.115.002533]
- 75 **Ozkan U**, Oğuzkurt L, Tercan F, Kizilkiliç O, Koç Z, Koca N. Renal artery origins and variations: angiographic evaluation of 855 consecutive patients. *Diagn Interv Radiol* 2006; **12**: 183-186 [PMID: 17160802]
- 76 **Id D**, Kaltenbach B, Bertog SC, Hornung M, Hofmann I, Vaskelyte L, Sievert H. Does the presence of accessory renal arteries affect the efficacy of renal denervation? *JACC Cardiovasc Interv* 2013; **6**: 1085-1091 [PMID: 24156968 DOI: 10.1016/j.jcin.2013.06.007]
- 77 **Sakakura K**, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, Kolodgie FD, Virmani R, Joner M. Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol* 2014; **64**: 635-643 [PMID: 25125292 DOI: 10.1016/j.jacc.2014.03.059]
- 78 **Mahfoud F**, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D, Linz D, Davies J, Kandzari DE, Whitbourn R, Böhm M, Melder RJ. Impact of Lesion Placement on Efficacy and Safety of Catheter-Based Radiofrequency Renal Denervation. *J Am Coll Cardiol* 2015; **66**: 1766-1775 [PMID: 26483099 DOI: 10.1016/j.jacc.2015.08.018]
- 79 **Henegar JR**, Zhang Y, Hata C, Narciso I, Hall ME, Hall JE. Catheter-Based Radiofrequency Renal Denervation: Location Effects on Renal Norepinephrine. *Am J Hypertens* 2015; **28**: 909-914 [PMID: 25576624 DOI: 10.1093/ajh/hpu258]
- 80 **Rong S**, Zhu H, Liu D, Qian J, Zhou K, Zhu Q, Jiang Y, Yang G, Deng C, Zhang D, Zhou Q, Lei H, He TC, Wang Z, Huang J. Noninvasive renal denervation for resistant hypertension using high-intensity focused ultrasound. *Hypertension* 2015; **66**: e22-e25 [PMID: 26238444 DOI: 10.1161/HYPERTENSIONAHA.115.05754]
- 81 **Sakakura K**, Roth A, Ladich E, Shen K, Coleman L, Joner M, Virmani R. Controlled circumferential renal sympathetic denervation with preservation of the renal arterial wall using intraluminal ultrasound: a next-generation approach for treating sympathetic overactivity. *EuroIntervention* 2015; **10**: 1230-1238 [PMID: 25349043 DOI: 10.4244/EIJY14M10_14]
- 82 **Mabin T**, Sapoval M, Cabane V, Stemmet J, Iyer M. First experience with endovascular ultrasound renal denervation for the treatment of resistant hypertension. *EuroIntervention* 2012; **8**: 57-61 [PMID: 22580249 DOI: 10.4244/EIJV8I1A10]
- 83 **Fischell TA**, Fischell DR, Ghazarossian VE, Vega F, Ebner A. Next generation renal denervation: chemical "perivascular" renal denervation with alcohol using a novel drug infusion catheter. *Cardiovasc Revasc Med* 2015; **16**: 221-227 [PMID: 25979565 DOI: 10.1016/j.carrev.2015.04.008]
- 84 **Ricke J**, Seidensticker M, Becker S, Schiefer J, Adamchic I, Lohfink K, Kandulski M, Heller A, Mertens PR. Renal Sympathetic Denervation by CT-Guided Ethanol Injection: A Phase II Pilot Trial of a Novel Technique. *Cardiovasc Intervent Radiol* 2016; **39**: 251-260 [PMID: 26634740 DOI: 10.1007/s00270-015-1261-6]
- 85 **Stiermaier T**, Okon T, Fengler K, Mueller U, Hoellriegel R, Schuler G, Desch S, Lurz P. Endovascular ultrasound for renal

- sympathetic denervation in patients with therapy-resistant hypertension not responding to radiofrequency renal sympathetic denervation. *EuroIntervention* 2016; **12**: e282-e289 [PMID: 27290688 DOI: 10.4244/EIJV12I2A43]
- 86 **Grassi G**, Seravalle G, Cattaneo BM, Bolla GB, Lanfranchi A, Colombo M, Giannattasio C, Brunani A, Cavagnini F, Mancia G. Sympathetic activation in obese normotensive subjects. *Hypertension* 1995; **25**: 560-563 [PMID: 7721398]
- 87 **Id D**, Bertog SC, Ziegler AK, Hornung M, Hofmann I, Vaskelyte L, Matic P, Gafoor S, Sievert H. Predictors of Blood Pressure Response: Obesity Is Associated With a Less Pronounced Treatment Response After Renal Denervation. *Catheter Cardiovasc Interv* 2015; **87**: E30-E38 [PMID: 26104216 DOI: 10.1002/ccd.26068]
- 88 **Zuern CS**, Eick C, Rizas KD, Bauer S, Langer H, Gawaz M, Bauer A. Impaired cardiac baroreflex sensitivity predicts response to renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol* 2013; **62**: 2124-2130 [PMID: 23973686 DOI: 10.1016/j.jacc.2013.07.046]
- 89 **Ewen S**, Ukena C, Linz D, Kindermann I, Cremers B, Laufs U, Wagenpfeil S, Schmieder RE, Böhm M, Mahfoud F. Reduced effect of percutaneous renal denervation on blood pressure in patients with isolated systolic hypertension. *Hypertension* 2015; **65**: 193-199 [PMID: 25331843 DOI: 10.1161/HYPERTENSION.114.04336]
- 90 **Laurent S**, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**: 1236-1241 [PMID: 11358934]
- 91 **Maroules CD**, Khera A, Ayers C, Goel A, Peshock RM, Abbara S, King KS. Cardiovascular outcome associations among cardiovascular magnetic resonance measures of arterial stiffness: the Dallas heart study. *J Cardiovasc Magn Reson* 2014; **16**: 33 [PMID: 24886531 DOI: 10.1186/1532-429X-16-33]
- 92 **Pettersen KH**, Bugenhagen SM, Nauman J, Beard DA, Omholt SW. Arterial stiffening provides sufficient explanation for primary hypertension. *PLoS Comput Biol* 2014; **10**: e1003634 [PMID: 24853828 DOI: 10.1371/journal.pcbi.1003634]
- 93 **Kaess BM**, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA* 2012; **308**: 875-881 [PMID: 22948697 DOI: 10.1001/2012.jama.10503]
- 94 **Vink EE**, Verloop WL, Bost RB, Voskuil M, Spiering W, Vonken EJ, Bots ML, Blankestijn PJ. The blood pressure-lowering effect of renal denervation is inversely related to kidney function. *J Hypertens* 2014; **32**: 2045-2053; discussion 2053 [PMID: 25023158 DOI: 10.1097/HJH.0000000000000282]
- 95 **Bristow JD**, Honour AJ, Pickering GW, Sleight P, Smyth HS. Diminished baroreflex sensitivity in high blood pressure. *Circulation* 1969; **39**: 48-54 [PMID: 4302539]
- 96 **Campese VM**. Pathophysiology of resistant hypertension in chronic kidney disease. *Semin Nephrol* 2014; **34**: 571-576 [PMID: 25416666 DOI: 10.1016/j.semnephrol.2014.08.011]
- 97 **Converse RL**, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, Victor RG. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327**: 1912-1918 [PMID: 1454086 DOI: 10.1056/NEJM199212313272704]

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