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Impact of Sympathetic Renal Denervation in Kidney Transplanted Patients – a randomized study for feasibility and efficacy

Dominik Sebastian Promny

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Für meine Eltern

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1 INTRODUCTION

Blood pressure (BP) is the pressure caused by the circulating blood upon the walls of the blood vessels. BP underlies control by a complex interaction of mechanical, electrical and hormonal forces in the body. With no further specification, "blood pressure" usually refers to the arterial pressure in the systemic circulation. The definition of arterial pressure describes the product of cardiac output and total peripheral resistance (Cowley, 2006, Hall, 2003).

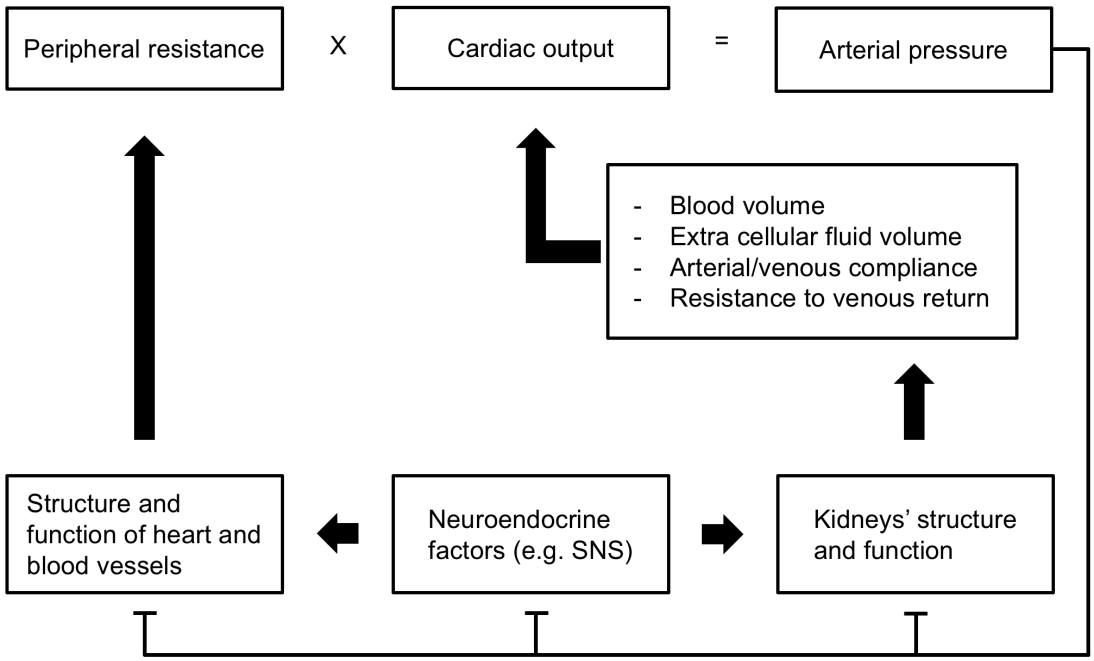


***Figure 1 Drivers of Arterial Blood Pressure**; SNS, Sympathetic nervous system. Adapted by permission from Macmillan Publisher Ltd: Nat Rev Genet Cowley, A. W., Jr. (2006). "The genetic dissection of essential hypertension." 7(11): 829-840.*

The interaction between the combined factors of extracellular blood volume, fluid volume, arterial and venous compliance (the ratio of an increase in pressure within the blood vessel depending on the increase in intraluminal volume) and resistance of the blood flow to venous return regulate the cardiac output. The kidneys are central organs in controlling the extracellular fluid volume and arterial pressure. The kidney's efficiency relies on several factors, including many intrinsic mechanisms that adjust renal blood flow and glomerular filtration (Cowley, 2006). All these aspects are the drivers of arterial blood pressure (Figure 1).

If the blood pressure in the arteries is elevated with levels 120-139 mm Hg systolic and 80-89 mm Hg diastolic it is classified as prehypertension. Values persistently higher than 140 / 90 mm Hg are referred to as hypertension (James, Oparil et al., 2014). Arterial Hypertension represents one of the major global public health concerns (Messerli, Williams et al., 2007). It

is accountable for vascular and renal morbidity, cardiovascular mortality, and strokes (Figure 2).

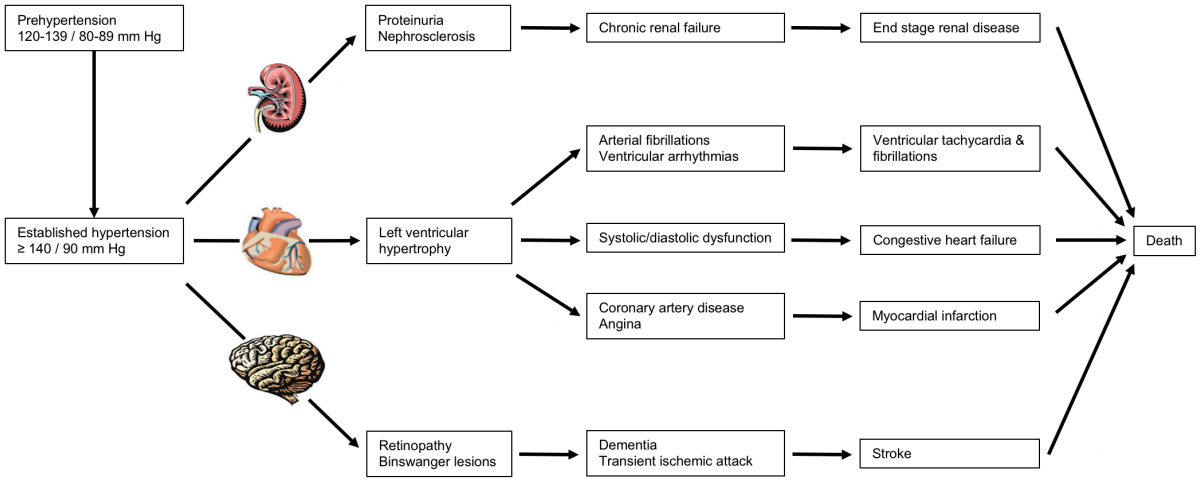


Figure 2 Consequences of hypertension. *Adapted from The Lancet 370(9587), Messerli, F. H., et al. "Essential hypertension.", 591-603, 2007 with permission from Elsevier.*

Furthermore, hypertension is one of the biggest capital strains of the economy and the health (insurance) systems (Lewington, Clarke et al., 2002). The problem is not anymore limited to economically developed countries but spread to an endemic worldwide burden over the past decades, due to the populations' lifestyle and nutrition changes (Ezzati, Lopez et al., 2002). In 2001, the cost of hypertension was estimated to $370 billion worldwide representing 10% of total global healthcare costs (Gaziano, Bitton et al., 2009). The pathophysiology of arterial hypertension is multifactorial, including lifestyle, dietary, metabolic, genetic factors, and is further influenced by the sympathetic nervous system (Aucott, Poobalan et al., 2005, Bramlage, Pittrow et al., 2004, Parati and Esler, 2012).

By the year 2000, already more than 25% of the adult population, equal to almost 975 million people, was affected by hypertension worldwide and around 30% or 1.56 billion people are estimated for 2025 (Kearney, Whelton et al., 2005). Corresponding to a worldwide analysis conducted in 2001, 7.6 million premature deaths (around 14% of total deaths), 54% of strokes and 47% of events due to ischemic heart disease are attributed to high BP levels (Lawes, Vander Hoorn et al., 2008). Additional analysis estimated that hypertension is responsible for even 9.4 million deaths annually worldwide, which is as many as all infectious diseases combined (Lim, Vos et al., 2012). Furthermore, the direct health-care costs and productivity losses for cardiovascular disease could amount to as much as $20 trillion globally over the coming two decades (Bloom, 2011). In 2015 treatment costs in Germany amounted to a total of around $9 billion (Neuhauser, Adler et al., 2015).

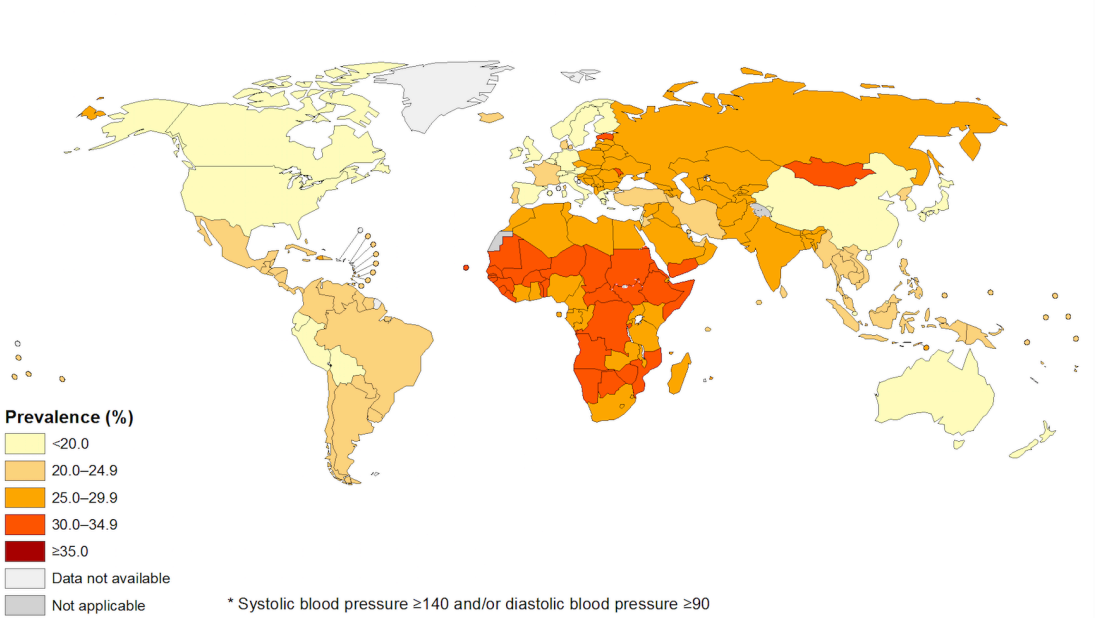


Figure 3 Prevalence of raised blood pressure*, ages 18+, 2014 (age standardized estimate), both sexes - The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frountiers or boundaries. Dotted and dashed lines represent approximate border lines for which there may not yet be a full agreement. Blood pressure values unit is mm Hg. Data Source World Health Organization, map production: Health Statistics and Information System (HSc) of WHO. © WHO 2015. All rights reserved. Reprinted from http://gamapserver.who.int/mapLibrary/Files/Maps/Global_Blood PressurePrevalence_2014_BothSexes.png*

Even with extensive medical treatments, in most patients BP goals are not yet achieved, despite appropriate multiple–antihypertensive therapy. These patients suffer the so-called resistant hypertension (RHTN), which is defined as a condition of persistent blood pressure elevation in spite of medical treatment consisting of at least a triple drug regime, including a diuretic (Gifford, 1988). The chapter 1.1 discusses this topic in detail. Due to the aging population and increasing trends in obesity and chronic kidney disease, the prevalence of resistant hypertension is projected to increase (Kearney, Whelton et al., 2005).

It became apparent that regardless of the initial baseline level, even a modest decrease in BP causes significant reduction of the overall cardiovascular morbidity and mortality (Czernichow, Zanchetti et al., 2011, Mancia, De Backer et al., 2007, Mancia, Laurent et al., 2009, Zhang, Zhang et al., 2011). To illustrate this: a lowering of the systolic blood pressure (SBP) by 10 mm Hg or the diastolic blood pressure (DBP) by only 5 mm Hg, already reduces the risk of a stroke event by at least one-third and the risk of coronary heart diseases by approximately one-fourth (Lewington, Clarke et al., 2002, MacMahon, Peto et al., 1990).

A controlled blood pressure is not just associated with lower risk for cardiovascular events, atherosclerosis or strokes but it is also significantly linked to a longer graft survival in

transplant recipients compared to a non-controlled blood pressure (Hillebrand, Suwelack et al., 2009). The focus is particularly on the renal transplanted patients, since about 70-90% of renal transplant recipients suffer arterial hypertension and require antihypertensive medication (Rubin, 2011, Schwenger, Zeier et al., 2001). It is to be assumed that the subject of resistant hypertension is quite common in renal transplanted patients (Arias-Rodriguez, Fernandez-Fresnedo et al., 2015). Therefore, hypertension following renal transplantation must be supervised more strictly in comparison to patients not suffering renal disease. Moreover, most transplant candidates are already hypertensive before renal transplantation (Azancot, Ramos et al., 2014). For patients suffering renal diseases international guidelines recommend a target blood pressure at **<130** mm Hg systolic and **<80** mm Hg diastolic (Kasiske, Zeier et al., 2010). These values are slightly lower than values for renal healthy patients, with **≤140** mm Hg systolic and **<90** mm Hg diastolic (James, Oparil et al., 2014). Chapter 1.2 outlines the importance and further aspects on the topic of blood pressure management in these patients.

Additionally, an important cause of post-transplant hypertension is the rise of sympathetic nerve activity in the native kidneys (Hausberg, Kosch et al., 2002). Already in the 1980s, research around physiological modulation of blood pressure discovered this interaction between renal sympathetic and somatic nerves (Esler, Jennings et al., 1984). Beyond medical therapy, the recognition of the renal sympathetic nerves as potential targets for the treatment of hypertension has inspired clinical investigation of the mechanistic relationship between high blood pressure and renal sympathetic nerve activity (see chapter 1.3). Also, it has influenced the examination of potential therapeutic opportunities as selective renal sympathetic denervation in patients with resistant hypertension. A procedure that should selectively remove certain contributors to resistant hypertension was developed, giving an opportunity to provide clinically meaningful benefit across a wide and varied patient population (Esler, Jennings et al., 1988).

In recent years, catheter-based radiofrequency denervation of the renal arteries has emerged as a promising treatment for resistant hypertension complementary to medical treatment (Krum, Schlaich et al., 2009), outlined in chapter 1.4. Initial randomized trials demonstrated a significant reduction in office blood pressure after sympathetic renal denervation (RDN) (Esler, Krum et al., 2010) with a persistent effect after up to three years (Esler, Krum et al., 2012, Krum, Schlaich et al., 2014) (chapter 1.5 gives an overview on previous studies). Smaller non-randomized studies emphasized the feasibility and safety of renal nerve ablation and effects on blood pressure in patients with end-stage renal disease (ESRD) (Schlaich, Bart et al., 2013). However, so far performance of RDN was not investigated in one particular group of patients, who essentially suffer from hypertension: the

group of kidney transplanted patients. The latest research results emphasize the need for understanding the mechanism of renal sympathetic denervation and better identification of patient groups who profit from this specific therapy.

Furthermore, the immunosuppressive therapy of the transplanted patients might be linked to the enhancement of the sympathetic nervous activation (see chapter 1.2) (Scherrer, Vissing et al., 1990, Zhang, Li et al., 2000). These immunosuppressive drugs, as for example calcineurin inhibitors, which are commonly used in organ transplantation recipients, also trigger vasoconstriction and might enhance that mechanism. There is growing evidence that calcineurin inhibitors mediate activation of renal sympathetic afferents (Zhang, Li et al., 2000) and sympathetic nervous activation (Scherrer, Vissing et al., 1990). Moreover, other specific factors such as graft function and renal artery stenosis of the graft artery influence BP (Zhang, Li et al., 2000).

This present study (Schneider, Promny et al., 2015) is a prospective and randomized trial evaluating the effectiveness and safety of catheter-based bilateral renal denervation for the treatment of resistant hypertension in kidney transplanted patients. The change in office-based systolic blood pressure from baseline to six months is measured as the primary efficacy endpoint. This study setting for renal sympathetic denervation provides a strong physiological rationale to give crucial insight into physiological pathways of sympathetic modulation and the mechanism of renal artery denervation in humans.

In the following pages the topics of resistant hypertension, blood pressure management in renal transplanted patients, the importance of the sympathetic nervous system, and the development and significance of renal denervation are highlighted and discussed in more detail.

1.1 Resistant Hypertension

Despite the recent advances and proven benefit of pharmacological therapy hypertension continues to be a major burden of the world's public health (Kearney, Whelton et al., 2005). As mentioned before, over the past two decades the blood pressure prevalence has been continuously rising, up to 30% in industrialized countries (Egan, Zhao et al., 2010, Falaschetti, Chaudhury et al., 2009, Wolf-Maier, Cooper et al., 2003). In the last few years, the approach to blood pressure treatment has shifted to blood pressure control instead of continues reduction of BP values. The proportion of patients with controlled blood pressure values has improved over the last couple of years from 19% in 2001 (Sharma, Wittchen et al., 2004), over 28% in 2006 (Falaschetti, Chaudhury et al., 2009) up to 37% in 2009 (Giannattasio, Cairo et al., 2012) compared to rates ≤ 10% in Europe back in the 1990s (Wolf-Maier, Cooper et al., 2004).

While controlling the blood pressure more closely, it emerged that some patients seemed to be resistant even to the individualized treatment. Therefore, the term of resistant hypertension was introduced to identify precisely this group of high-risk patients who may benefit from a specialized care, including assessment and treatment of secondary causes of hypertension (Gifford, 1988). The American Heart Association (AHA) primarily defined resistant hypertension as a blood pressure that remains above goal levels despite optimal doses of at least three antihypertensive drugs of different classes, one of which ideally would be a diuretic (Calhoun, Jones et al., 2008). Targeted goal levels are <140 mm Hg systolic and 90 mm Hg diastolic in properly office measurements and mean 24-h ambulatory BP <130 mm Hg systolic and 80 mm Hg diastolic. Also, patients still be considered resistant with the addition of a fourth or more antihypertensive drug even if blood pressure values reach goal levels (Calhoun, Jones et al., 2008).

The AHA definition does not distinguish between resistant hypertension and pseudo-resistant hypertension. The causes for falsely elevated BP values in pseudo-resistant hypertension are most likely improper blood pressure measurements, medication nonadherence or white-coat hypertension (Sarafidis, 2011, Sarafidis, Georgianos et al., 2013). Consequently, the term apparent resistant hypertension was used in epidemiological studies to explicate that pseudo resistant hypertension was not excluded. The term refers to values of ≥140 mm Hg systolic and 90 mm Hg diastolic only measured in office and not confirmed elsewhere (Judd and Calhoun, 2014).

The results of cross-sectional studies and hypertension outcome studies suggest that resistant hypertension is not very uncommon. Until a couple of years ago, the exact numeric **prevalence** seemed to be more of a vague estimation (Figure 4) (Sarafidis, 2011, Sarafidis and Bakris, 2008a). In the recent years, studies with the intention to define the epidemiology

of resistant hypertension were performed. The prevalence has been reported to range from 8% to 17.5% of the overall hypertensive population, depending on the population examined and the level of medical screening (Daugherty, Powers et al., 2012, de la Sierra, Segura et al., 2011, Egan, Zhao et al., 2010, Fagard, 2012, Persell, 2011). According to European Society of Hypertension (ESH) Guidelines it can be assumed that the true prevalence is approximately 10% (Mancia, Fagard et al., 2013).

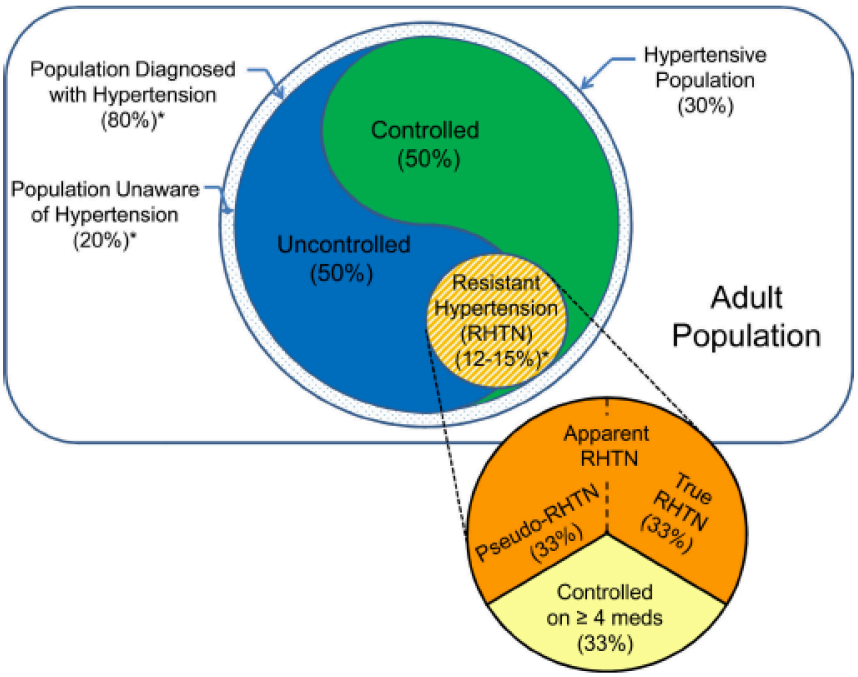


Figure 4 Venn diagram of the prevalence of resistant hypertension. *Areas of subpopulations show scale with estimated prevalences in percentages. Prevalences are based primarily on epidemiology studies performed within the United States (Egan, Zhao et al., 2010, Persell, 2011); RHTN, resistant hypertension; *Estimated prevalence among all hypertensive individuals. Reprinted by permission from Macmillan Publishers Ltd: J Hum Hypertens, Judd, E. and D. A. Calhoun. "Apparent and true resistant hypertension: definition, prevalence and outcomes." 28(8): 463-468, copyright 2014.*

In an analysis of the National Health and Nutrition Examination Survey (NHANES), based on large-scale population studies, only 53% of participants, who were treated for hypertension, were controlled to <140/90 mm Hg (Hajjar, Kotchen et al., 2006, Hajjar and Kotchen, 2003). An even lower fraction can be found in patients with chronic kidney disease and diabetes mellitus. For patients with chronic kidney disease, only 37% were controlled to <130/80 mmHg (Peralta, Hicks et al., 2005). For NHANES participants with diabetes mellitus, only 25% were controlled (Hajjar and Kotchen, 2003). Furthermore, the prevalence of resistant hypertension can be anticipated to increase because of a progressively older and heavier population in association with a rising occurrence of diabetes and CKD (Calhoun, Jones et al., 2008, Sarafidis and Bakris, 2008a). A conclusion about the prognosis of hypertension is both difficult and complex.

As already mentioned, hypertension correlates with a higher risk of developing cardiovascular events – including stroke, myocardial infarction, renal failure, and heart failure (Klag, Whelton et al., 1996, Lewington, Clarke et al., 2002). So far, the **prognosis** of resistant hypertension alone has not been evaluated accurately.

Table 1 Patients characteristics associated with resistant hypertension

Older age
Higher baseline blood pressure
Chronic kidney disease
Diabetes
Obesity
Excessive dietary salt ingestion
Left ventricular hypertrophy
Black race
Female sex

Resistant hypertension is nearly always multifactorial in **etiology**. Studies indicate that there are associations between hypertension and various factors as age, gender, race, and the presence of other diseases (Table 1). Specifically, higher age, female gender, Black race, and the presence of diseases such as chronic kidney disease, diabetes, and left ventricular hypertrophy have been linked to a higher prevalence of hypertension (Brown, Castaigne et al., 2000, Calhoun, Jones et al., 2008, Cushman, Ford et al., 2002, Hyman and Pavlik, 2000, Lloyd-Jones, Evans et al., 2000, Sarafidis, Georgianos et al., 2013, Wright, Bakris et al., 2002). Researches have also credited lifestyle factors such as obesity, dietary salt, and alcohol (Aucott, Poobalan et al., 2005, Bramlage, Pittrow et al., 2004). These factors are most significant, because they are linked with more severe hypertension, an increased need for antihypertensive agents, and a decreased probability of reaching target values. Sleep apnea, renal parenchymal disease, renal artery stenosis, and possibly primary aldosteronism, all secondary causes for hypertension, are present more often in patients with resistant hypertension and should be considered (Table 2) (Anderson, Blakeman et al., 1994, Calhoun, Jones et al., 2008, Mosso, Carvajal et al., 2003, Peppard, Young et al., 2000).

Table 2 Secondary causes of resistant hypertension

Common
Renal artery stenosis
Obstructive sleep apnea
Renal parenchymal disease
Primary aldosteronism
Uncommon (e.g. Pheochromocytoma, Cushing's disease, hyperparathyroidism, aortic coarctation, intracranial tumor)

Most likely, a pseudoresistance is evoked by poor blood pressure measurements. The most common mistakes are application of a blood pressure cuff, which is too small, measuring before the patient has sat quietly for adequate time and settled down, single instead of triple readings and recent smoking (Table 3) (Calhoun, Jones et al., 2008, Moser and Setaro, 2006, Sarafidis and Bakris, 2008b).

Table 3 "Pseudoresistance" Factors

Improper blood pressure measurement
White coat effect
Heavily calcified or arteriosclerotic arteries that are difficult to compress
Related to antihypertensive medication
Inadequate doses
Inappropriate combinations
Physician inertia (failure to change or increase dose regimens when not at goal)
Poor patient adherence
Complicated dosing schedules
Side effects of medication
Memory or psychiatric problems
Poor relations between doctor and patient
Inadequate patient education
Costs of medication

The so called white-coat-effect, a condition when blood pressure values are normal or significantly lower while out-of-office compared to persistently elevated clinical blood pressure values, is as prevalent (20-30%) with the resistant hypertension population as in the more general hypertensive population (Brown, Buddle et al., 2001, Hermida, Ayala et al., 2005). The effect is associated with sympathetic nerve activity and power spectral analysis of heart rate variability (Doumas and Douma, 2010, Grassi, Cattaneo et al., 1998, Mancia and

Parati, 2004). Interestingly, patients with resistant hypertension linked to a “white coat” phenomenon appear to be at a lower cardiovascular risk and manifest less severe target organ damage compared to those patients with persistent hypertension during ambulatory monitoring. (Muxfeldt, Bloch et al., 2003, Pierdomenico, Lapenna et al., 2005, Redon, Campos et al., 1998).

Another major cause for the lack of blood pressure control is the poor adherence to antihypertensive therapy (Yiannakopoulou, Papadopulos et al., 2005). During the first twelve months of treatment, approximately 40% of patients with newly diagnosed hypertension tend to discontinue their antihypertensive medications (Caro, Speckman et al., 1999, Mazzaglia, Mantovani et al., 2005). Throughout five to ten years’ follow-ups, less than 40% of patients stick with their initially prescribed antihypertensive treatment (Caro, Speckman et al., 1999, Van Wijk, Klungel et al., 2005).

All the above-mentioned influence and need to be considered in the diagnostic and treatment algorithm for resistant hypertension (Figure 5).

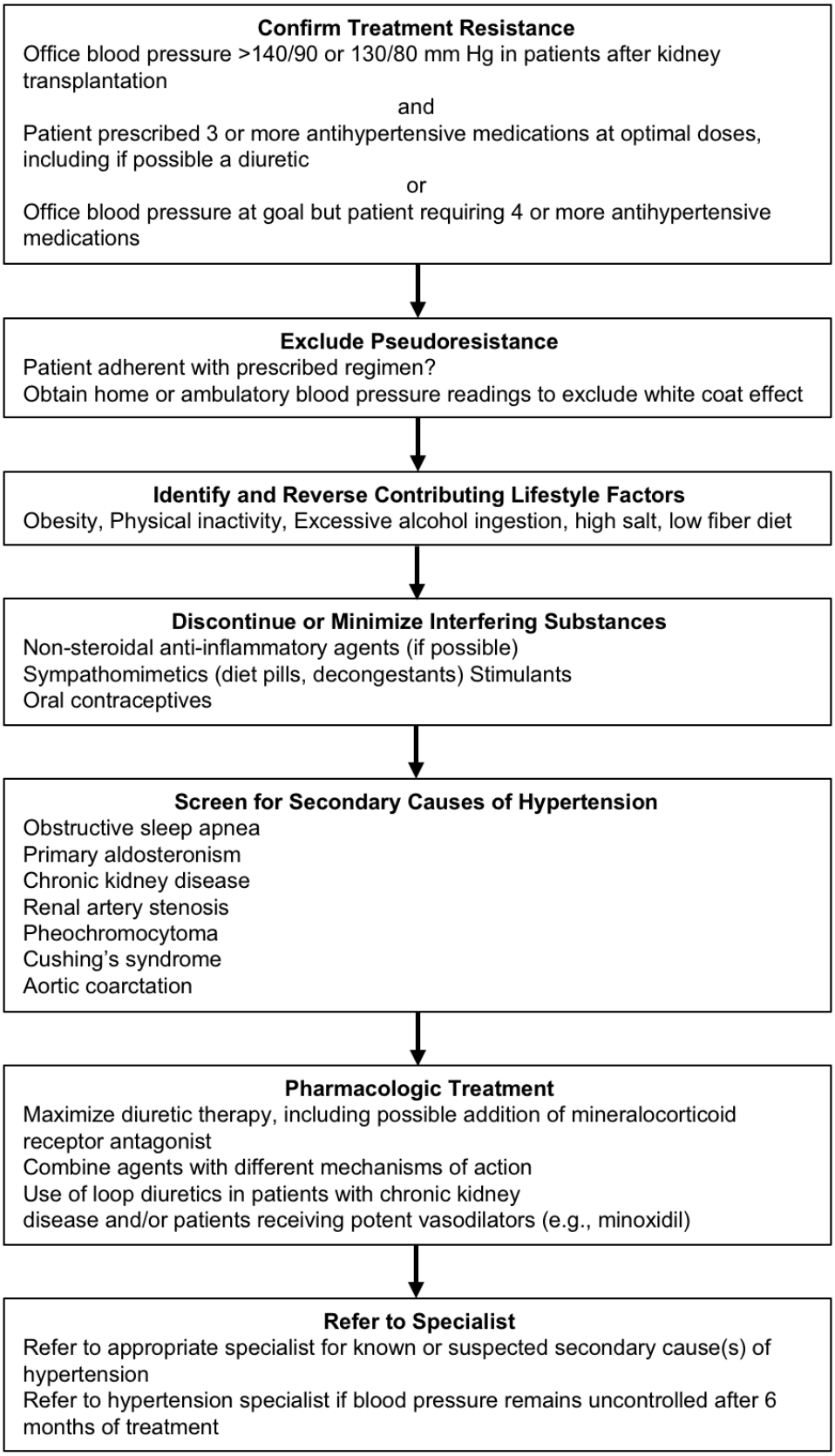


Figure 5 Diagnostic and treatment recommendations for resistant hypertension*. Adapted from Calhoun, D. A., et al. (2008). "Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research." Circulation 117(25): e510-526.)*

1.2 Blood pressure management

Generally, the goal of hypertension treatment is to reduce long-term cardiovascular risk and especially in the case of kidney transplanted patients prolong the graft survival with a sufficient blood pressure therapy. Although, the management of elevated blood pressures is anything but simple. It often takes several months to adjust the right individual therapy, consisting of lifestyle, diet, and medication adaptions. Moreover, higher drug costs and more physician visits are caused by poor control of hypertension for any reason. As mentioned before, a patient population in which arterial hypertension is prevalent in approximately 70-90% are kidney transplant recipients (Kasiske, 1987, Ponticelli, Montagnino et al., 1993). These patients need to be treated by hypertension specialist.

Before kidneys are transplanted these patients suffer chronic kidney disease (CKD) and eventual end stage renal disease. A subset of patient with high incidence of resistant hypertension, benefiting greatly from better BP control, although have been excluded from major RDN trials so far (Chertow, Beddhu et al., 2016, Converse, Jacobsen et al., 1992, Hausberg, Kosch et al., 2002). Hypertension is associated with a more pronounced progression of CKD (Walker, Neaton et al., 1992). A seminal US hypertension outcome study, the so called *"The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)"*, which included over 30.000 diverse participants, showed that suffering chronic kidney disease was the strongest predictor of treatment resistance (Muntner, Davis et al., 2014). Furthermore, the National Kidney Foundation Kidney Disease Outcome and Quality Initiative (NKF/KDOQI) classified CKD as a high-risk group warranting intensive hypertension treatment (2004). Factors contributing to the pathogenesis and higher prevalence of hypertension in CKD patients include increased activity of the renin-angiotensin-aldosterone system (RAAS) and sympathetic activity, impaired sodium handling, and increased arterial stiffness (Converse, Jacobsen et al., 1992, Hall, Mizelle et al., 1990, Peralta, Hicks et al., 2005). Due to these different multiple factors adjustments to the goal values are complicated. As mentioned in the previous chapter, only 37% were controlled to <130 mm Hg systolic over 80 mm Hg diastolic. Chertow et al. (Chertow, Beddhu et al., 2016) referred to the BP management in CKD suffering patients as that it is rather a marathon than a sprint.

Moreover, a controlled blood pressure is of immense importance for kidney transplanted patients, because it is significantly associated with a longer graft survival (Hillebrand, Suwelack et al., 2009). Opelz et al. (Opelz, Wujciak et al., 1998) investigated the impact of systolic and diastolic blood pressure during the post-transplant course of nearly 30.000 patients transplanted from 1987 to 1995 in the Euro-Transplant database. They described a consistent association between measured systolic and diastolic blood pressure values at

yearly intervals and subsequent graft survival. It was observed that patients with a systolic blood pressure above 180 mm Hg had a more than two times higher risk of renal allograft failure during follow-up. Mange et al. (Mange, Cizman et al., 2000) also reported that blood pressure level and allograft survival correlates, indicating that lower blood pressure is consistently better for kidney function. Therefore, this group of patients is in particular need of a more accurate, individually adapted and supervised antihypertensive drug regime.

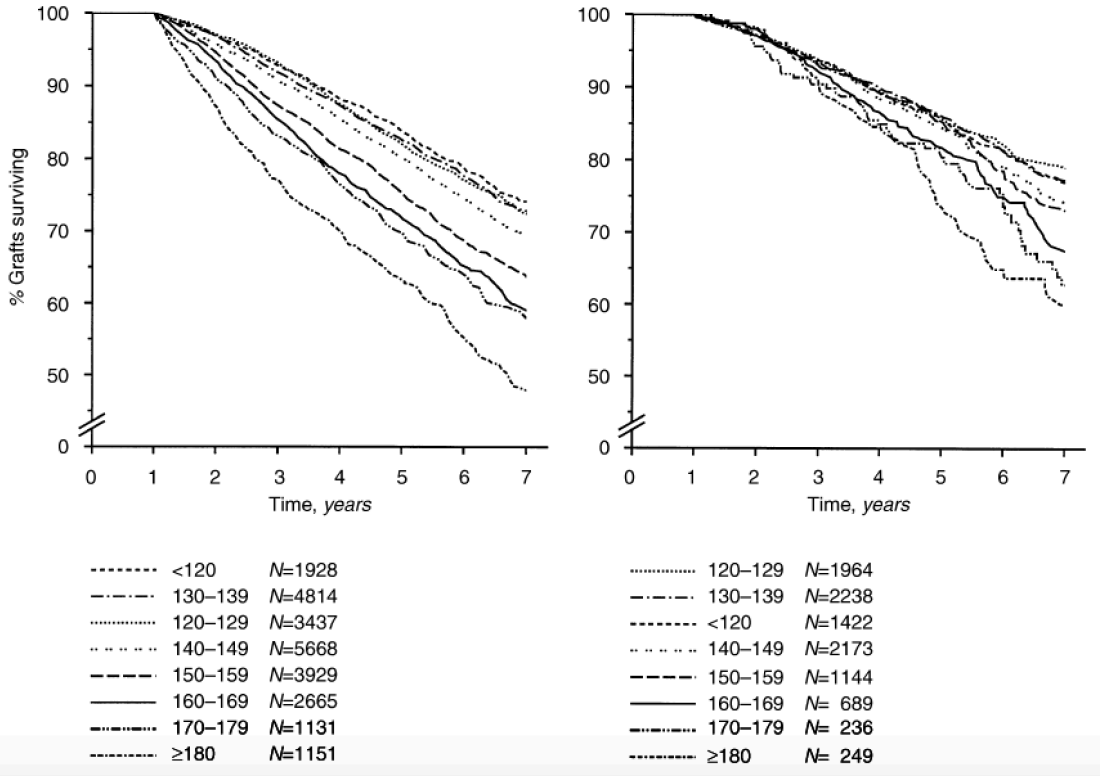


Figure 6 Association between systolic blood pressure and graft survival at one year with long term outcome in patients. *With (left) compared to without (right) antihypertensive medication (Opelz, Wujciak et al., 1998). Used with permission from Kidney International, Volume 53, pages 217-222, 1998*

Currently, there is no universal agreement for optimal blood pressure goals in kidney transplant recipients but discussions are ongoing. The *Kidney Disease: Improving Global Outcomes* (KDIGO) clinical practice guidelines for the care of the kidney transplant recipient suggests maintaining blood pressure level at <130 mm Hg systolic and <90 mm Hg diastolic (Kasiske, Zeier et al., 2010). *European best practice guidelines* indicate in patients with additional proteinuria even a target blood pressure level of <125 mm Hg systolic and <75 mm Hg diastolic (2002). The latest published *"2014 Evidence-Based Guidelines for the Management of High Blood Pressure in Adults"* emphasizes that the population with chronic kidney disease should maintain a systolic blood pressure of <140 mm Hg and a diastolic blood pressure <90 mm Hg (James, Oparil et al., 2014). One of the most recent published studies on blood pressure control sets the focus back on strict reduction of BP values instead

of constant control, as their results showed a 25% decrease of cardiovascular events when keeping systolic BP <120 mm Hg compared to <140 mmHg (Egan, Li et al., 2016).

1.2.1 Multi-drug treatment strategy

Usually, hypertension therapy begins with a monotherapy, most of the times an angiotensin-converting enzyme inhibitor (ACEi) or β-blocker in a low dosage. In the course, the dosage is increased and further drugs are prescribed. Therefore, to achieve a successful antihypertensive therapy many patients require a combination of drugs from different drug classes working by complementary mechanisms to reduce the blood pressure sufficiently (Chobanian, Bakris et al., 2003, Mancia, De Backer et al., 2007).

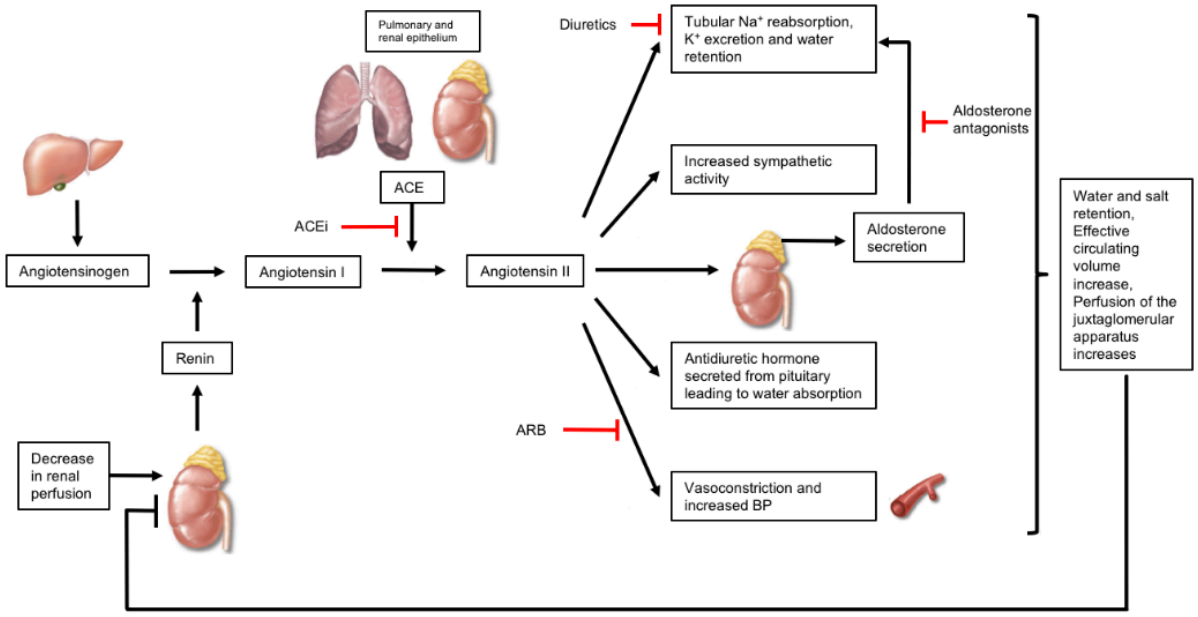


Figure 7 Renin-angiotensin-aldosterone system overview. *Contact points of antihypertensive agents. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; Na^+, sodium; K^+, potassium. Adapted from Schrier RW, ed. Renal and Electrolyte Disorders 5th ed. 1997.*

For this purpose, a quick overview on the agents most commonly used. Detailed information on the single agents are published elsewhere (Mancia, De Backer et al., 2007, Sarafidis, Georgianos et al., 2012). Agents targeting the renin-angiotensin-aldosterone system (RAAS) include angiotensin-converting enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARB), direct renin inhibitors, β-blockers, and diuretics (Figure 7). These agents target various components of the RAAS, which controls sodium and blood-volume homeostasis. Further, calcium channel blockers (CCB) reduce peripheral resistance and dilate the arteries. Lower postsynaptic vasoconstrictor effects are achieved by α-blockers, although benefit could not be shown in controlled trials (Mancia, De Backer et al., 2007). Additionally,

centrally-acting agents influence the hypothalamus and decrease the sympathetic outflow (Izzo, Black et al., 2008).

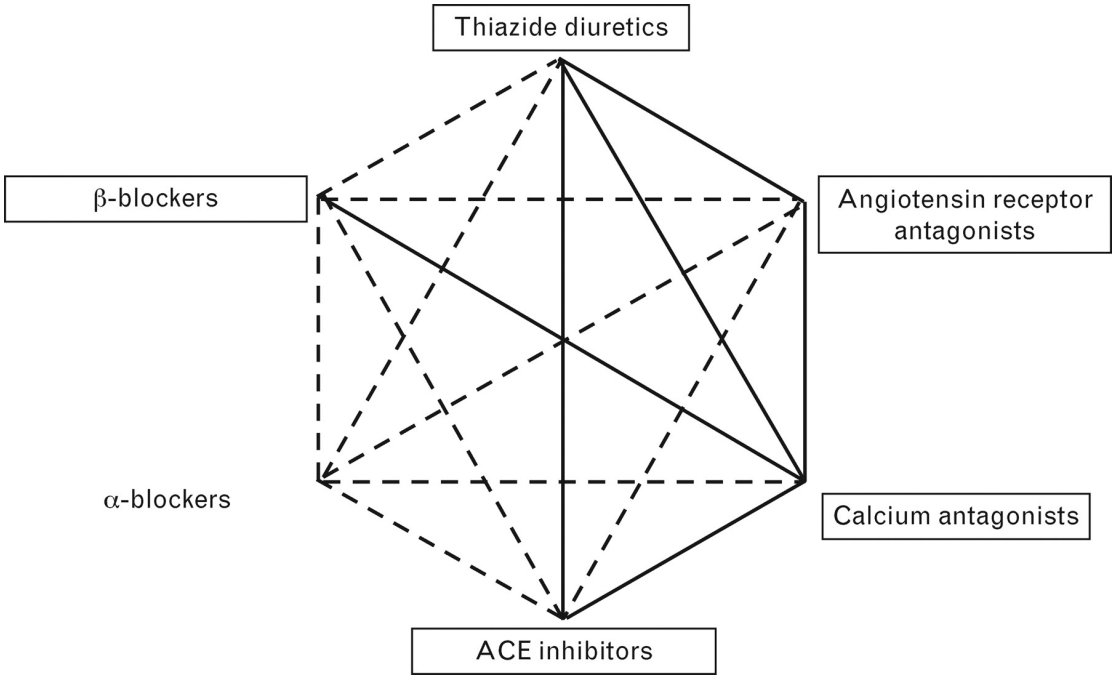


Figure 8 ***Preferred combinations of antihypertensive agents.*** *Solid lines indicate preferred combinations. The combination of an ACE inhibitors and an angiotensin receptor antagonist may cause increased side effects without added benefit and therefore is not recommended. Framed classes represent agents proven to be beneficial in controlled intervention trials. ACE, angiotensin-converting enzyme. Mancia, G., et al. (2007), "2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)." J Hypertens 25(6): 1105-1187 by permission of Oxford University Press.*

For an effective treatment, the regime should target various mechanisms responsible for BP control. At first, volume overload managed with diuretics, which are cornerstones for the therapy of treatment resistant hypertension, and aldosterone antagonists, secondly sympathetic overactivity covered by β-blockers and centrally acting agents, and control of vascular resistance, which can especially be achieved by inhibition of the RAAS with ACEis and ARBs and through promotion of smooth-muscle relaxation with CCBs or α-blockers. The aldosterone antagonists provide substantial additional antihypertensive profits in patients suffering treatment resistant hypertension, if added to a multidrug treatment regime (Chapman, Dobson et al., 2007, Vaclavik, Sedlak et al., 2011).

As mentioned before, in this trial we concentrated on kidney transplanted patients suffering resistant hypertension. These patients are already taking, by definition, at least three or more antihypertensive drugs, of which one is a diuretic. However, blood pressure values remain elevated.

1.2.2 Medication adherence

Furthermore, a key factor for controlled blood pressure and long-term graft survival in renal transplant recipients is a good medication adherence (Denhaerynck, Dobbels et al., 2005). Poor medication adherence increases acute rejection rates, chronic rejection, graft loss and death (Butler, Roderick et al., 2004). Medication non-adherence rises with increasing number of drugs and transplant duration (Morrissey, Flynn et al., 2007). Often the medication regimes for transplant recipients are already very complex before the transplantation, and they get even more intricately afterwards. The regimes consist of immunosuppressive agents, prophylactic antibacterials and antiviral medication, in addition to agents required for treatment of patients' underlying diseases such as diabetes mellitus, coronary artery disease, proteinuria, and especially hypertension (Cianciolo, Capelli et al., 2014, Hillebrand, Suwelack et al., 2009, Nauta, Bakker et al., 2011, Peev, Reiser et al., 2014, Stoumpos, Jardine et al., 2014). In the majority, these drug regimens include multiple antihypertensive drugs of different classes (Rubin, 2011, Schwenger, Zeier et al., 2001). Overall, transplant recipients typically take five to fifteen different medications, with some requiring multiple doses throughout the day (Hilbrands, Hoitsma et al., 1995, Raiz, Kilty et al., 1999). This complexity of a medication regime has an impact on the rate of compliance (Caro, Speckman et al., 1999, Van Wijk, Klungel et al., 2005). Poor adherence to the antihypertensive treatment is certainly one of the biggest problems in blood pressure management (Yiannakopoulou, Papadopulos et al., 2005). A multi study analysis showed that medication adherence rates were notably enhanced when multidimensional interventions were implemented (Low, Williams et al., 2014). Furthermore, the frequency of medication administration also influences the patients' adherence, as shown in a review of more than 75 studies published between 1986 and 2000 (Claxton, Cramer et al., 2001). Significance was higher for adherence to medications that were to be taken once a day than to those which needed to be administered three or four times daily. In addition, the patients' forgetfulness should not be underestimated, as it becomes a contributing factor to noncompliance when a regime is exceedingly complex (Raiz, Kilty et al., 1999). Therefore, it is of great importance for the successful treatment that kidney transplanted patients are instructed and strictly supervised in taking their medications correctly in frequency and dose. Another treatment goal should be the reduction of the total number of medications. Hence, patients undergo renal denervation treatment with the intention for decreasing blood pressure values and accordingly the number of needed antihypertensive medications.

1.2.3 The downside of immunosuppressants

After the kidney transplantation, the patients begin to take immunosuppressive drugs to regulate the body's immune system and to reduce the body's rejection of the new implanted kidney. Some of the immunosuppressive drugs eventually have a systematic influence on the

blood pressure, increasing the systolic and diastolic values and thereby impeding blood pressure control. This effect can be seen within the commonly used immunosuppressive calcineurin inhibitors (for example cyclosporine) and corticosteroids (Hillebrand, Suwelack et al., 2009, Ligtenberg, Hene et al., 2001). Corticosteroids influence blood pressure elevation mostly through their mineralocorticoid actions in facilitating sodium and water retention. Therefore, dietary salt intake can also be a significant factor in exacerbating the hypertensive process (Hashimoto, Takase et al., 2016). Thus, the best course of treatment is the lowest possible dose of corticosteroids in combination with the use of a diuretic therapy and modification of dietary salt consumption (Luft, 2012). In terms of calcineurin inhibitors, it seems as if cyclosporine has different possible mechanisms influencing blood pressure (Figure 9) (Weir, 2004). It has been discussed that cyclosporine can affect various neurohormonal pathways, e.g. influence the regulation of the sympathetic nervous system, activation of the renin-angiotensin system, and increase in the production of endothelin (Kon, Sugiura et al., 1990, Scherrer, Vissing et al., 1990, Weir, 2003). Additionally, calcineurin inhibitors provide a salt retentive milieu, inducing a salt sensitive form of hypertension (Gardiner, March et al., 2004). It is indicated that the tacrolimus-induced hypertension is mediated mainly by the renal sodium chloride co-transporter activation. Therefore, thiazide diuretics may be especially effective in preventing the complications of calcineurin treatment (Hoorn, Walsh et al., 2011).

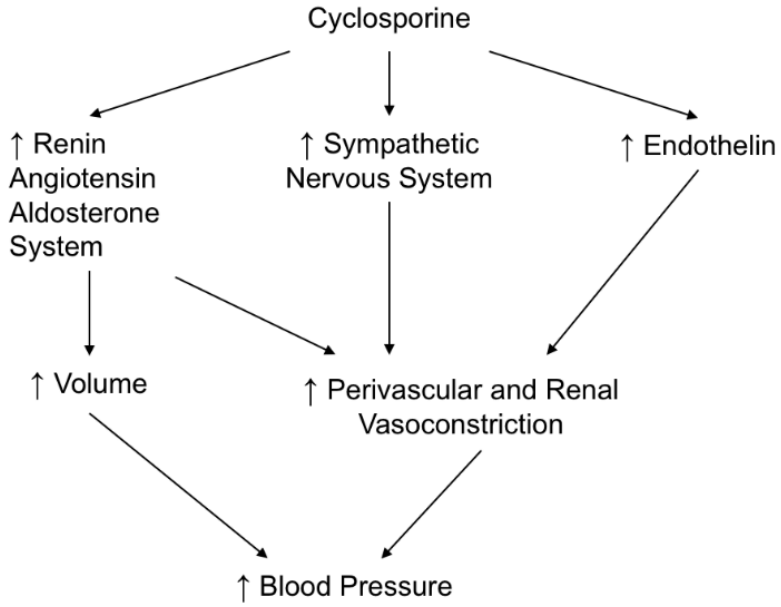


Figure 9 Possible mechanism involved in cyclosporine-induced hypertension.

1.2.4 Genetic Predisposition

One more fact to consider is the genetic aspect of hypertension. A donor's genetic predisposition for hypertension should not be underestimated. Experimental renal transplantation studies have shown that normotensive recipient rats of a renal graft from genetically hypertensive donor rats develop post-transplantation hypertension. (Rettig, Schmitt et al., 1993) Additionally, clinical studies have indicated that recipients of a renal graft from a donor with a genetic predisposition to hypertension require more antihypertensive medication and develop higher blood pressures values than recipients of a kidney from a normotensive donor without a family history of hypertension (de Wardener, 1990, Guidi, Menghetti et al., 1996, Luke, 1993). Further investigations are subject of current research.

1.3 Sympathetic Nervous System

1.3.1 Structure and Regulation

The Sympathetic Nervous System (SNS) is part of the autonomic nervous system. Its antagonist is the parasympathetic nervous system. The SNS operates without conscious control and its activation is not uniform, it rather varies and adapts to the present (health) condition of the body (Wehrwein, Orer et al., 2016). If rapid adjustment or response to the environment is needed the SNS is mainly involved in the body's reaction. In the so called "fight or flight" response, which prepares the body for escape, the SNS performs such functions as: accelerating the heart rate, increasing arterial BP, dilating coronary vessels, emptying the blood reservoirs, dilating bronchi, releasing glucose, and inhibiting gastrointestinal activity (Figure 10). Furthermore, the SNS innervates and connects multiple organs such as brain, heart, kidneys, blood vessels and adrenals, each of which play an important role in the regulation of the body's BP. During the last decades, a significant amount of research has been pursued to uncover and better understand the role of the SNS (Abramczyk, Zwolinska et al., 1999, Converse, Jacobsen et al., 1992, Wallin and Charkoudian, 2007).

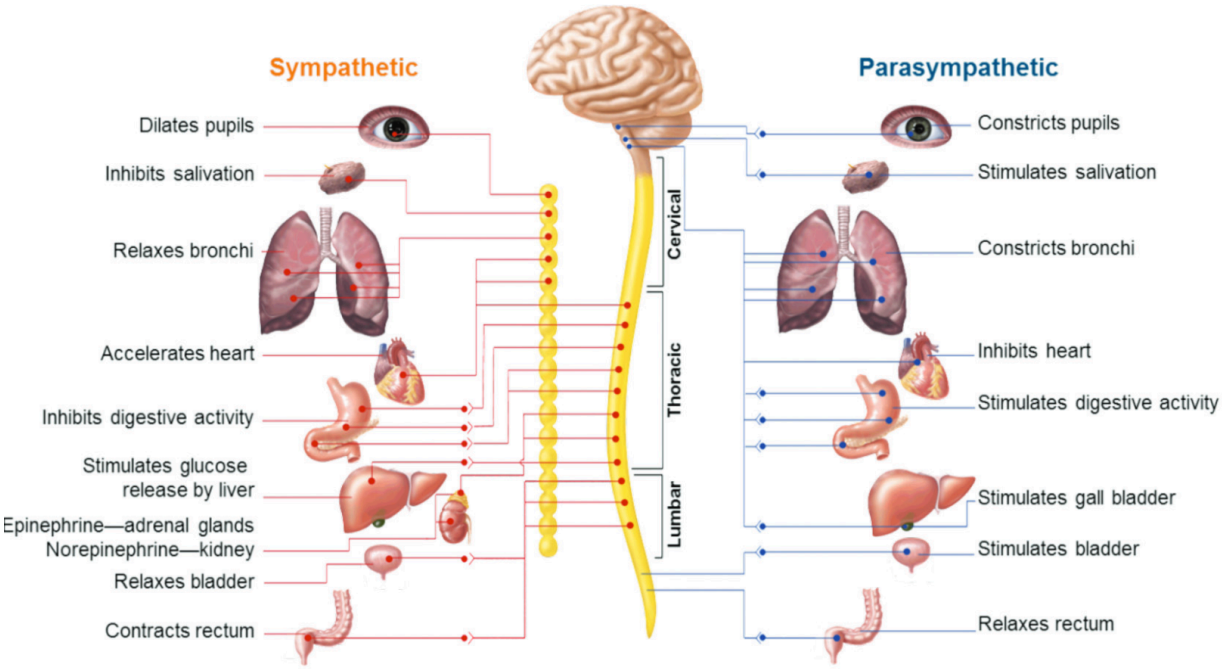


Figure 10 Functions of the peripheral nervous system. *Sympathicus nervous system activated during a "fight or flight" situation and parasympathetic nervous system initiated in a "rest and digest" condition. Printed with permission by Medtronic GmbH. © Medtronic 2016*

A variety of experimental research on animals and humans outline the importance of SNS overactivity for the development and progression of hypertension (Mancia and Grassi, 2014). A baseline sympathetic tone is produced by the signals from the SNS which contributes to

the development and progression of disease states if elevated (Smith, Graham et al., 2004). Generally, increased sympathetic tone causes peripheral vascular resistance, reduces renal blood flow, scales up sodium retention, impairs glucose handling, and in the end triggers adverse cardiac and vascular remodeling (Papademetriou, Doumas et al., 2011, Schlaich, Sobotka et al., 2009a). Strikingly elevated SNS activity can be seen among chronic kidney disease and congestive heart failure (Floras, 2009, Grassi, Quarti-Trevano et al., 2011). Furthermore, SNS hyperactivity can be observed in several other disease states, including the metabolic syndrome, obesity, structural and functional myocardial alterations, obstructive sleep apnea, diabetes, polycystic ovary syndrome, and cirrhosis (Floras, 2009, Prabhakar and Kumar, 2010, Stadlbauer, Wright et al., 2008, Sverrisdottir, Mogren et al., 2008).

SNS regulation is multifactorial and several mechanisms modulate the sympathetic activity at the peripheral and central levels of neurogenic regulations (Grassi, Quarti-Trevano et al., 2011, Mark, 1996). In the context of the renal system, it has been determined that the integration of the kidneys into the sympathetic nervous system is versatile and that renal sympathetic nerves play a key role in BP regulation and hypertension (Schlaich, Sobotka et al., 2009a). On the one hand kidneys act as generators of sympathetic signals (afferent signals) and on the other hand they are the recipients of sympathetic signals (efferent signals) (Figure 11) (DiBona and Esler, 2010).

The course of the sympathetic afferent fibers originates from the kidneys and proceeds to the central nervous system. These afferent signals influence sympathetic outflow to the kidneys and other organs involved in cardiovascular control, as for example heart or peripheral blood vessels. A feedback loop is initiated by the increased sympathetic drive. This loop adversely affects the vasculature, heart and kidneys and thus plays a decisive role in the pathophysiology of hypertension (Figure 11) (Schlaich, Sobotka et al., 2009a).

The efferent fibers transmit stimuli from the central nervous system by enhancing the noradrenaline production and therefore contribute to volume and BP homeostasis. This is implemented by facilitating tubular sodium reabsorption and consequent salt and water retention, renin secretion with subsequent renin-angiotensin-aldosterone system stimulation and renal vasoconstriction with renal blood flow reduction (Bertog, Sobotka et al., 2012, DiBona and Esler, 2010, Grassi, Seravalle et al., 2011, Schlaich, Sobotka et al., 2009b). All these are factors involved in BP regulation.

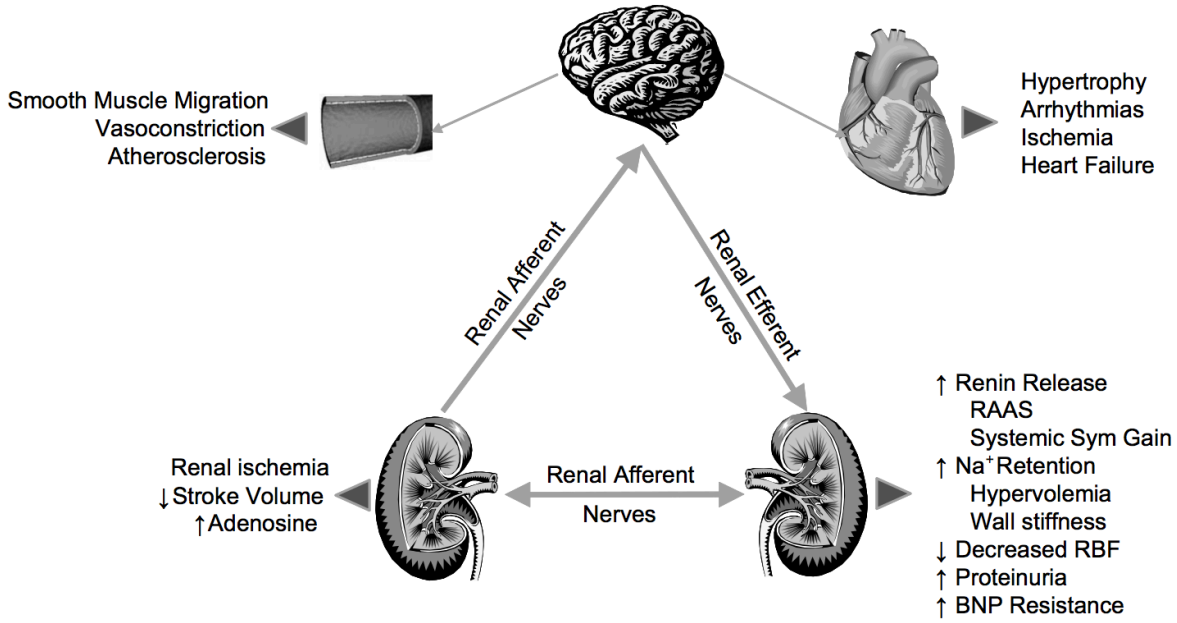


***Figure 11 CNS Integration**. Renal injuries can induce activation of sensory afferent signals in different forms. Due to central integration, afferent signals result in increased sympathetic outflow, which is not just focused toward the kidneys, thereby triggering increased renin secretion, sodium retention, and vasoconstriction. Moreover, organs as the heart and the peripheral vasculature featured with a dense sympathetic innervation, are affected, which results in the adverse effects of sympathetic activation and contribute to the rise in blood pressure. RAAS, renin-angiotensin-aldosterone system; Na^+, sodium; RBF, renal blood flow; BNP, brain natriuretic peptide; sym, sympathetic. Reprinted with permission from Schlaich, M. P., et al. (2009). "Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept." Hypertension 54(6): 1195-1201.*

Given that the renal efferent sympathetic fibers have their origin in the brain, the fibers subsequently run through the spinal cord. Thence, reaching the kidney from the second sympathetic ganglia while coursing further through the adventitia of the renal arteries (Sobotka, Mahfoud et al., 2011). These efferent fibers innervate the peripheral segments of the renal cortex and terminate in glomerular arterioles with the possibility of affecting renal function. Enhanced sodium and water absorption, increased renin release, reduced renal blood flow, catecholamines or other vasoactive substances and decreased glomerular filtration rate emerge as results of overactivity of the efferent sympathetic fibers (DiBona, 2005). In hypertensive patients, it is observed that sympathetic signaling is increased, which causes over-stimulation of these components and contributes to the increase in BP, as mentioned earlier (Schlaich, Sobotka et al., 2009a).

1.3.2 Experimental Research

By the 1980s it was well established that kidneys are essential sensory organs with important afferent innervation and numerous chemoreceptors and baroreceptors. In the aspect of neurophysiological research, Webb and Brody (Webb and Brody, 1987) published their investigation on signal trafficking via afferent sympathetic fibers in a rat model in 1987. They determined that with electric stimulation of afferent sympathetic fibers, it is possible to reduce BP in a dose-dependent manner. They also demonstrated that BP responses could be abolished by spinal transection and interruption of the efferent sympathetic fibers coursing through the spine.

In 1995, Campese and Kogosov showed that the activation of the noradrenergic neurons in the hypothalamus and the development of hypertension in rats with chronic renal insufficiency could be prevented by the resection of the afferent renal nerves through ventral rhizotomy. This is a selective destruction of nerve roots in the spinal cord (Campese and Kogosov, 1995).

A few years earlier, Converse et al. (Converse, Jacobsen et al., 1992) already investigated patients on hemodialysis who have undergone bilateral nephrectomy, resulting in a total interruption of both, the afferent and efferent, sympathetic fibers. They demonstrated that these patients have significantly lower peripheral vascular resistance and decreased BP values. Hausberg et al. (Hausberg, Kosch et al., 2002) took a precise look at renal transplanted patients before and after surgical removal of the native kidneys and they could conclude similar results. A lower muscle sympathetic nervous activity was observed in all transplanted patients after removal of the second native kidney. One should bear in mind that in the majority of kidney-transplant recipients nowadays the transplant kidney is placed in the inguinal area and the endogenous kidneys are not removed. Hence, patients continue to struggle with high BP values.

Considering the SNS reaction after renal nerve stimulation or denervation was applied, Osborn et al. (Osborn, DiBona et al., 1981) could show in a dog model in 1981 that renin secretion via beta-1 adrenergic receptors can be directly mediated using low frequency stimulation of the renal nerves. O'Hagan et al. (O'Hagan, Thomas et al., 1990) investigated deoxycorticosterone acetate-treated miniature swine with established hypertension and demonstrated that renal denervation results in immense natriuresis and BP reduction. This is comparable to the research done by Huang et al. (Huang, Fang et al., 1998), who determined in a hyperinsulinemia-induced hypertension rat model that renal denervation can

avoid hypertension development if done timely or it can normalize BP after hypertension is diagnosed.

Renal denervation has been effective in models of multiple species and in varying etiology, which leads to the proposal that the renal nerves are of great importance in the pathogenesis of hypertension, possibly as an essential contributor in the final common pathway (DiBona and Esler, 2010). Therefore, research was expanded on the humans' SNS. Promising results were published by Schauerte et al. (Schauerte, Scherlag et al., 1999), which indicated that it is possible to stimulate and ablate autonomic nerves on the outside of blood vessels. Because of the discovery of causative activation of the sympathetic nervous system, the role of renal nerves in the development of hypertension and the simplification of a possible approach of the sympathetic fibers by catheter based techniques, it seemed that resistant hypertension was the perfect candidate for interventional approaches (Doumas and Douma, 2010). To further evaluate whether and to what extent the organism, especially the SNS, is impacted by these kind of interventions, diverse examinations are performed.

1.3.3 Activity measurement

SNS hyperactivity is responsible for the development and progression of hypertension (Mancia and Grassi, 2014). To figure out to what intensity and extent, it is obvious to measure the activity. It has been described that the autonomic nervous system activity is indirectly measurable via ambulatory blood pressure measurements (Hojo, Noma et al., 1997). The use of the ambulatory blood pressure monitoring enabled the identification of four different patterns of the nocturnal BP profile: (1) extreme dippers, whose BP declined >20% at night compared to day values, (2) dippers, whose BP decreased between 10% to 20% at night compared to day values, (3) nondippers, whose BP declined <10% at night, and (4) reverse dippers, whose night BP was higher than day BP. It has been published that the different BP pattern are associated with different rates of target organ damage and clinical outcome and further a possible involvement in resistant hypertension (Cuspidi, Macca et al., 2001, Higashi, Nakagawa et al., 2002, Imai, 1999, Jerrard-Dunne, Mahmud et al., 2007, O'Brien, Asmar et al., 2003, Pickering, Shimbo et al., 2006).

Furthermore, the direct assessment of sympathetic activity either in the way of microneurographic techniques or by measuring norepinephrine spillover is quite accurate but unfortunately highly impracticable in a clinical setting. A more realizable way to determine valuable information about the activity of the autonomic nervous system is a noninvasive approach by analyzing the interrelationship between spontaneous fluctuations of arterial BP and heart rate, also referred to as the Baroreflex.

1.3.3.1 Baroreflex

The Baroreflex is the most important neural mechanism in short-term control of BP. It relates heart rate changes to alterations of BP, also known as the cardiac baroreflex sensitivity (BRS) (Bristow, HONOUR et al., 1969). Impaired cardiac BRS, which has been associated to sympathetic overactivity, is a recognized occurrence in hypertensive patients. Influencing factors of the baroreflex sensitivity are increasing age and elevated pressures (Gribbin, Pickering et al., 1971).

Regarding systemic hypertension, abnormalities of the baroreflex have been recognized for some time (Chapleau, 1999). In response to sustained blood pressure elevations as well as short-term fluctuations, arterial baroreceptors are rapidly reset. Increasing blood pressure values cause intensification of the firing of baroreceptor afferents. However, for persistent elevations of blood pressure, despite this particular adjustment, the response of the baroreceptor reduces over time leading to the establishment of a new threshold. Thus, a sensitivity decrease of baroreceptors to any given change in blood pressure in the chronic hypertension setting can be observed. Possible contributions for the baroreceptor resetting may include both peripheral and central influence (Krum, Sobotka et al., 2011).

The noninvasive assessment of BRS remains problematic since ECG and arterial blood pressure, necessary for the evaluation, are both highly complex biological signals distracted especially by movement in addition to further interferences. Therefore, this difficulty was addressed by a specially developed methodological approach, based on an adaptation of the phase-rectified signal averaging (PRSA) technology that is robust against interference and movement (Bauer, Morley-Davies et al., 2010). Zuern et al. (Zuern, Eick et al., 2013) investigated whether an impaired cardiac BRS in patients with resistant hypertension would predict a successful response after renal denervation. They demonstrated that BRS assessment enables identification of patients most likely to benefit from RDN and likewise patients who do not profit, which is why we took the BRS assessment into account in our trial.

1.3.3.2 The heart rate turbulence

Furthermore, Schmidt et al. (Schmidt, Malik et al., 1999) discovered that in healthy persons a characteristic short-term oscillation of heart rate follows spontaneous ventricular premature complexes (VPC). This phenomenon is referred to as heart rate turbulence (HRT). The occurrence of HRT is the physiological, two-phase response of the sinus node to VPCs. However, the underlying mechanisms are not completely understood. It is assumed that these turbulences might be triggered by the above mentioned autonomous Baroreflex.

The VPC causes a short distraction of the arterial BP. With an intact autonomous feedback control system, the distraction will be registered immediately and instantly replied to by a

HRT. If a disorder occurs within this feedback mechanism the response is weakened or absent altogether. Due to this condition, we considered it possible that HRTs might also be present in patients suffering resistant hypertension and potentially prove as prognostic markers.

This can be recorded in so called VPC Tachograms which unmasks the average pattern of sinus R-R intervals surrounding VPCs (Bauer, Malik et al., 2008). The transient acceleration phase of heart rate (R-R interval shortening) immediately after the compensatory pause followed by a subsequent and a gradual deceleration phase (R-R interval prolongation) combine to the HRT. (Figure 12).

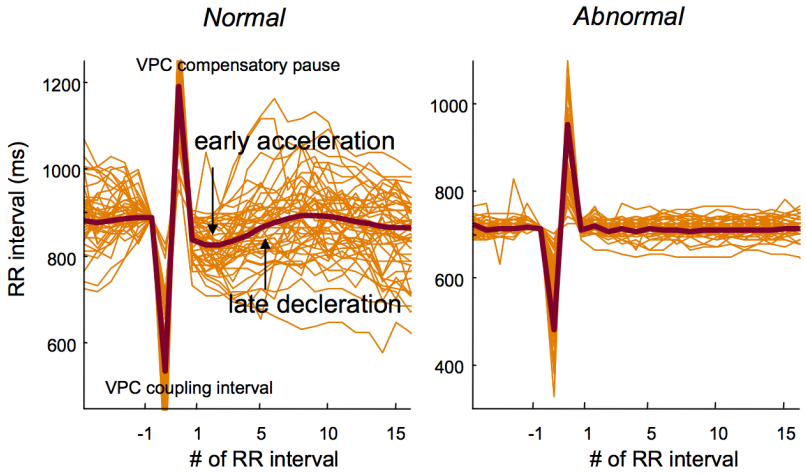


Figure 12 Ventricular premature complex tachograms. *Normal (left) and abnormal (right) heart rate turbulence. Orange: single VPC tachograms; bold: averaged VPC tachogram over 24 hours. VPC, ventricular premature complex. Reprinted from Bauer, A., et al. (2008). "Heart Rate Turbulence: Standards of Measurement, Physiological Interpretation, and Clinical Use: International Society for Holter and Noninvasive Electrophysiology Consensus." J Am Coll Cardiol 52(17): 1353-1365, with permission from Elsevier.*

The subsequent heart rate deceleration through vagal recruitment is caused by a sympathetically mediated overshoot of arterial pressure (Malik, Wichterle et al., 1999). Hence, in patients with reduced baroreflex the HRT pattern is not as pronounced but β-Blockers and ACEi apparently improve HRT (Bauer, Malik et al., 2008).

As β-Blockers and ACEi are common in the antihypertensive treatment of resistant hypertension, on the one hand one could assume that HRT pattern could be increased in these patients. On the other hand, the given sensitivity decrease of baroreceptors due to the constant high blood pressure levels could attenuate the HRT pattern in kidney transplanted patients suffering resistant hypertension.

1.4 Renal Denervation

1.4.1 Historical Background

In the seventeenth century Thomas Willis was one of the first to publish identifiable illustrations of the sympathetic nervous system at his London neuroanatomical school in the book *"The Anatomy of Brain and Nerves"* (reprinted in "Soul Made Flesh" (Zimmer, 2004)). Claude Bernard and Charles Brown-Sequard conducted different experiments in the nineteenth century stating that stimulation of the sympathetic nerves caused vasoconstriction and elevation of blood pressure levels and vasodilatation on nerve section, which designated that the sympathetic fibers exert a tonic, vasoconstrictor influence. These observations led to their categorization as the "pressor nerves" (Hamilton, 1982).

Brandford's meticulous experiments on dogs (Bradford, 1889) in 1889 led to the finding that stimulation of splanchnic and dorsal nerves triggers changes in blood pressure. Results varied with the stimulated anatomic area and the selected electric impulse frequency, whether blood pressure increased or decreased. At the beginning of the twentieth century, Geisbock consolidated the different observations and reasoned that human hypertension was most likely neurogenic in origin, being initiated and sustained by the sympathetic nervous system (Julius S, 1976).

In 1923 researchers recommended neurosurgical treatment of hypertension for the first time, cutting as many 'pressor nerves' as possible to remove their systemic vasoconstrictor influence (Hammerström, 1947). Just two years later, in 1925, Adson was the first to execute a surgical sympathectomy for the treatment of malignant hypertension (Allen and Adson, 1940).

A significant but only temporary decrease could be seen in a group of 85 patients, who underwent decapsulation between 1925 and 1935 (Sen, 1936). Sen used the technique of renal decapsulation, which was regarded as a form of sympathectomy by disrupting the sympathetic fibers between the capsule and the renal cortex. Initially, this technique was performed to treat unexplained hematuria and perinephritis.

In 1934 Page and Heuer presented the first case of bilateral sympathetic denervation of the kidney to treat severe essential hypertension (Page and Heuer, 1935). Their case showed that the renal function was not negatively influenced and that the procedure could be considered a safe intervention.

Since long-term results were not satisfying enough, treatment became more radical. The technique of splanchnicectomy, a surgical removal of splanchnic nerves, showed convincing results in the majority of patients suffering from malignant hypertension (Smithwick and

Thompson, 1953). A 22-year old patient with known severe hypertension for more than three years underwent bilateral supradiaphragmatic splanchnicectomy in June 1934 (Peet, 1948). Thereupon, her blood pressure values decreased from values up to 280/190 mm Hg down to 110/90 mm Hg. The success led to the establishment of this technique for the subsequent two decades. The most important limiting complications were postural hypotension and syncope, observed in many patients postoperatively. Unfortunately, it was also associated with high operative morbidity (Smithwick and Thompson, 1953).

A milestone in the treatment of hypertension was reached in the mid 1950s. The first oral antihypertensive medication became available for the treatment of hypertension (Clough, 1953). For the first time and from then on, well-tolerated regimes could be subscribed long-term (Freis, Wanko et al., 1958). Paton and Zaimis (Paton WDM, 1951) discovered ganglionic blocking drugs and thereby ushered in the era of anti-adrenergic drugs. Blood pressure values decreased and the surgical risk could be reduced, but unfortunately the complications did not decline initially. In fact, the extent was equally frequent and disabling. Over the course of time, ganglion blockers were replaced by beta-adrenergic receptor blocking drugs, alpha-adrenergic receptor blockers, centrally acting sympathetic nervous inhibitors including methyldopa, clonidine, and neurone-blocking drugs such as guanethidine. The combination of these anti-adrenergic drugs, diuretics and direct-acting vasodilators, such as hydralazine, were the agents of choice in antihypertensive therapy from 1960 to 1990 (van Zwieten, 2004).

From the 1990s on, the renin–angiotensin system got into focus in the antihypertensive therapy. The new substance classes of angiotensin converting enzyme inhibitor drugs, including Ramipril and Enalapril, and angiotensin receptor blocking drugs such as Candesartan were significantly more tolerated and at least as equally effective as antiadrenergic drugs. Furthermore, anti-renin drugs, (dihydropyridine) calcium channel blocking drugs and different types of diuretics complemented the choice of antihypertensive drugs. Eventually, antiadrenergic antihypertensive drugs were replaced at the top of the international cardiovascular society hypertension guidelines (Mancia, Laurent et al., 2009).

Meanwhile, the sympathetic nervous system forfeited its earlier importance in discussion of essential hypertension pathogenesis and treatment. For some it was even considered to be passé in hypertension care.

However, for approximately 10% of the patients suffering steady high blood pressure levels despite the subscription of ACE-inhibitors, diuretics, angiotensin receptor blockers, or calcium channel blockers, goal blood pressures were not achieved (de la Sierra, Segura et al., 2011). These drug-resistant patients emphasized the need for a new treatment strategy.

In fact, new approaches were devised targeting the sympathetic nervous system once again: surgically implanted barostimulator devices (Yoruk, Bisognano et al., 2016) and particularly catheter-based renal denervation (Krum, Schlaich et al., 2009).

The knowledge of the physiology of the renal sympathetic nerves was a necessary prerequisite for the subsequent development of radiofrequency renal denervation. Regional noradrenaline isotope dilution methodology, measuring the outward flux of transmitter from renal sympathetic nerves to plasma, demonstrated that a high level of activation of the renal sympathetic outflow was present in untreated resistant hypertensive patients (Esler, Jennings et al., 1984, Esler, Jennings et al., 1988). Selective cardiac noradrenaline spillover measurements (Esler, Jennings et al., 1988) and microneurography recordings (Grassi, Colombo et al., 1998, Lambert, Straznicky et al., 2007) showed that the sympathetic nervous outflow is also commonly present in the heart and skeletal muscle vasculature. However, considering the hypertension pathogenesis, it is the renal sympathetic activation, which is mainly responsible (DiBona, 2005).

The first to suggest that renal denervation might be a successful approach to treat essential hypertension were Howard Levin and Mark Gelf in 2002 (provisional patents 60/370190 (April2002), 60/415575 (October 2002), and 60/442970 (January 2003)). Ardian, a Californian start-up company, initiated a developmental program to design a radio frequency ablation catheter suitable for human use after the acquirement of the Levin and Gelf's patent rights. This purpose-designed catheter was tested for safety and renal denervation capacity in pigs (Rippy, Zarins et al., 2011).

1.4.2 Development and Principals of Renal Denervation

Through the years, renal denervation has been performed in various techniques both in experimental models and in humans by surgical exposure of renal nerves. Early on, the renal nerves were resected and interrupted using only a surgical scalpel in more invasive surgeries (Hannawi, Ibrahim et al., 2015). Since the technique has progressed, electrocautery, cryoablation and radio frequency ablation have also been applied in these interventions. With the introduction of transcatheter techniques and further progress in technology, the next logical step was to advance to transvascular methods to interrupt nerve integrity.

In 1999, a series of experiments by Schauter et al. (Schauerte, Scherlag et al., 1999, Schauerte, Scherlag et al., 2000) indicated that it is possible to stimulate and ablate autonomic nerves on the outside of blood vessels. An innovative approach to stimulate and ablate the vagal nerve was conducted to treat patients suffering vagally mediated atrial fibrillation (an abnormal heart rhythm).

The technique used than was similar to the one presently used for catheter-based renal denervation. Today, either a single-tip electrode, e.g. Medtronic system, or a multielectrode system, e.g. St. Jude's system, is used for radio frequency thermal ablations (Table 3).

Given resistance to drug therapy, the discovery of causative activation of sympathetic nervous system, the role of renal nerves in the development of hypertension and the simplification of the approach to the sympathetic fibers by catheter based techniques, resistant hypertension seemed to be the perfect candidate for interventional approaches (Doumas and Douma, 2010).

Because the fibers proceed in the adventitia of the renal arteries and are located mostly within two to three millimeters from the inner layer of the renal artery, sympathetic fibers can be easily accessed and disrupted transvascularly using thermal energy (Figure 13) (Oldham, 1950).

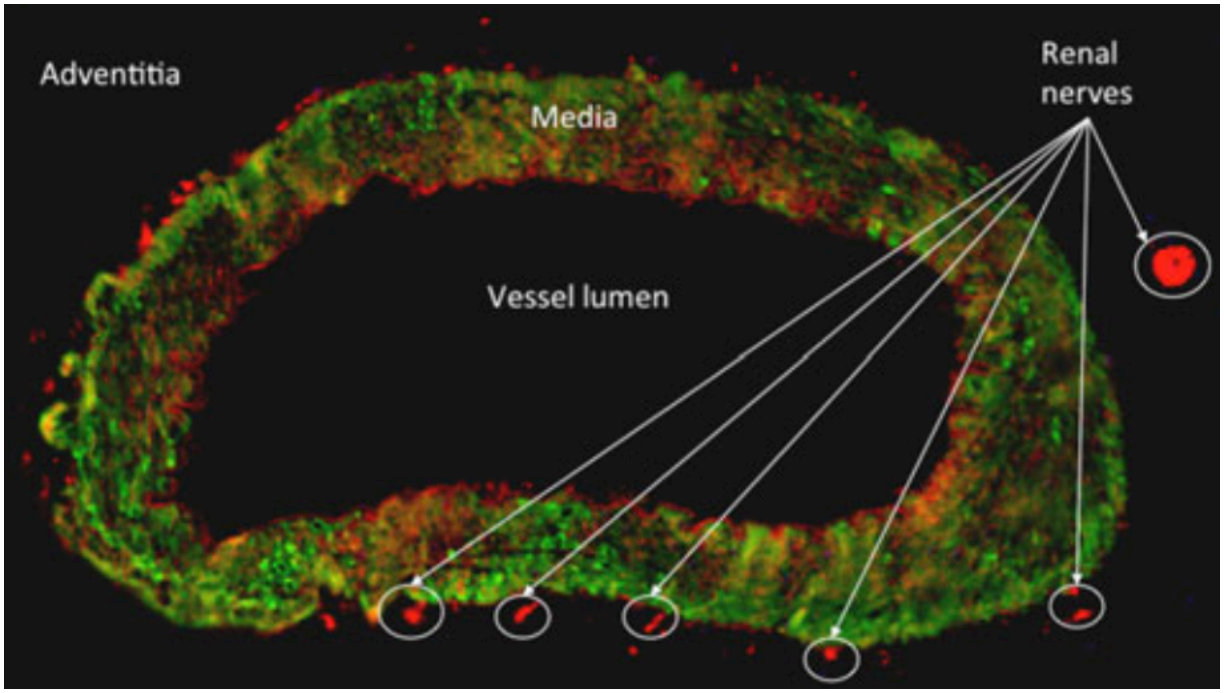


Figure 13 Course of sympathetic nerves of renal artery. *Stained with tyrosin hydroxylase antibody. Sobotka, P. A., et al. (2011). "Sympatho-renal axis in chronic disease." Clin Res Cardiol 100(12): 1049-1057, reprinted with permission of Springer.*

The objective of radio frequency ablations is to place discrete lesions in a circumferential pattern and to avoid placements at the same cross-section of the vessel, because otherwise an effective nerve ablation is hard to achieve (Figure 13 and 14). Table 4 provides an overview of currently most frequent used devices. Additionally, each of these devices is connected to an individual generator, which is programmed with a special protocol for the ablation process. These protocols differ in treatment time, totally delivered energy, and tolerable temperature.

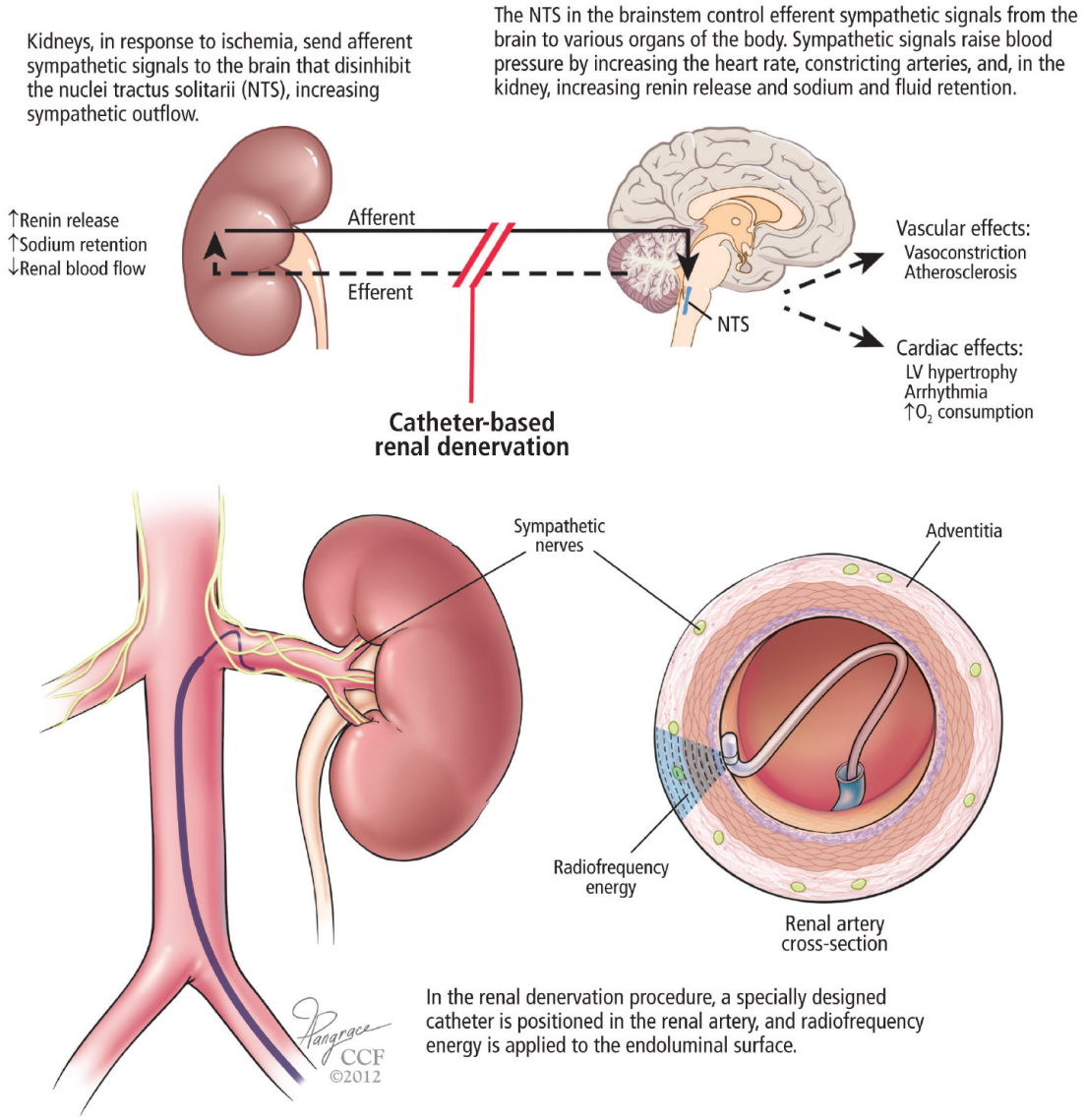


Figure 14 Renal sympathetic denervation illustration. *Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2016. All Rights Reserved.*

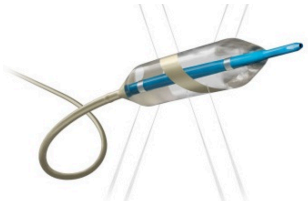
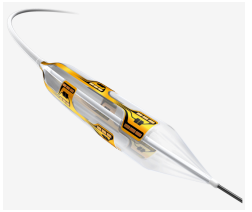
The first device used in humans was a 6-French steerable RF ablation catheter, which is inserted percutaneously through a femoral sheath and a guiding catheter engaging each renal artery sequentially (Ardian/Medtronic) (Krum, Schlaich et al., 2009). This device was continuously developed as the Medtronic Symplicity Flex™ catheter. It is the most tested device among the others. Achieving ablation temperature up to 75 °C with an approximate energy delivery of 5-8 W in 120s per ablation. The lesions created with this device are in a less predictable geometrical pattern and it might be difficult to obtain an adequate vessel wall contact. Tortuous vessels imped the ablations causing ablation aborts due to overheating and therefore repeated ablations (Krum, Schlaich et al., 2009, Schlaich, Sobotka et al., 2009a, Witkowski, Prejbisz et al., 2011).

The St. Jude's multielectrode ablation system, so-called EnligHTN, is equipped with four unipolar electrodes mounted on a nitinol basket and placed without the use of a guidewire (Papademetriou, Tsioufis et al., 2014). This achieves a circumferential distribution of lesions. Therefore, thermal injury and fiber interruption can be delivered in a more predictable way. The ablation duration for this device lasts 90s and reaches a temperature of up to 75 °C at a power of 6 W. For a second ablation, the catheter is retracted and rotated.

The other devices are not as widely used. In the Vessix V2 system (Vessix Vascular-Boston Scientific) and the OneShot system (Covidien) the electrodes are also mounted on a balloon. The Vessix system is operated with a temperature maximum of 68 °C and an application time of only 30 s at an energy level of 1 W (Wilson, Winsor-Hines et al., 2015). Mentionable for the OneShot system is the integrated low pressure system allowing constant cooling of the artery during the ablation. It reaches an energy level of up to 25 W and is applied for 120 s with a maximum temperature of 60 °C (Ormiston, Watson et al., 2013a). Further technique being developed and studied are devices using cryoablation instead of RF, catheter systems allowing micro needle delivery of guanethidine or ethanol to cause chemical ablation and external body delivery of focused ultrasound energy to achieve renal denervation.

It is legitimate to ask why it took so long for this novel therapy to be materialized. One possible reason is that renin-angiotensin blocking drugs were the omnipresent antihypertensive therapy over the past few decades. This can be ascribed to their low side-effect-rate and especially to their high efficacy. Also, clinical researchers, mostly international hypertension experts, have often tended toward trials on drugs, which antagonize the renin-angiotensin system and thus have disregarded the sympathetic nervous system in many cases (Daien, Duny et al., 2012). Another argument that should not be underestimated is the funding. Most experimental hypertension research in which the major pharmaceutical companies invested concerned the renin-angiotensin system. However, over time the assessment of the importance of the sympathetic nervous system in the context of hypertension has changed.

Table 4 Renal Denervation Devices – Overview. *Printed with permission by Medtronic GmbH. © Medtronic 2016; printed with permission by St. Jude Medical Inc. © St. Jude Medical 2014; printed with permission by Ltd. © Covidien 2015; printed with permission by Boston Scientific Corp. © Boston Scientific 2016*

	Medtronic Symplicity Flex™	**St. Jude Medical EnligHTN™**	**Covidien OneShot™**	**Boston Scientific Vessix™**
CE marking	02/2008	12/2011	02/2012	04/2012
				
Size	6 Fr, one size fits all	8 Fr, large and small baskets	7-8 Fr, balloon diameter 5, 6 & 7 mm	8 Fr, balloon diameter 4, 5, 6 & 7 mm
Renal artery treatment range	≥ 4 mm	4 – 8 mm	4 – 7 mm	3 – 7 mm
Treatment time	2 min/ablation, recommended minimum 4 ablations/artery	90 s/ablation, 8 ablations/artery	One single, 2 min ablations/artery	30 s/ablation, 1 – 2 ablations/artery
Over-the-wire system	No	No	Yes	Yes
Cooling features	No	No	Yes	No
Total energy delivery	Max. 8 W	Max. 6 W	Max. 25 W	Max. 2 W
Maximum temperature	75 °C	75 °C	60 °C	68 °C
Catheter length	90 cm	115 cm	74 cm	90 cm

1.5 Previous Studies

Referring to the abovementioned fact that resistant hypertension might be the perfect candidate for interventional approaches, various designed studies investigated for the last couple of years if the SNS could be influenced in humans and which results could be achieved by these interventions. The first catheter-based renal denervation procedure in a patient suffering drug-resistant hypertension was performed on the 6th of June in 2007. From then on, several studies began to investigate the impact of renal denervation and research is continuing. Figure 15 gives an indication for systolic and diastolic office blood pressure reduction of different trials at six months after renal denervation.

The Symplicity HTN-1 trial was the first in human study evaluating 50 patients with severe resistant hypertension (systolic BP of ≥160 mm Hg) launched in June 2007 (Krum, Schlaich et al., 2009). It was designed as an open label, nonrandomized study focused on safety and proof-of-concept of therapeutic RDN. They used the Symplicity® Arch™ catheter by Ardian Inc. (Palo Alto, CA, USA), later acquired by Medtronic CardioVascular Inc. (Santa Rosa, CA, USA). The mean office BP was 177/101 mm Hg despite a mean of five antihypertensive medications. After the first month, the achieved office BP reduction through renal denervation was substantial systolic and diastolic (-14/-10 mm Hg) and even more distinct at the six months (-22/-11 mm Hg) and twelve months follow-up (-27/-17 mm Hg). In a small fraction of patients, ambulatory blood pressure measurements (ABPM) was performed after approximately one month, with slightly different results. The BP reduction showed a less pronounced magnitude than the one observed with office BP measurements (-11 mm Hg in systolic BP). At 36 months, significant changes were seen in office BP (-32/-14 mm Hg). Reductions of 10 mm Hg or higher in SBP were measured in 69% of patients at one month, 81% at six months, 85% at twelve months, 83% at 24 months, and 93% at 36 months (Krum, Schlaich et al., 2014).

In the second Symplicity trial (Symplicity HTN-2), launched in June 2009, a prospective, open-label and randomized but again not blinded study, a group with optimal medical therapy and RDN was compared to a group with optimal medical therapy only. A total number of 106 patients with resistant hypertension and similar characteristics to the proof-of-concept study Symplicity HTN-1 were enrolled (Esler, Krum et al., 2010). The same Symplicity® Arch™ (Palo Alto, CA, USA) catheter was used for RDN performance. A significant systolic and diastolic BP reduction could already be determined after the first month and an even higher decrease could be observed after six months (-32 /-12 mm Hg) in comparison to a minimal reduction in the control group (-1/ 0 mm Hg). At 36 months, the systolic and diastolic blood pressure reduction did not significantly differ (-33 / -14 mm Hg). Furthermore, in Symplicity HTN-2 the ABPM systolic and diastolic decrease was recognizable (-11 / -7 mm Hg) (Esler,

Bohm et al., 2014) and the home-based BP measurements also decreased (-20 / -12 mm Hg) after six months. Then RDN was permitted in control group patients, transferring in a crossover arm. Subsequent, a total of 62.9% of these patients experienced a mean systolic BP reduction (-23.7 / -8.4 mm Hg) after six months (Esler, Krum et al., 2012).

A total number of 535 patients with severe resistant hypertension were enrolled in the most recent Symplicity HTN-3 trial, Conducted between 2011 and 2013 (Bhatt, Kandzari et al., 2014, Kandzari, Bhatt et al., 2012). They were randomly assigned in a 2:1 ratio to undergo either renal denervation, performed with the second-generation Medtronic Symplicity Flex™ catheter (Santa Rosa, CA, USA), or a sham-procedure. In contrast to Symplicity HTN-2, patients also had an elevated 24h ambulatory systolic blood pressure (≥135 mm Hg) besides a persistently elevated systolic blood pressure ≥160 mm Hg in an office measurement. At six months, no major change in the difference for SBP could be observed between the two groups (-14 mm Hg in denervation group vs. -11 mm Hg in the control group). The systolic ABPM change was small in the denervation group (-7 mm Hg) and in the control group (-5 mm Hg). Subgroup analysis suggested RDN might have been more successful at lowering blood pressure in non-black individuals and in patients less than 65 years of age. These changes turned out to be not significant after adjusting for a multivariate analysis. However, the percentage of nondippers that were transformed to dippers was higher in the denervation group (21.2%) than in the sham group (15.0%) (Bakris, Townsend et al., 2014).

The EnligHTN I study, with similar inclusion criteria as in the Symplicity trials, indicated a great BP drop in 46 patients at just one month after denervation (-28 / -10 mm Hg) (Mancia, Fagard et al., 2013). The office BP values persisted around the same level for the next 12, 18 and 24 months (after 12 months -27/-11mm Hg, after 18 months -24 / -10 mm Hg and after 24 months -29 / -13 mm Hg). In this trial the St. Jude's multielectrode ablation system was used to achieve a circumferential distribution of lesions using a multielectrode ablation device different to the Medtronic system used in the Simplicity trials. In ABPM a considerable BP reduction could not be determined throughout the twelve months (≤-10 /≤-5 mm Hg). Reduction in home measurements stayed consistently around the same level (≤-10/≤-5 mm Hg). Additionally, the renal function was investigated during the follow ups and at twelve months there were no signals of worsening renal function (Worthley, Tsioufis et al., 2013). Interestingly, after 18 months BP reduction reduced slightly (-24/-10 mm Hg) but then increased again at 24 month follow-up (-29/-13 mm Hg). The same changing behavior could be seen in ABPM results with a declining reduction at 18 months (-7/-4 mm Hg) but an increasing reduction after 24 months (-13/-7 mm Hg).

For the EnligHTN II study patients were assigned to three groups depending on their office systolic BP levels and their estimated glomerular filtration rate (Lobo, Saxena et al., 2015). In

the 129 patients of Group A with an office systolic BP ≥160 mm Hg and eGFR ≥45 mL/min per 1.73 m^2 the average reduction was -18.2 mm Hg for office systolic BP (OSBP) and -7.9 mm Hg in daytime ambulatory systolic BP (ASBP) after six months. After twelve months, the reduction stagnated at the same level (-17.2 mm Hg for OSBP and -7.6 mm Hg for ASBP). Considering the results of the two other groups (Group B ≥140 mm Hg and eGFR ≥45 mL/min per 1.73 m^2; Group C ≥140 mm Hg and eGFR ≥15 mL/min per 1.72 m^2), the investigators could not record changes as pronounced as in Group A.

In a pilot study in 2013 the OneShot system was used in a group of eight patients with resistant hypertension. Using a balloon-mounted spiral electrode, the study achieved results after six months that are similar to the ones of Symplicity and EnligHTN trials (-31/-10 mm Hg) (Ormiston, Watson et al., 2013b).

Witkowski et al. (Witkowski, Prejbisz et al., 2011) performed a study in a group of ten patients suffering resistant hypertension and additionally sleep apnea. As mentioned before, a group of patients known for an enhanced sympathetic activity and their complicated hypertension treatment (Fisher, Young et al., 2009). The study indicated a significant reduction in office BP at three and six months after RDN (-34/-13 mm Hg) but only a small change in systolic BP measured by ABPM (-6 mm Hg).

Mahfoud et al. (Mahfoud, Ukena et al., 2013) explicitly examined the BP response as measured by ABPM in 346 patients who underwent renal denervation for uncontrolled hypertension. Of those, 303 patients were found by daytime ABPM to have true resistant hypertension, and 43 had pseudoresistant hypertension (office SBP, 161 ± 20 mm Hg; ABPM SBP, 121 ± 20 mm Hg). At three, six and twelve months' follow-ups, office SBP decreased by 21 mm Hg after three months, by 24 mm Hg after six months and by 27 mm Hg after twelve months. The office diastolic BP changed by 9 mm Hg after three months, by 9 mm Hg after six months and by 12 mm Hg after twelve months. In patients with true treatment-resistant hypertension, there was a significant reduction in 24-hour SBP (10/10/12 mm Hg) and DBP (5/5/7 mm Hg) at three, six and twelve months, respectively. For pseudoresistant patients the office BP reduced to a comparable extent, but there was no effect on ABPM.

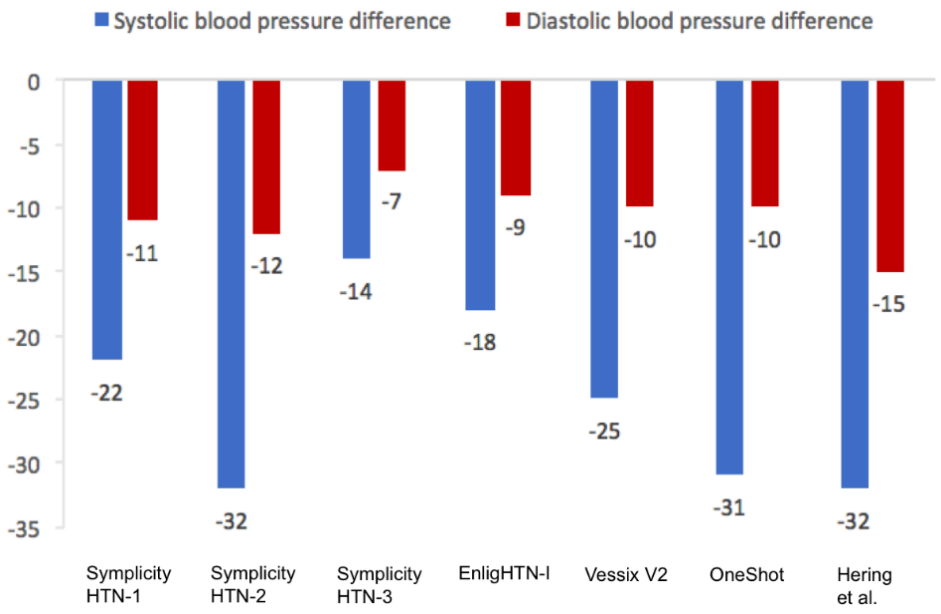


Figure 15 Office blood pressure reductions in different previous studies after 6 months.

The results of this larger-scale study agree with the findings of the three Symplicity trials and the two EnligHTN studies, confirming the antihypertensive effect of renal denervation, although once again demonstrating a considerably less pronounced BP reduction in the ABPM assessment.

A further study investigating the success of renal denervation is the DENERHTN study implemented by Azizi et al. (Azizi, Sapoval et al., 2015). This was a multicenter, prospective, open-label randomized controlled trial with blinded endpoint evaluation in patients with resistant hypertension. Though, the study design differs in one important aspect in comparison to the mentioned studies. In fact, the 106 enrolled patients in the DENERHTN study received standardized triple antihypertensive treatment (Indapamide 1.5 mg, Ramipril 10 mg or, if not tolerated Irbesartan 300 mg, and amlodipine 10 mg or 5 mg in the presence of ankle edema) during a 4 week-period. They used the same Medtronic catheter for the renal denervation treatment as the one used in Symplicity HTN-3 and this trial. After randomization, in both groups patients were treated with a stepped-care antihypertensive drug regime added to the initial standardized triple therapy, including Spironolactone 25 mg, Bisoprolol 10 mg, Prazosin 5 mg, and Rilmenidine 1 mg from the second to the fifth month if the measured home blood pressure was higher than or equal to 135/85 mm Hg. Eventually, the mean change in daytime ambulatory systolic BP at six months was -15.8 mm Hg in the renal denervation group compared to -9.9 mm Hg in the control group.

Desch et al. (Desch, Okon et al., 2015) implemented an additional study applying a sham controlled study design, alike the Symplicity HTN-3 design. In the per-protocol group analysis,

they found, that the patients who underwent RDN experienced a significantly more pronounced decrease in their mean ABPM and daytime SBP at 6-month follow-up compared to the control group (-8.3 mm Hg vs -3.5 mmHg).

In 2016 Mathiassen et al. (Mathiassen, Vase et al., 2016) published the results of their sham-controlled, double-blinded, randomized, single-center trial, in which they investigated the efficacy of RDN on ambulatory BP control. Patients with daytime SBP ≥ 145 mm Hg, after one month of therapy on stable medication, were randomly enrolled to either of the two groups. The experienced operator used the same unipolar catheter as in the Symplicity HTN-3 and DENERHTN studies in the RDN group. The achieved BP reduction presented similar, as a reduction of -6.2 mm Hg and -6.0 mm Hg was achieved at three month and six month follow-up in the denervation group. There was no statement about, whether the circumferential ablation pattern has been achieved properly, necessary for a successful ablation.

A meta-analysis by Sun et al. (Sun, Li et al., 2016) of RDN vs. pharmacotherapy for resistant hypertension published in 2016 showed that catheter-based RDN treatment significantly decreases systolic and diastolic BP in comparison to pharmacotherapy. However, in the evaluation of the truly randomized control trials there was no significant difference observed anymore.

Furthermore, substantial BP reduction results after three and six months post renal denervation were also achieved in a study presented by Hering et al. (Hering, Mahfoud et al., 2012). They investigated a group of patients with resistant hypertension and additionally moderate and severe chronic kidney disease. A group of patients that should be handled with care and is often affected by hypertension (Chertow, Beddhu et al., 2016, Converse, Jacobsen et al., 1992, Hausberg, Kosch et al., 2002). They determined systolic and diastolic office BP reductions of -25/-11 mm Hg after three months, -32/-15 mm Hg at six-month follow-up, and -33/-19 after twelve months. Like the abovementioned studies the ABPM recordings showed minor reductions of -5/-6 mm Hg after six months and unfortunately also turned out to be not significant. However, there were no adverse events concerning the kidneys in any kind.

The reasonably convincing results raised the question whether and to what extent further groups of patients suffering hypertension and further diseases could benefit from renal denervation treatment. One of these groups of patients with high incidence of resistant hypertension is the subset of kidney-transplanted patients (Thomas, Taber et al., 2013). Up to 93% of patients after kidney transplantation require antihypertensive medication (Kurnatowska, Krolikowski et al., 2012). Until today there is a gap of knowledge as there are

still only a few studies available that have investigated the success of renal denervation in kidney-transplanted patients (Dobrowolski, Bemelman et al., 2015, Protasiewicz, Poczatek et al., 2014). Therefore, we designed a trial concerning possible effects on blood pressure after renal denervation treatment in kidney-transplanted patients to figure out to what extent this certain group of patients could profit from RDN ablations.

2 MATERIAL & METHODS

2.1 Study Design and Study Population

This trial is a regulatory study designed as an investigator-initiated, prospective, single-center, randomized trial. It evaluates the safety and efficacy of catheter-based renal denervation in kidney transplanted patients with their native kidneys in situ for the treatment of resistant hypertension despite compliance with at least three antihypertensive medications of different classes, of which one is a diuretic with best medical therapy using guideline recommended drugs in each disease state (www.clinicaltrials.gov identifier NCT01899456).

All patients underwent a complete physical and history examination, review of medication, assessment of vital signs, and blood chemistry evaluation at baseline and at six months after RDN. Treating physicians and patients were encouraged not to change antihypertensive medications except when medically required. Patients were randomized 1:1 to receive either renal denervation of the native kidneys or just medical treatment only. All patients provided signed informed consent and were followed for six months. Patients' treatment was performed between July 2013 and March 2014. The trial is without extramural funding and was approved by the local Ethics Committee and the Federal Office for Radiation Protection.

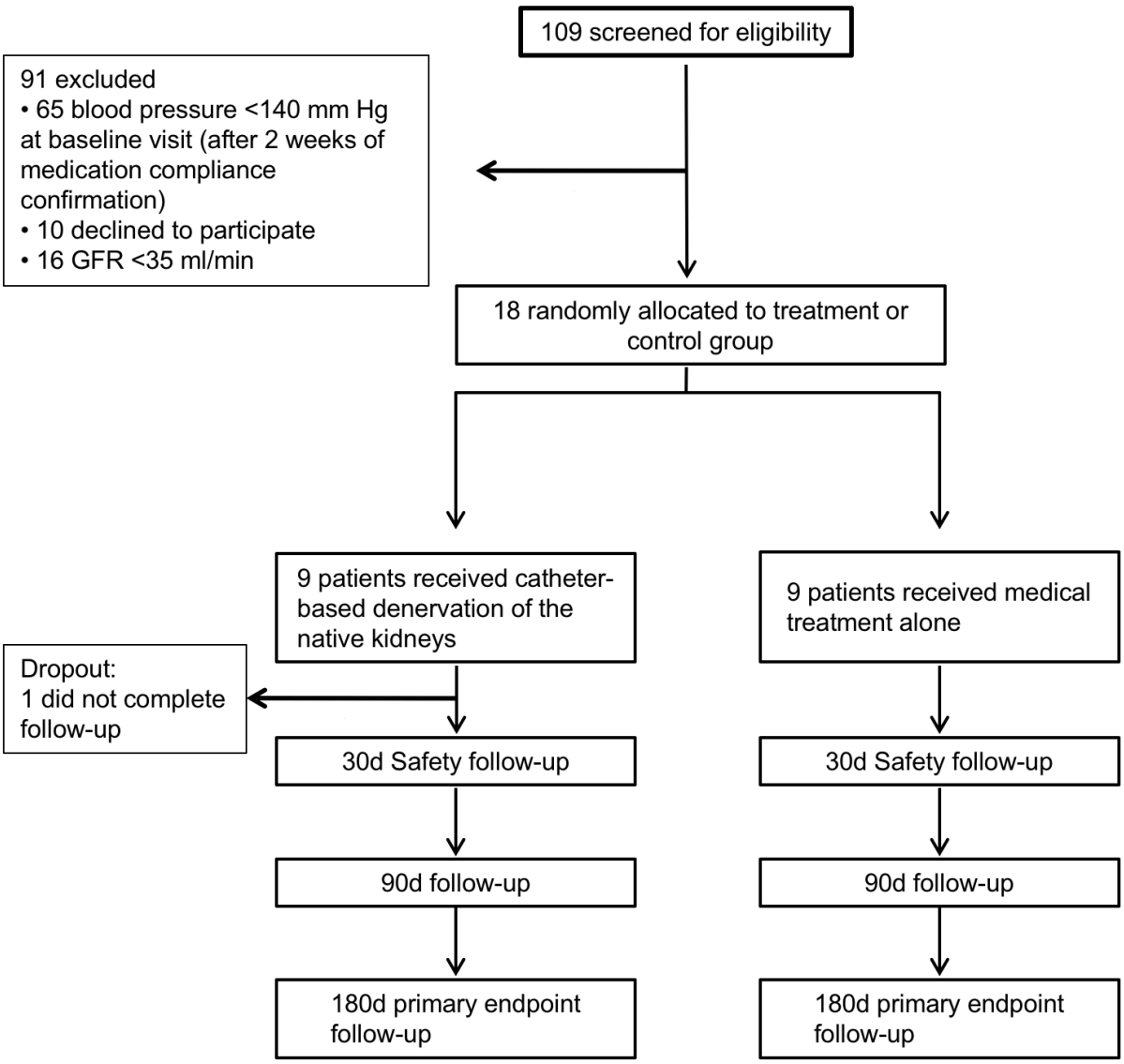


Figure 16 Study flow. *30 days follow-up: office blood pressure measurement, medication regime check; 90 days follow-up: office blood pressure measurement, medication check; 180 days follow-up: office blood pressure measurement, ambulatory blood pressure measurement, laboratory profile, sympathetic nervous system activity measurement*

2.1.1 Inclusion Criteria

The initial patient recruitment and screening identified patients of the age of 18 to 85 years with average office systolic blood pressure values >140 mm Hg despite receiving a stable antihypertensive treatment of at least three medications of different classes, of which one must be a diuretic (Table 5). Patients were enrolled at the earliest six months after transplantation, in which the native kidneys remained in situ.

Table 5 Trial Inclusion criteria

Patient after renal transplantation (> 6 month) without resection of native kidneys
Age ≥ 18 and ≤ 85 years at time of randomization
Stable medication regimen including 3 or more antihypertensive medications of different classes, including at least 1 diuretic (with no changes for a minimum of 2 weeks prior to screening) and no expected changes for at least 6 months
Office SBP ≥140 mm Hg based on an average of 3 blood pressure readings measured at both an initial and a confirmatory screening visit
Written informed consent

Following institutional ethics approval, potentially eligible patients provided informed consent and entered a screening period. During this period, patients measured their home blood pressure for at least two weeks and confirmed that antihypertensive medications were taken daily. If there were any antihypertensive drug changes, patients were asked to redo the 2-week-measurement prior to their enrollment; needed for an enrollment with a stable and reliable blood pressure value. Patients were included if blood chemistry values showed a sufficient kidney function with an estimated glomerular filtration rate ≥30 ml/min per 1.73 m^2 (based on the Modification of Diet in Renal Disease criteria), a satisfactory creatinine level ≤2,5 mg/dL and of course elevated BP values (Table 5).

2.1.2 Exclusion Criteria

Patients were excluded due to anatomical renal abnormalities as renal-artery stenosis of more than 50%, renal-artery aneurysm, prior renal-artery intervention, multiple renal arteries, or a treatable segment of less than 20 mm in length.

If patients did not provide a satisfactory renal function, in the meaning of eGFR values <30 ml/min per 1.73 m^2 (based on the Modification of Diet in Renal Disease criteria) and creatinine levels >2,5 mg/dL, they were not included. Furthermore, patients suffering severe medical conditions were also excluded. Additionally, patients were not enrolled if they had a known secondary cause of hypertension other than chronic kidney disease (Table 6).

Subjects meeting these criteria would undergo renal angiography to determine anatomic eligibility. Only patients fulfilling all clinical and anatomic requirements were randomized.

Table 6 Trial Exclusion criteria. *ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.*

Renal artery anatomy ineligible for treatment including:
Main renal arteries with <4 mm diameter or with <20 mm treatable length
Multiple renal arteries where the main renal artery is estimated to supply <75% of the kidney
Renal artery stenosis (>50%) or renal artery aneurysm in either renal artery
History of prior renal artery intervention including balloon angioplasty or stenting
eGFR of <30 mL/min/1.73 m^2
>1 in-patient hospitalization for a hypertensive crisis within the past year
≥1 episode(s) of orthostatic hypotension (reduction of SBP of ≥20 mm Hg or DBP of ≥10 mm Hg within 3 minutes of standing) coupled with symptoms within the past year or during the screening process
Pregnant, nursing, or planning to be pregnant
Chronic oxygen support or mechanical ventilation (eg, tracheostomy) required other than nocturnal respiratory support for sleep apnea
History of or currently have any of the following medical conditions:
Primary pulmonary hypertension
Type 1 diabetes mellitus
Severe cardiac valve stenosis for which a significant reduction of blood pressure is contraindicated
Myocardial infarction, unstable angina pectoris, syncope, or a cerebrovascular accident within 6 months of the screening period
History of pheochromocytoma, Cushing's disease, coarctation of the aorta, hyperthyroidism, or hyperparathyroidism
Any condition that would prohibit or interfere with ability to obtain an accurate blood pressure measurement using the protocol-specified automatic blood pressure monitor (e.g. arm diameter too large for the cuff, arrhythmia that interferes with automatic monitor's pulse sensing and prohibits an accurate measurement)
Any serious medical condition that may adversely affect the safety of the participant or the study (eg, patients with clinically significant peripheral vascular disease, abdominal aortic aneurysm, bleeding disorders such as thrombocytopenia, hemophilia, or significant anemia)
Scheduled or planned surgery or cardiovascular intervention in the next 6 months
Any known, unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or would be unlikely or unable to comply with study follow-up requirements
Currently enrolled in another investigational drug or device trial

2.2 Measurements

2.2.1 Office Blood Pressure

All office-based blood pressure measurements were performed using an automatic oscillometric Omron M2 HEM-7121-E blood pressure monitor (Omron Healthcare, Vernon Hills, IL). Measurements were conducted before RDN, at 30 days, 90 days and at six months. Patients seated comfortably for 5 minutes with feet flat on the ground prior to taking blood pressure measurements. For each visit measurements were done at the same arm, which was identified at screening, regarding that the arm with an implanted shunt would not be used for blood pressure measurements. Office-based blood pressures were determined by the average of three sitting blood pressure measurements taken one minute apart. Additional readings would be performed, if the lowest and highest SBP values differed more than 15 mm Hg. The last three consecutive consistent readings were recorded. The patient was excluded from the trial, if SBP values fluctuated more than 20 mm Hg after six measurements.

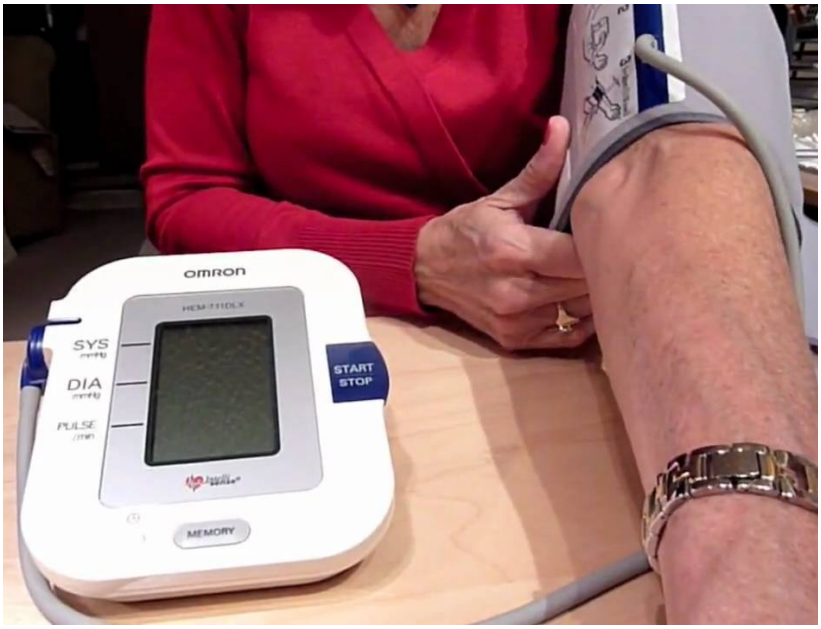


Figure 17 Office blood pressure measurement

2.2.2 Ambulatory Blood Pressure Monitoring

During the screening period, a 24-hour ABPM with a Spacelabs ABPM 90207 (Spacelabs Healthcare, Snoqualmie, WA, USA) device was performed to assess elevated blood pressure trend throughout day and night times at enrollment and at six months follow up. Readings were recorded every 15 to 20 minutes during the daytime and every 60 minutes during the night. Only ambulatory BP assessments that met the European Society of Cardiology and European Society of Hypertension guidelines (with ≥70% validity of daytime and nighttime readings) were regarded as technically sufficient for inclusion in the analysis

(Mancia, Fagard et al., 2013). Mean systolic and diastolic BP as overall 24-h average, mean systolic and diastolic BP during daytime, and mean systolic and diastolic BP during nighttime were recorded for every patient.

Furthermore, the dipping behaviors of each patient were captured at enrollment and at six months' follow-up visit. The use of the ambulatory blood pressure monitoring enabled the identification of four different patterns of the nocturnal BP profile: (1) extreme dippers, whose BP declined >20% at night, (2) dippers, whose BP decreased between 10% to 20% at night, (3) nondippers, whose BP declined <10% at night, and (4) reverse dippers, whose night BP was higher than day BP.

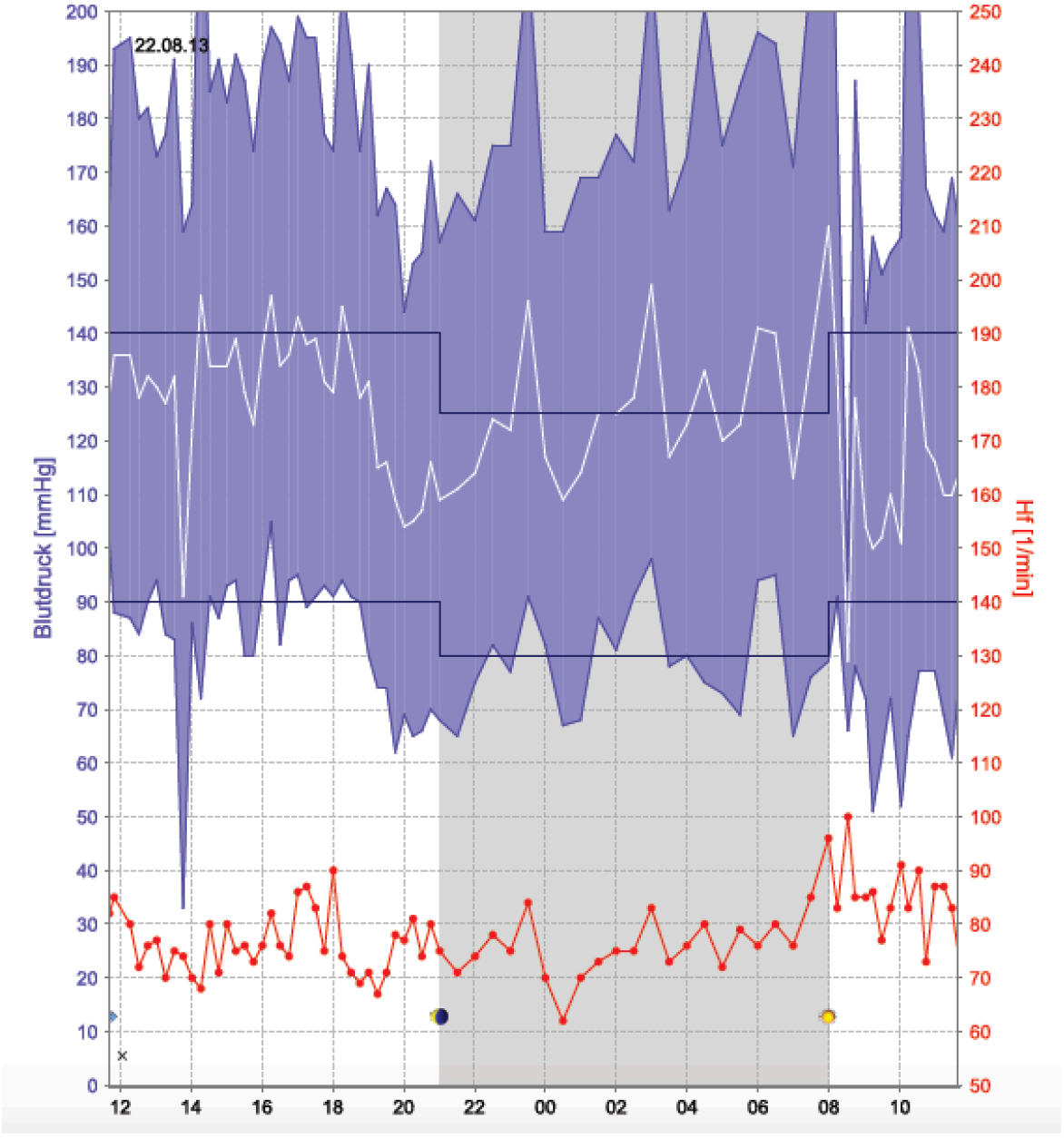


Figure 18 Ambulant blood pressure monitoring profile *recorded with HMS Hypertension Management Software; IME, Stolberg, Germany.*

2.2.3 SNS Activity Measurements

2.2.3.1 Baroreflex

For the assessment of cardiac Baroreflex sensitivity at baseline all patients underwent a simultaneous 30-min noninvasive continuous arterial BP monitoring using a finger photoplethysmographic device (Finapres; TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands) and high-resolution electrocardiographic recordings (1.6 kHz sampling of orthogonal XYZ leads, TMS International, Enschede, The Netherlands). During the recordings, patients laid in supine resting position, ideally after routine morning medications. Patients were only enrolled if they were in sinus rhythm, which is obligatory for estimation of cardiac BRS.

An experienced, technician blinded to the clinical status of the patient, verified the raw signals and eliminated artifacts. Particularly, ectopic beats were carefully removed and calibration signals within the BP signals were eliminated. QRS classifications were carefully reviewed and manually corrected as appropriate to analyze only normal sinus rhythm cycles. Cardiac BRS was evaluated from the series of RR intervals and systolic BP values by phase-rectified signal averaging (PRSA), in accordance with previously published technologies (Barthel, Bauer et al., 2012, Bauer, Barthel et al., 2009, Muller, Morley-Davies et al., 2012, Schumann, Kantelhardt et al., 2008).

The exact methodology of BRS_{PRSA} assessment has been described in publications by Bauer et al. in 2010 and Müller et al. in 2012 (Bauer, Morley-Davies et al., 2010, Müller, Morley-Davies et al., 2012). Briefly, heartbeat intervals occurring at the time of systolic pressure increases are identified within the BP time series. Subsequently, segments of R to R intervals (R-R-intervals) of an electrocardiogram near increase of systolic BP are distinguished and averaged. The resulting bivariate PRSA signal shows R-R oscillations associated to increases of systolic BP, whereas the averaging process cancels out heart rate variability due to other causes. The central amplitude of the bivariate PRSA signal is quantified by Haar wavelet analysis (Bauer, Kantelhardt et al., 2006) and normalized to the average SBP increase to obtain an estimate of BRS (Muller, Morley-Davies et al., 2012). The cardiac BRS was assessed by the sequence method (BRS_{SEQ}) (Parati, Di Rienzo et al., 1988). This method identifies progressive increases of systolic BP over three or more consecutive beats in which R-R intervals simultaneously prolong. The slope between systolic BP and R-R interval is calculated for all events, if the correlation coefficient between SBP and R-R interval is ≥0.85. BRS_{SEQ} is finally obtained by the averaging of all single slopes.

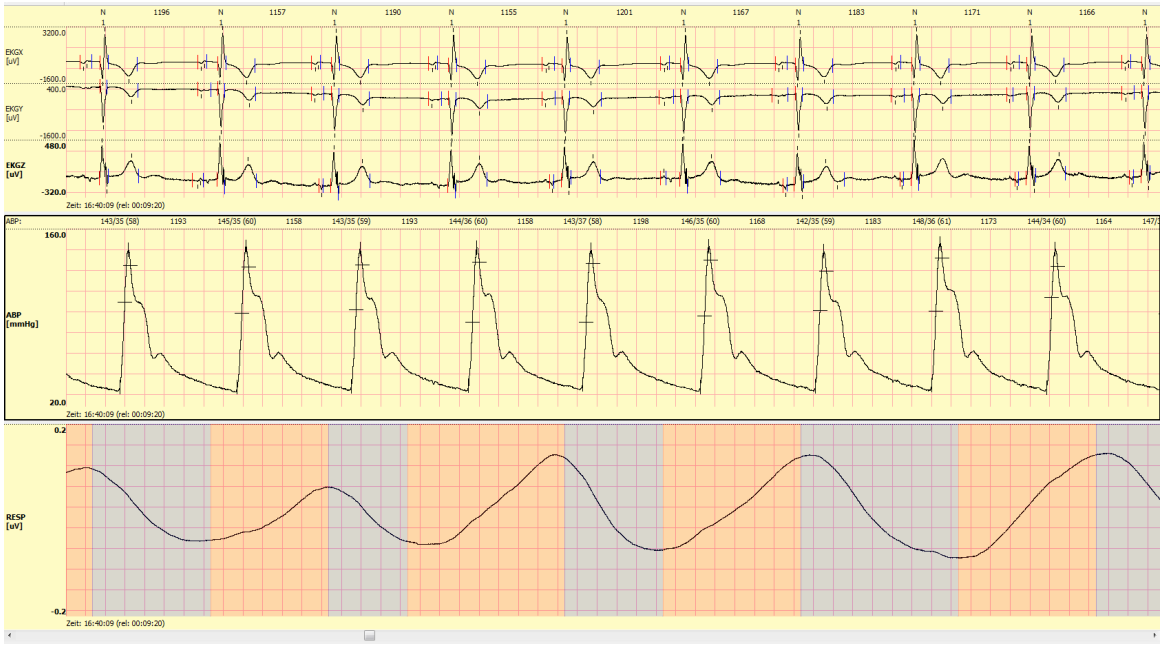


Figure 19 Sympathetic nervous system measurements *recorded with RASHlab Software; TUM, Munich, Germany.*

2.2.3.2 Heart Rate Turbulence

Simultaneously, **Heart rate turbulence** was obtained as an average response to ventricular premature complexes (VPCs) for over 30 minutes Holter recordings. An Oxford Excel Holter system (Oxford Instruments, Abingdon, UK) was used to process the Holter recordings.

Bauer et al. described the technical assessment of HRT in detail in 2008 (Bauer, Malik et al., 2008). Briefly, the R-R intervals following spontaneous VPCs are averaged to record a so-called local VPC tachogram unmasking the average pattern of sinus R-R intervals surrounding VPCs (Figure 12). For VPCs used for HRT computation it is required to fulfill exact criteria with respect to prematurity and compensatory pause. Details concerning these filter criteria have also been defined by Bauer et al. (Bauer, Malik et al., 2008). Two R-R intervals prior to the ectopic and 15 subsequently need to be identified. These are then used to analyze the turbulence onset (TO), and the turbulence slope (TS). Post-ectopic changes can only be visualized by signal averaging because these changes of cycle-length are in the range of milliseconds and masked by heart rate variability of other origin.

The acceleration starts instantly after an ectopic beat and persists for only a few R-R intervals. Subsequent declaration reaches a maximum between the third and seventh sinus cycle; the longest R-R interval usually appears close to the tenth cycle after a VPC. These variations are subtle and can be recognized only after computer algorithm. Therefore, special HRT software is used, which is commercially available on GE Healthcare and Getemed Holter systems. However, as the algorithms have been published in detail HRT (www.h-r-t.com) can also be obtained from the series of R-R intervals by a custom-made software.

2.3 Laboratory Profile

For renal transplanted patients, it is of immense importance that kidney related blood chemistry values are under regular precise control. Among these values particularly creatinine and the so-called glomerular filtration rate (GFR) should be highlighted.

Serum creatinine is an easily determinable byproduct of the muscle metabolism, which is excreted unchanged by glomerular filtration of the kidneys. Creatinine itself originates from different biological processes involving creatine, creatine phosphate, and adenosine triphosphate as further components of the processes. If serum creatinine blood levels increase it can be a first indication that the filtration in the kidney becomes insufficient. Therefore, serum creatinine is an important indicator for kidney function and can be used to calculate the creatinine clearance that correlates closely with the glomerular filtration rate.

The GFR is not a single blood chemistry value as creatinine that directly is determined from blood or serum, but rather a calculated assessment of renal activity. It estimates the amount of blood that passes through the glomeruli at each minute. The glomerulus is a network of capillaries located at a nephron in the kidney and is involved in the filtering process of the blood forming urine. The GFR is one of the most important criteria for the evaluation of the severity of renal dysfunction. Furthermore, GFR is an important therapeutic decision criterion for renal replacement therapy in patients with advanced kidney disease. Therefore, in the group of kidney transplanted patients there are more low level GFR values to be expected because a transplanted kidney does not automatically restore complete renal function as in kidney healthy people.

Varying equations are available for the GFR calculation differing in the single variables. One of the most popular ones among the leading international kidney associations is the calculation by the Cockcroft-Gault formula (Cockcroft and Gault, 1976). Necessary for the calculation of the equation are the patient's age, weight (in kilogram) and serum creatinine (in mg/dL).

Another equation is the so called MDRD-formula (Modification of Diet Renal Disease), which was introduced in 1999 by Levey et al. (Levey, Bosch et al., 1999). The MDRD formula is composed of the serum creatinine, age, sex, and race. It was evaluated on a collective of patients with known kidney disease.

The presupposed target range for this study is >30 ml/min/1,73m^2 signifying no patients suffering severe CKD are enrolled, which in turn means that the kidney function is good enough to cope the contrast agents used during the intervention of the renal denervation.

2.4 Randomization

Patients were randomly allocated to the intervention group or to the control group with sealed envelopes, containing a computer-generated sequence, in a 1:1 ratio to undergo catheter-based renal denervation. Patients were randomized after the screening period at the time of the outpatient visit. The study center used stratified randomization. Although, data analyzers have not been masked concerning treatment group assignment and blindly evaluated by independent physicians.

2.5 Renal Artery Duplex

A renal artery duplex imaging was performed prior to renal denervation treatment which results were assessed by an independent physician. If a clinically significant stenosis (e.g. renal artery to aorta peak systolic velocity ratio >3.5, or peak systolic velocity >200 cm/s with evidence of poststenotic turbulence) could be identified via ultrasound, the renal denervation would not be performed. If a stenosis was identified during the six months follow up, confirmatory angiography would be performed, and results would be compared with baseline images by an independent core laboratory.

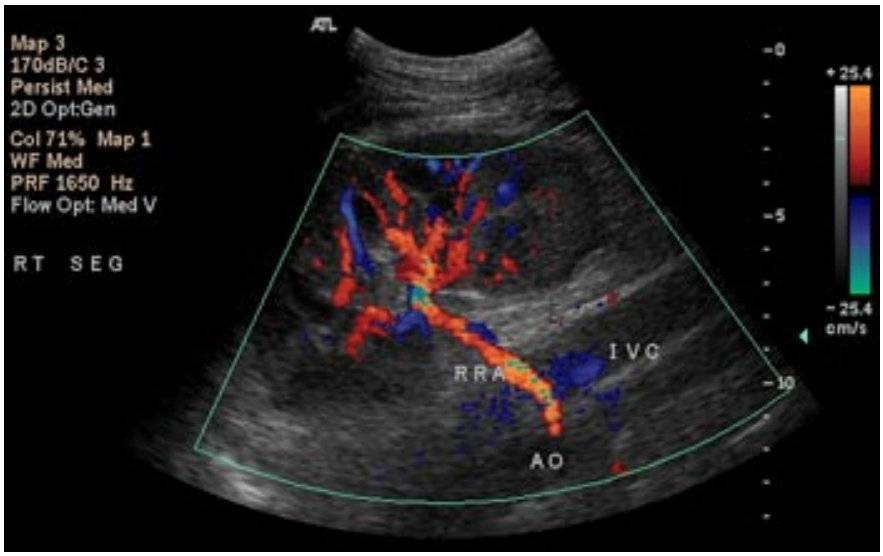


Figure 20 Color flow doppler of kidney and renal artery. *RRA, right renal artery; AO, aorta; IVC, inferior vena cava; © 2016 UC Regents.*

2.6 Renal Denervation Procedure

A specifically designed 6-Fr compatible catheter, radiofrequency generator and algorithm (Symplicity Flex™; Medtronic, Inc., Mountain View, CA, USA) were developed to realize a successful renal denervation (Figure 21) (Krum, Sobotka et al., 2011, Schlaich, Krum et al., 2011).

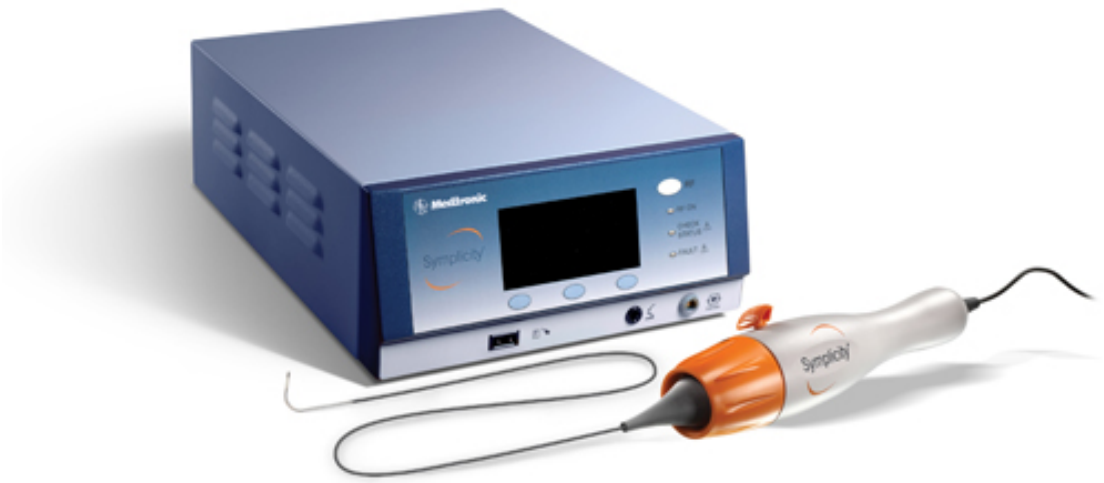


Figure 21 Symplicity G2™ Generator and Symplicity Flex™ renal denervation catheter *Printed with permission by Medtronic GmbH. © Medtronic 2016*

The ablation began with the introduction of the ablation catheter (Symplicity Flex™; Medtronic, Inc., Mountain View, CA, USA) into each native renal artery using a 6-Fr guiding catheter. The catheter is equipped with a monopolar platinum-iridium electrode at the distal tip of the catheter used in combination with a standard dispersive electrode. Through fluoroscopic guidance, the platinum-iridium tip is placed in the vasculature adjacent using the catheter's radiopaque feature. Therefore, it is possible to rotate and deflect the ablative tip to make direct hits with the vessel intima and to deliver ablative energy to various foci along the course of the renal artery. Continuous blood flow, possible through the design of the catheter, enables cooling of the renal artery intima throughout the treatment period to minimize thermal side effects on the arterial wall.

Access side were performed via femoral access of the contralateral side depending on the transplanted kidney which is regularly implanted in the iliac fossa. After placing the catheter's tip on target, treatment involves approximately six applications in both renal arteries according to an operator independent algorithm using low-power (8 W) radiofrequency energy for a total time of 120 seconds each. In case of prior abortion of ablation due to catheter tip temperatures reaching preprogrammed limits, ablation was continued after cooling, to a total application time of 120 seconds. The generator provides the radiofrequency energy per an automated algorithm designed uniquely for renal artery

ablation. The front panel displays information such as temperature, impedance, and treatment time (Figure 21). To secure a successful application, treatments are delivered in a helical pattern within the renal artery by rotation of the catheter and approximately 5 mm pullback from distal to proximal between ablations. Preclinical evaluation has determined that an ablation produces distinct focal lesions; but these lesions have no known clinically related late-term consequences to the vessel or kidney as noted in follow-up angiograms in prior studies (Esler, Krum et al., 2010). Pain during the radiofrequency delivery was managed with intravenous analgesics and sedatives. Heparin was given as anticoagulant at a dosage of 50 – 70 IU/kg. All randomized patients receiving the renal denervation treatment were hospitalized overnight post procedure and had been monitored as standard of care.

2.7 Follow-up Assessment

Both patient groups had been maintained on the baseline antihypertensive medical treatment without changes for the next six months after enrollment. The ambition was to maintain the initial antihypertensive regime. Even though, if clinically important events would have occurred, resulting in a necessary blood pressure medication revision, such alterations would have been discussed, permitted and documented.

Patients were followed three times over a total timespan of six months. Follow-ups were held one, three and six months after patients' enrollment. At one-month follow-up patients were asked for any complaints and office blood pressure was measured in the way that patients were seated comfortably for five minutes with feet flat on the ground prior to taking blood pressure measurements. Measurements were taken using the same arm as identified at screening, again regarding that the arm with an implanted shunt was not used for blood pressure measurements. Office-based blood pressures were determined by the average of three sitting blood pressure measurements, each taken one minute apart. If the lowest and highest SBP values were more than 15 mm Hg apart, additional readings were performed. The last three consecutive consistent readings were assessed. The antihypertensive medication regime was checked for any necessary adaptions. In case changes would have been necessary the patient's antihypertensive medication would have been adapted defined as an escape medication change, alterations of antihypertensive medications are permissible in the presence of an adverse event or change in symptoms, SBP <115 mm Hg or increase in SBP >15 mm Hg above baseline. Blood samples and urine samples were taken to primarily control the renal function.

At the three-months follow-up patients were asked for any discomforts, the office blood pressure was measured, and the antihypertensive medication regime was checked for any necessary adaptions.

The final follow-up examination was held six months after enrollment. Once again, the office blood pressure was measured, patients were asked for any complaints, and the antihypertensive medication regime was checked again for any necessary adjustments. Additionally, 24-hour ambulatory blood pressure monitoring was recorded from each patient. Measurements were taken using the same arm as identified at screening, regarding that the arm with an implanted shunt was not used for blood pressure measurements. Also, blood samples and urine samples were taken to among others control the renal function. Completive, a final baroreflex and heart rate turbulence measurement was recorded. Therefore, patients lay down comfortably for five minutes prior to taking baroreflex measurements. The finger photoplethysmographic device / measuring cuff was installed on the same finger as identified at enrollment, ECG electrodes were attached and recording lasted for 30 minutes in which the patient was not allowed to move lying in a supine position.

Patients were asked to hand in their own home-measured blood pressure logbooks at each stage of follow-up, which were checked for any necessary medication adaptions. Likewise, the patients were instructed to seat themselves comfortably for five minutes with feet flat on the ground prior to taking blood pressure measurements. Measurements were taken using the same arm as identified at screening, depending on the measuring device, regarding that the arm with an implanted shunt was not used for blood pressure measurements. Home-based blood pressures were determined by a daily morning and an evening measurement.

Designated study staff was responsible for performance of blood pressure measurement according to protocol-directives that include patient position and cuff size. In the presence of an adverse event or change in symptoms, SBP <115 mm Hg or increase in SBP >15 mm Hg above baseline adjustments of antihypertensive medications were permissible. This case was defined as an escape medication change, as already mentioned.

2.8 Efficacy and Safety Endpoints

The primary efficacy endpoint for this study is an achieved change in office-based systolic blood pressure from baseline to six months. The change in average 24-hour SBP by ambulatory blood pressure monitoring is the major secondary effectiveness analysis endpoint. In addition to ABPM, daytime and nighttime ambulatory BP differences from baseline to six months, as well as differences in the change between the two groups, were assessed. Furthermore, we evaluated effects on sympathetic activity by baroreflex sensitivity and heart rate variability measurements at six months compared to baseline.

Incidences of major adverse events (MAE) occurring through the first month postrandomization are primary safety endpoints. Most notably, MAE include all causes of mortality, renal artery damage and further complications (Table 7).

Table 7 Major adverse events

Through 1 months postrandomization, composite of
All-cause mortality
Significant embolic event resulting in end-organ damage (eg, kidney/bowel infarct, lower extremity ulceration or gangrene, or doubling of serum creatinine)
Renal artery perforation or dissection requiring intervention procedure, thrombin injection, or blood transfusion (requiring more than 2 units of packed red blood cells within any 24-hour period during the first 7 days postrandomization)
Hospitalization for hypertensive crisis not related to confirmed nonadherence with medications
New renal artery stenosis >70%, confirmed by angiography within 6 months of randomization

Further primary safety endpoints concern the renal function, assessed through GFR, serum creatinine, proteinuria, and renovascular complications detected by duplexsonography after RDN. An additional safety endpoint is the occurrence of a new renal artery stenosis >70% confirmed by angiography within six months after enrollment. Secondary efficacy endpoints evaluating blood pressure reduction at six months include effects on sympathetic activity assessed by heart rate variability, escape medication variations, change in office diastolic blood pressure, alteration in patient-recorded home blood pressure and hospitalizations rates (eg. hypertensive emergencies, heart failure, etc.).

2.9 Statistical Analysis Plan

This study was initially powered for the primary efficacy endpoint and for the change in mean 24-hour ambulatory systolic blood pressure at six months (secondary efficacy endpoint). The intention of this study was to assess if renal denervation is superior to medical treatment alone in kidney transplanted recipients with resistant hypertension. It was calculated that with a sample size of 20 patients per group, the study would have at least 80% power to highlight the benefit of renal denervation over control intervention. With respect to the primary endpoint, one would assume at least an 18 mm Hg difference between groups and a 20 mm Hg standard deviation of the change in systolic blood pressure from baseline to six months. GraphPad 6.0 software (GraphPad Software, La Jolla, CA, USA) was used to calculate the sample size.

Though, the further patient enrollment of the very sensitive population of transplant recipient was hampered by the results of the first sham controlled Symplicity HTN-3 trial. These results indicated that the general benefit of RDN was possibly overestimated in nonblinded studies. Therefore, a premature analysis was coherent.

All analyses were done with data for all patients at randomization minus one lost to follow-up. Categorical data are reported as numbers (percentage); continuous data are reported as mean (SD). Continuous variables between groups were assessed, including the primary endpoint, with Student's two-sample t-test unless otherwise specified. The categorical variables were compared with Fisher's exact test. The within-group paired data were evaluated by a paired t-test unless otherwise specified. A two-sided alpha level for all superiority testing was set to a level of 0.05. SPS version 20.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.

3 RESULTS

From beginning of July 2013, to March 2014, 18 out of 109 screened patients (Figure 16) were eligible and gave written consent to the study. They were randomly allocated either to the renal denervation group or to the control group. The patients' baseline characteristics, which did not significantly differ in between the groups, are shown in Table 8.

Table 8 Baseline demographic and clinical characteristics. *Data are mean (SD) or number (%). ACE, angiotensin-converting enzyme; AT1-Antagonist, angiotensin-receptor antagonist; CAD, coronary artery disease; GFR, glomerular filtration rate (* calculated based on Cockcroft-Gault formula); HbA1c, hemoglobin A1c; KTx, kidney transplantation; MI, myocardial infarction; TIA, transient ischemic attack.*

	***Renal denervation group* (n=9)**		***Control group* (n=9)**		***P-value***
Age, years	62	(9)	60	(8)	0,56
Men	7	(78)	8	(89)	0,55
Body mass index, kg/m^2	31	(6)	33	(8)	0,46
Race					
Caucasian	8	(89)	8	(89)	
Middle East	1	(11)	1	(11)	
Time since KTx, years	3,3	(1,3)	6,1	(4,2)	0,08
Current smoker	1	(11)	1	(11)	1,00
Diabetes mellitus	8	(89)	3	(33)	0,01
Obstructive sleep apnea	2	(22)	3	(33)	0,62
Stroke	2	(22)	0	(0)	0,15
TIA	1	(11)	1	(11)	1,00
Peripheral artery disease	4	(44)	1	(11)	0,13
CAD	6	(67)	5	(56)	0,65
MI	1	(11)	0	(0)	0,33
Family history of hypertension	4	(44)	5	(56)	0,66
Hyperlipidemia	6	(67)	6	(67)	1,00
Renal artery diameter	3,9	(1,49)			
Antihypertensive medication					
No. of antihypertensive agents	5,1	(1,3)	4,3	(0,5)	0,11
ACE inhibitor	5	(56)	5	(56)	1,00
AT1 antagonist	0	(0)	2	(22)	0,15
α-blocker	5	(56)	4	(44)	0,66
Aldosterone antagonist	0	(0)	0	(0)	1,00
β-blocker	7	(78)	8	(89)	0,55
Calcium channel blocker	8	(89)	9	(100)	0,33
Diuretic	9	(100)	8	(89)	0,33
Central acting sympatholytic agent	7	(78)	2	(22)	0,02
Direct-acting vasodilator	3	(33)	0	(0)	0,06

Immunosuppressive drugs					
Calcineurin inhibitors	9	(100)	6	(67)	0,06
Mycophenolic acid	9	(100)	6	(67)	0,06
Glucocorticoids	6	(67)	6	(67)	1,00
Other	0	(0)	2	(22)	0,15
Blood Pressure at baseline					
Mean office BP systolic, mm Hg	155	(14)	146	(6)	0,10
Mean office BP diastolic, mm Hg	80	(13)	79	(9)	0,82
Mean ABPM systolic, mm Hg	140	(13)	143	(12)	0,46
Mean ABPM diastolic, mm Hg	79	(8)	82	(11)	0,18
Laboratory at baseline					
Creatinine, mg/dL	1,8	(0,4)	1,9	(0,5)	0,95
GFR,* mL/min/1,73m^2	40,8	(10,2)	42,0	(9,8)	0,80
Albumin, g/dL	4,4	(0,0)	4,5	(0,3)	0,65
Creatinine, mg/dL (urine)	91,2	(0,4)	95,6	(60,4)	0,86
Total protein, g/L (urine)	119,2	(2,2)	73,4	(85,8)	0,56
HbA1c, %	6,0	(0,0)	5,4	(1,5)	0,83

Of the total 18 eventually analyzed patients, the primary endpoint for 8 patients who underwent renal denervation and 9 patients allocated to the control group was achieved. Due to missed visits and medical incompliance one patient in the denervation group could not be followed up with.

The patients in the two study groups showed similarity concerning age, sex, comorbidities, antihypertensive therapy and renal function. Patients in the control group started off with a lower baseline office systolic blood pressure than the denervation group (control group: 146 ± 6 mm Hg vs. RDN group: 155 ± 14 mm Hg).

A noteworthy difference was seen in the average number of antihypertensive drugs taken by the patients. The patients of the renal denervation group consume almost one antihypertensive drug more (5.1 vs. 4.3) compared to the control group patients. The most frequent used antihypertensive drug groups were diuretics (94% of the patients) and calcium channel blockers (94% of the patients), followed by β-blocker (83% of the patients) and ACE-inhibitors (56% of the patients).

On average, the patients' kidney transplantation was realized 4.8 years ago. Randomization resulted in an average timespan of 3.3 years for the denervation group compared to 6.1 years for the control group. We did not realize a correlation between the transplantation date and the success of the ablations.

Considering the procedural characteristics (Table 9), 7 out of 9 patients in the denervation group had a reduced vessel diameter. The mean diameter of renal arteries was 3.92 ± 1.36 mm. On average, treated patients received a total of 12.6 ± 6.2 ablations of in total 120

seconds each. 36% were repetitive ablations in case of abortion. In these patients, abortion of ablation occurred due to the catheter tip temperature limit, in most instances in the second half of the 120 seconds. After cooling down the ablation was continued in a helical pattern to a total time of 120 seconds. However, a correlation between the aborted procedure rate and response rate was not evident.

Table 9 Procedural characteristics. *Data are mean (SD) or number (%).*

Renal denervation group (n=9)		
Renal artery diameter, mm	3,90	(1,49)
Total ablations	12,6	(6,2)
Successful ablations (120 s)/patient	8,13	(2,75)
Aborted ablation attempts (60 to <120 s)	4,5	(5,5)
Contrast agent, mL	67,2	(17)

The mean change in office BP from baseline to six months after enrollment revealed considerable results as the primary efficacy endpoint of this study. Accordingly, the six months follow-up **office-based blood pressure** values in the renal denervation group showed a significant decrease by 23/9 mm Hg (±14.5/8.7 mm Hg) (P = 0.003 for SBP and P = 0.02 for DBP) from 157/83 mm Hg (±12.5/12.8 mm Hg) at baseline to 134/74 mm Hg. However, office-based BP measurements did not change in the control group; only an alteration of +1/-1 mm Hg (±13/10.1) from 147/79 mm Hg (±5.3/9.6) at baseline was recorded (P = 0.77 for systolic and P = 0.77 for diastolic blood pressure). Therefore, a significant reduction difference of 24/8 mm Hg in office-based blood pressure between the two groups was determined (P < 0.001 for systolic and P = 0.09 for diastolic blood pressure) at the time of the six-months follow-up (Figure 22 & 23).

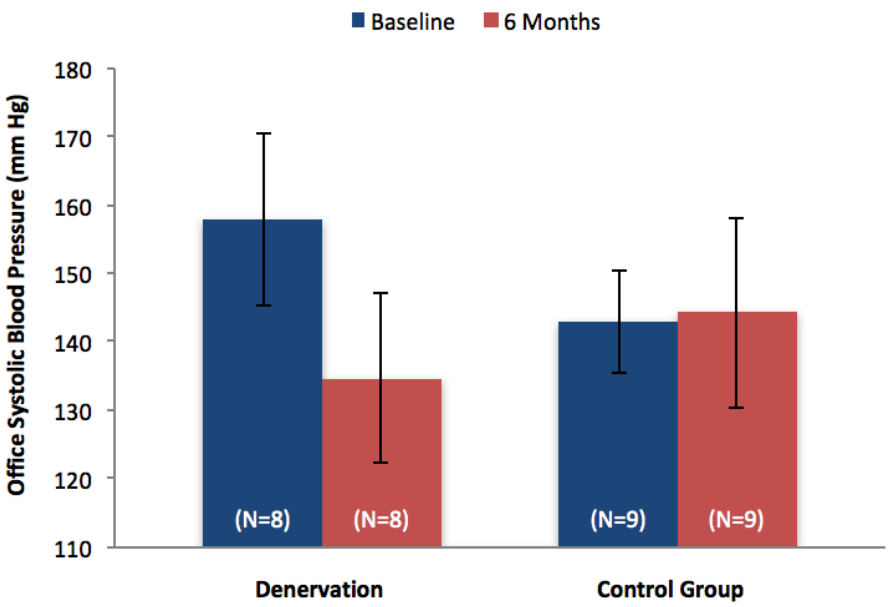


Figure 22 Primary efficacy endpoint, change in systolic office blood pressure. *P=0.003*

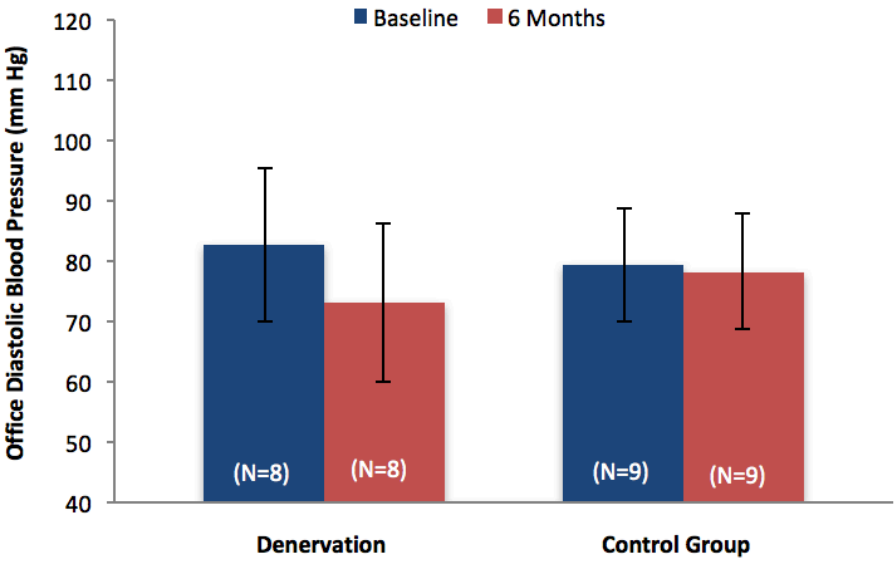


Figure 23 Primary efficacy endpoint, change in diastolic office blood pressure. *P=0.02*

In the process of the 30 days, 90 days and finally 180 days follow-ups the office systolic BP values decreased constantly in the RDN group (Figure 24).

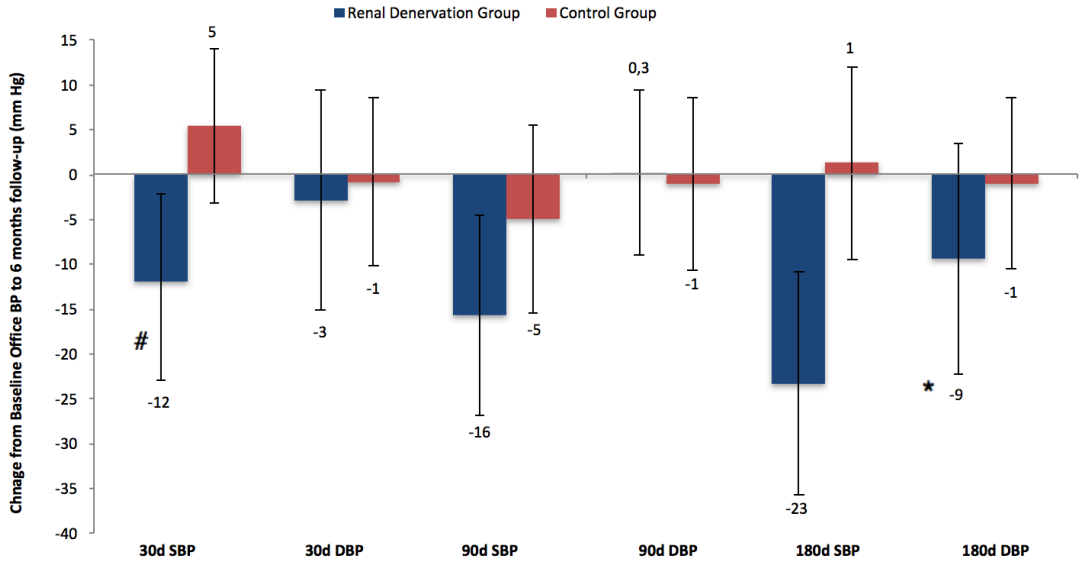


Figure 24 Primary efficacy endpoint, paired changes in office-based blood pressure after 30 days, 90 days and 180 days. *#P=0.003, *P=0.02; d, days; DBP, diastolic blood pressure; SBP, systolic blood pressure.*

The ambulatory blood pressure monitoring values had to be considered in more detail to outline the changes in between the study arms. We recorded differently pronounced changes for the separate ABPM subcategories (Figure 25).

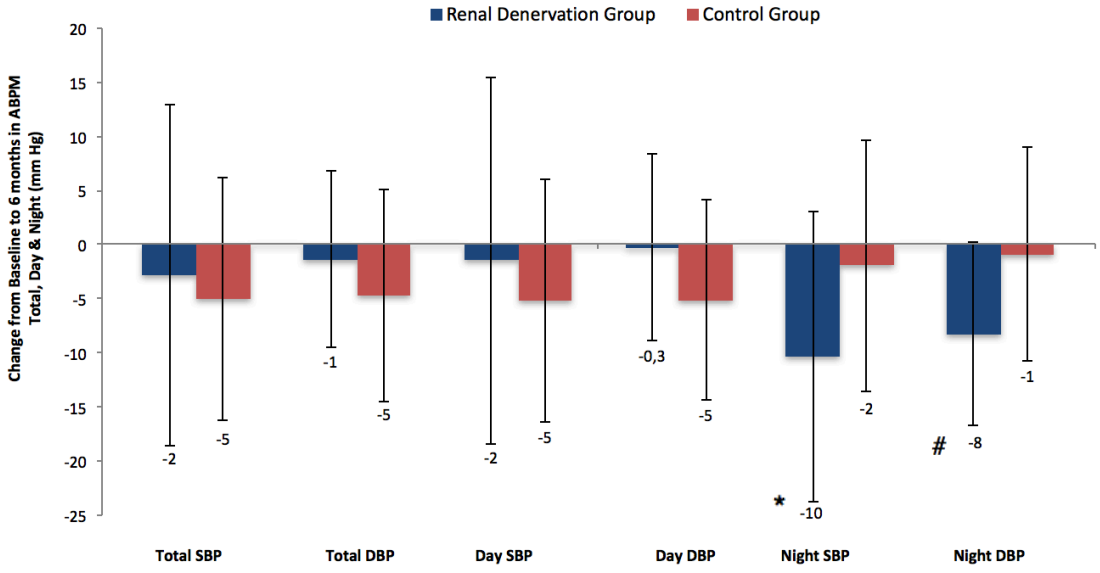


Figure 25 Secondary efficacy endpoint, paired changes in overall ambulatory blood pressure monitoring, at daytime and nighttime after 6 months. *#P_{DEN} = 0.21, #P_{CG} = 0.21, *P_{DEN} = 0.18, *P_{CG} = 0.53; ABPM, ambulatory blood pressure monitoring; CG, control group; DEN, renal denervation group; DBP, diastolic blood pressure; SBP, systolic blood pressure.*

Surprisingly, no significant changes in overall mean **ABPM**, neither for systolic nor diastolic values, were recorded in the denervation group (-2.88/-1.38 ± 11.1/6.0 mm Hg, P = 0.21 for SBP and DBP P = 0.18) or control group (-5.0/-4.67 ± 11.1/9.6 mm Hg, P = 0.21 for SBP and P = 0.53 for DBP) (Figure 26 & 27).

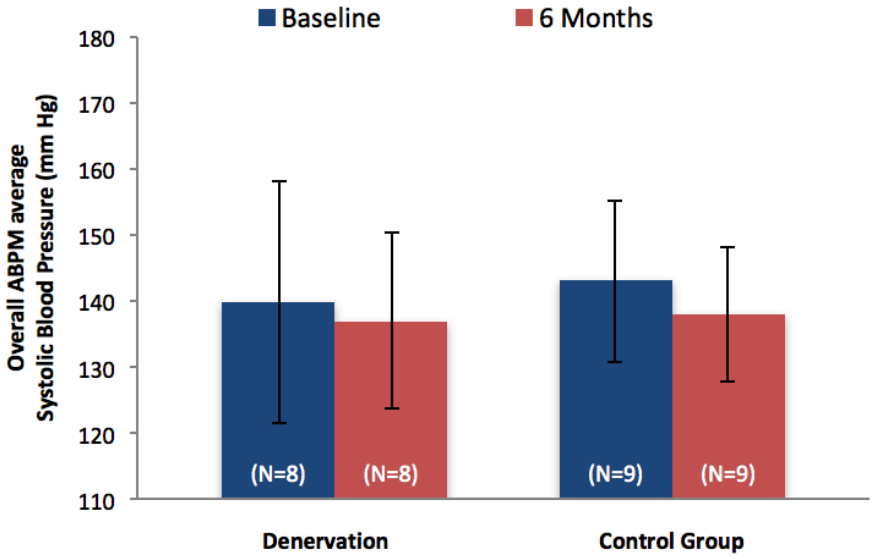


Figure 26 Overall average ambulatory blood pressure measurements for <u>systolic</u> blood pressure. *P_{DEN} = 0.21, P_{CG} = 0.21; ABPM, ambulatory blood pressure monitoring; CG, control group; DEN, renal denervation group.*

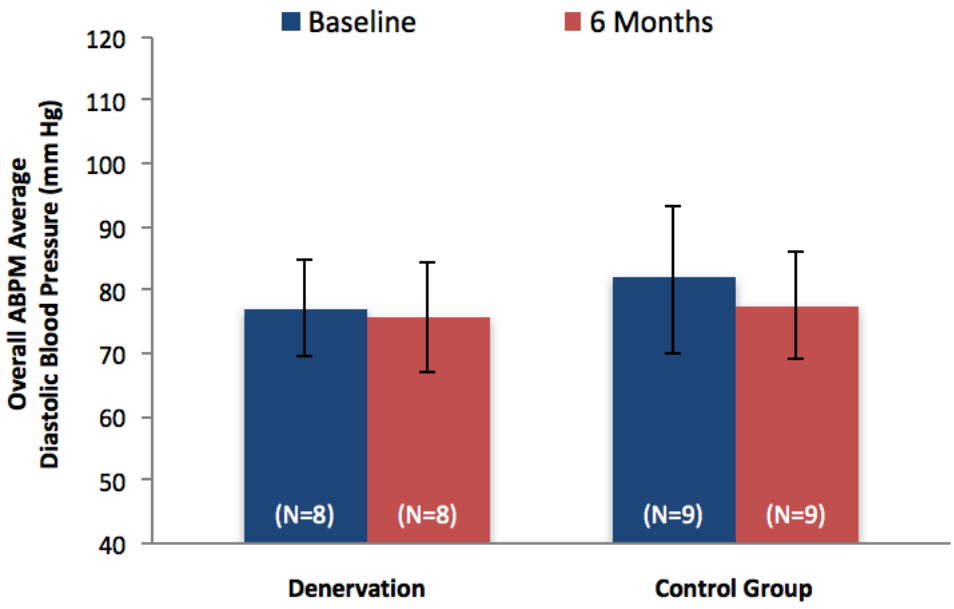


Figure 27 Overall average ambulatory blood pressure measurements for <u>diastolic</u> blood pressure. *P_{DEN} = 0.18, P_{CG} = 0.53; ABPM, ambulatory blood pressure monitoring; CG, control group; DEN, renal denervation group.*

Analyzing only the **daytime** results there was only a minimal change in the denervation group (1.5/-0.25 ±13.4/7.7 mm Hg; SBP P = 0.76, DBP P = 0.93) though a slight change of -5.18/-5.1 ±12.17/9.7 mm Hg (SBP P = 0.25, DBP P = 0.15) in the control group (Figure 28 & 29).

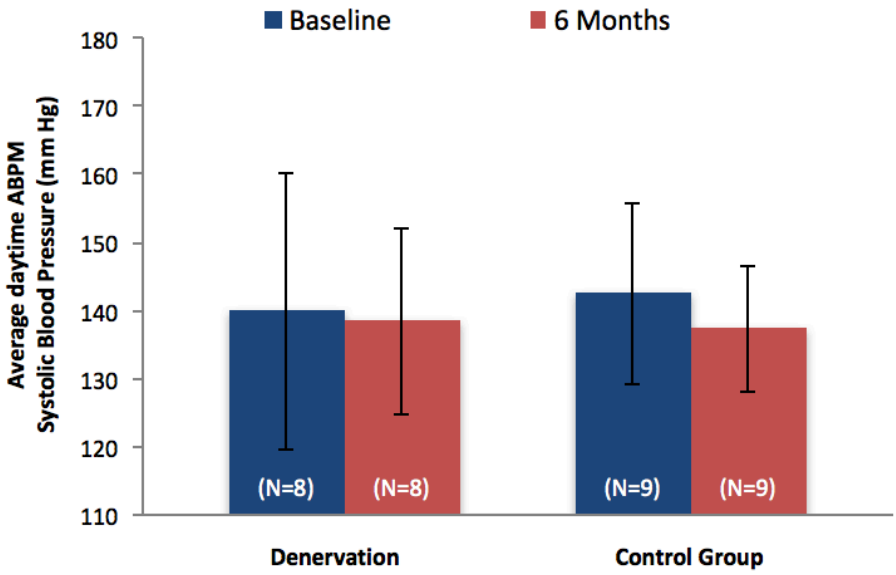


Figure 28 Average <u>daytime systolic</u> ambulatory blood pressure monitoring results from baseline to six months. *P_{DEN} = 0.76, P_{CG} = 0.25; ABPM, ambulatory blood pressure monitoring; CG, control group; DEN, renal denervation group.*

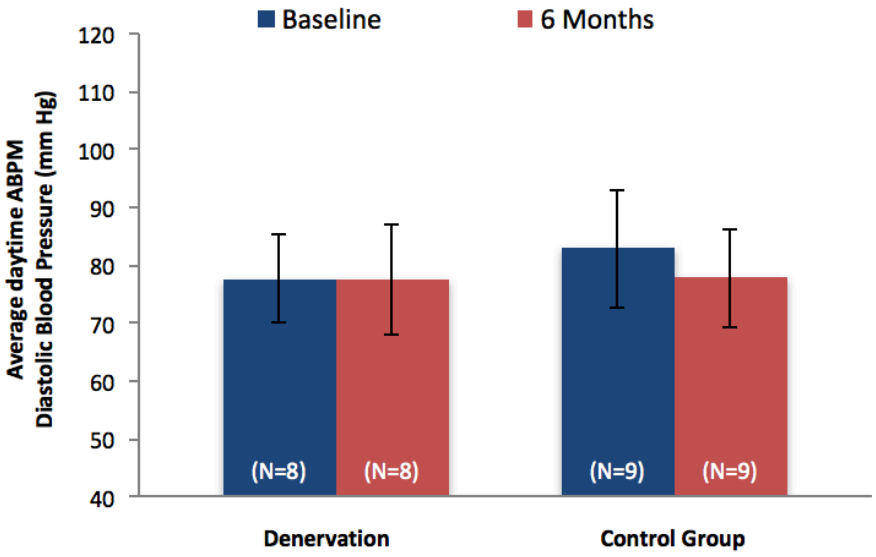


Figure 29 Average <u>daytime diastolic</u> ambulatory blood pressure monitoring results from baseline to six months. *P_{DEN} = 0.93, P_{CG} = 0.15; ABPM, ambulatory blood pressure monitoring; CG, control group; DEN, renal denervation group.*

Contrary, analyzing just the **systolic nighttime ABPM** results after six months, values changed -10.38 ± 12.8 mm Hg (P = 0.06) in denervation group versus -1.97 ± 12.2 mm Hg (P = 0.64) in the control group (Figure 30). Concerning the **diastolic ABPM at nighttime** a decrease of 8.3 ±12.17 mm Hg (from 76.1 ± 9.3 to 67.8 ± 10.2 mm Hg; P = 0.09) was recorded in the denervation group versus 0.9 ± 9.9 mm Hg (from 78.2 ± 13.0 mm Hg to 77.3 ± 10.1; P = 0.8) in the control group (Figure 31). Eventually, the difference in nocturnal ABPM change between the groups was systolic 12.35 mm Hg (P = 0.18) and diastolic 7.4 mm Hg (P = 0.19).

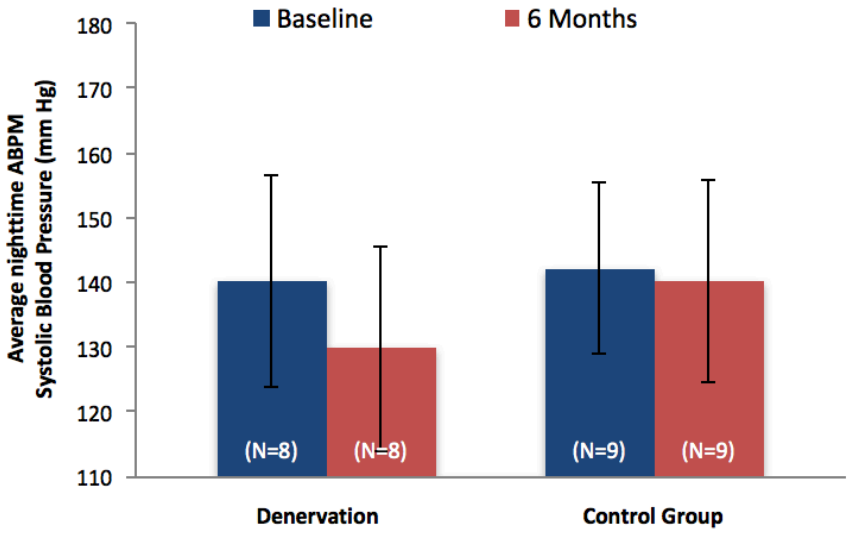


Figure 30 Average <u>nighttime systolic</u> ambulatory blood pressure monitoring results from baseline to six months. *P_{DEN} = 0.06, P_{CG} = 0.64; ABPM, ambulatory blood pressure monitoring; CG, control group; DEN, renal denervation group.*

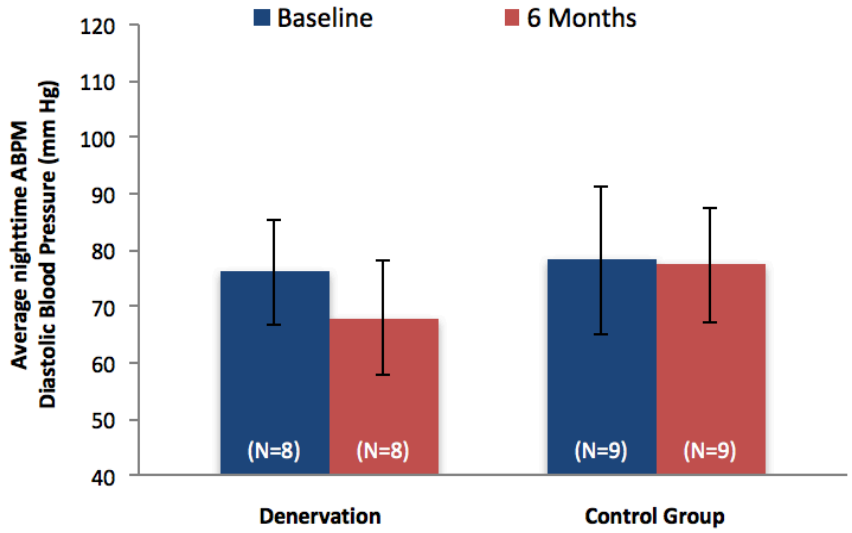


Figure 31 Average <u>nighttime diastolic</u> ambulatory blood pressure monitoring results from baseline to six months. *P_{DEN} = 0.09, P_{CG} = 0.8; ABPM, ambulatory blood pressure monitoring; CG, control group; DEN, renal denervation group.*

Studying the **dipping behavior**, on the one hand in the denervation group 3 patients converted from non-dippers to dippers, and on the other hand no conversions were observed in the control group (P = 0.035). In 50% of the denervation group patients the **nocturnal diastolic BP** improved significantly by more than 10% in comparison to just one patient of the control group (Figure 32). Altogether, there were no patients with an extreme dipping behavior in neither of the two groups.

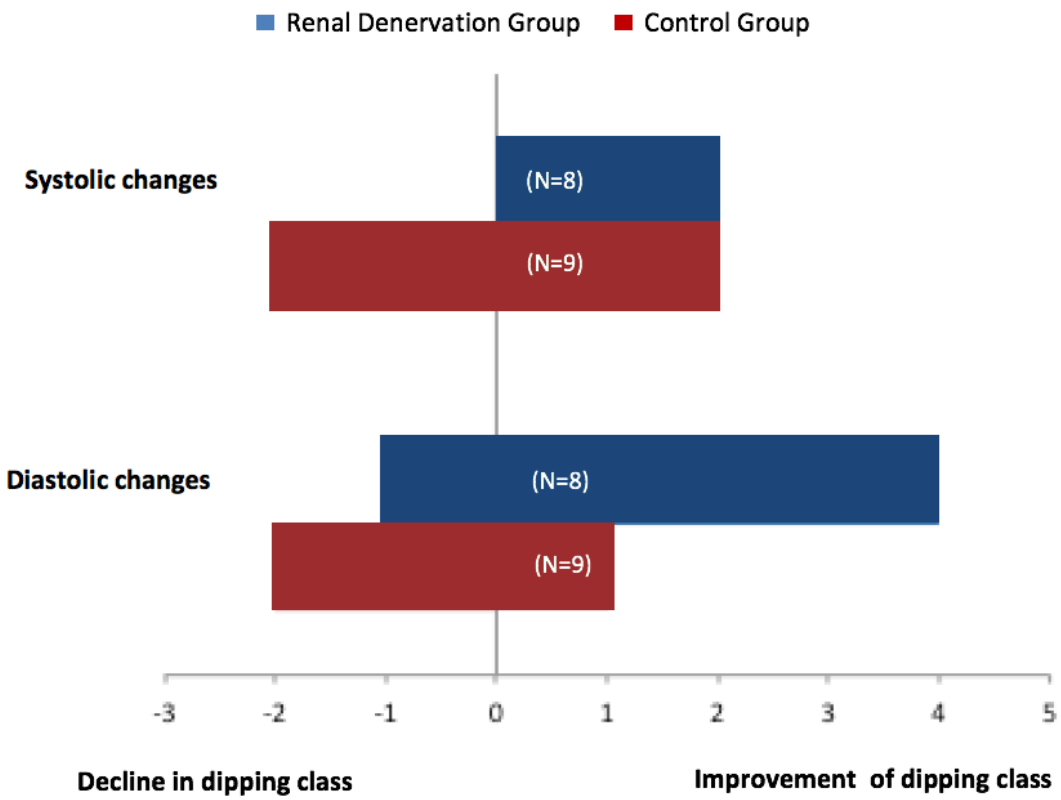


Figure 32 Change in nocturnal dipping behavior at 6 months. *Number of patients with improvement of nocturnal BP dipping >10% versus decline in nocturnal BP >10%. P*

The recorded median spontaneous **baroreflex** sensitivity (BRS_{PRSA}) at baseline was 1.1 ms/mm Hg (interquartile range (IQR) 0.50 – 3.32 ms/mm Hg). In the denervation group baroreflex sensitivity had improved in 6 of 7 patients at six months follow-up (median $DBRS_{PRSA}$ 0.52 ms/mm Hg, IQR 0.07 – 1.60 ms/mm Hg). For one patient of the denervation group, pre-procedure BRS data was unavailable due to technical issues. Contrary, in the control group baroreflex sensitivity had improved in just 3 but worsened in 6 patients after six months (median $DBRS_{PRSA}$ -0.50 ms/mm Hg, IQR -2.2 – 0.29 ms/mm Hg) (Figure 33). However, there was no significant correlation between an increased BRS and BP values nor in dipping behavior in any patient.

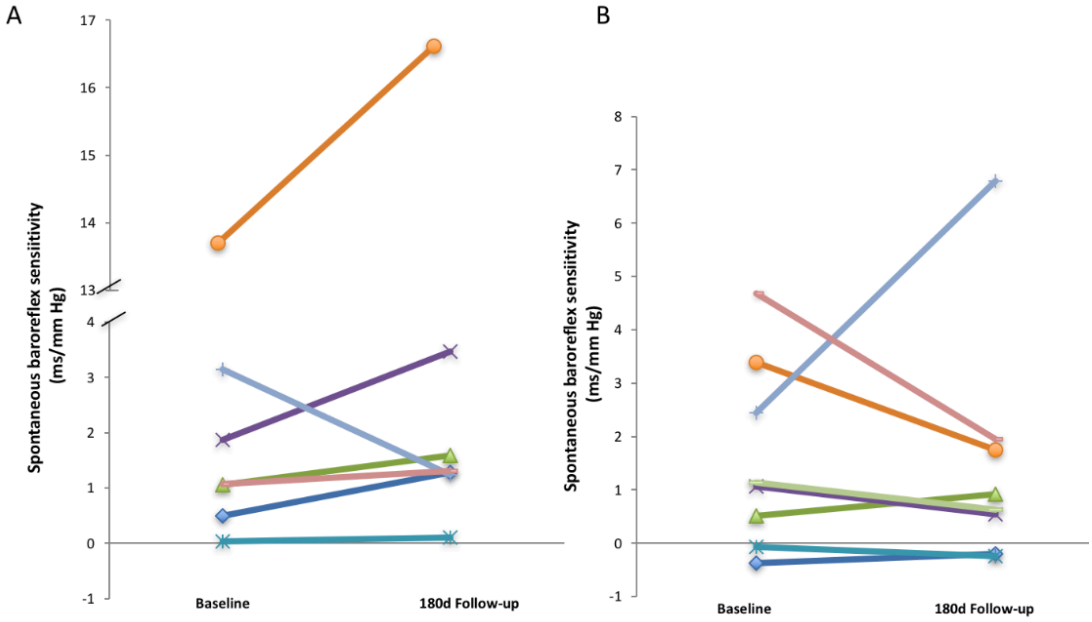


Figure 33 Individual spontaneous baroreflex sensitivity (BRS_{PRSA}) at baseline and after 6 months. *(A) Renal Denervation Group, (B) Control Group. Data are expressed as ms/mm Hg.*

Generally, there were insufficient VPCs measured for significant analysis in both groups. Consecutive, heart rate turbulence results could only be determined in two patients of the ablation group and in none of the patients in the control group.

Considering the enrollment **glomerular filtration rate** the RDN group (39.9 ± 10.5 mL/min/1.73m^2) started off with a slightly lower baseline GFR than the control group (42.9 ± 9.9 mL/min/1.73m^2). Looking at the one month follow-up values a minimal improvement was seen in the RDN group (40.5 ± 10.9 mL/min/1.73m^2) compared to a minor deterioration in the control group (40.9 ± 10.1 mL/min/1.73m^2). After six months, this trend remained the same – RDN group evened out around the improved level (40.6 ± 13.5 mL/min/1.73m^2) compared to decreasing control group values (38.8 ± 12.0 mL/min/1.73m^2) (Table 10). For serum creatinine, there was no change after 48h post-procedure (P=0.8) after the ablation and slight increase after six months (P=0.62) in both groups (0.36 mg/dL in the RDN group vs. 0.08 mg/dL in the control group). Concerning the further patients' laboratory results, it turned out that the excess of serum proteins in the urine decreased. Proteinuria reduced at six months follow-up in the ablation group by an average value of 94.6 ± 153.7 mg/dL compared with a change of 32.5 ± 62.1 mg/dL in the control group.

Table 10 Safety Endpoints. *Values are mean (SD), change from baseline to 6 months and difference in change in measured concentrations of eGFR (mL/min/1.73 m^2), serum creatinine (mg/dL) and proteinuria (mg/dL) for renal denervation and control groups. eGFR was calculated based on Modification of Diet in Renal Disease Study criteria.*

	Denervation group				**Control group**						
	Baseline		Mean change		Baseline		Mean change		Difference in mean change in (95% CI)		P-value
eGFR	39,9	(10,5)	-2,15	(2,8)	42,9	(9,9)	-1,37	(2,8)	3,52	(-5.1–12.14)	0,39
Serum creatinine	1,9	(0,4)	-0,1	(0,6)	1,9	(0,5)	-0,07	(0,6)	-0,04	(-0,19–0,12)	0,62
Proteinuria	133,4	(226,9)	-94,6	(153,7)	73,5	(83,8)	-32,5	(62,9)	-62,1	(-180.5–56.4)	0,31

Unfortunately, two patients developed a pseudo-aneurysm at the femoral vascular access site. Both could be managed conservatively by pressure application or thrombin injection without any sequelae.

Altogether, safety endpoints were not reached in any of the patients.

4 DISCUSSION

The primary **intention** of this randomized, non-blinded investigation was to demonstrate the feasibility and safety of renal artery denervation in the group of kidney transplanted patients suffering resistant hypertension. As well as to realize a reduction in blood pressure through a functional nephrectomy via bilateral radiofrequency ablation of the renal sympathetic nerves. The expected blood pressure reduction by renal denervation is based on two mechanisms: (1) central sympathetic inhibition consequential from destruction of renal afferent nerves and (2) ablation of the postganglionic sympathetic nerves directed to the kidneys (Hering, Lambert et al., 2013, Schlaich, Sobotka et al., 2009b).

4.1 Was the trial capable of achieving efficacy endpoints?

Based on our **results** this trial validates the feasibility and safety of renal denervation in this population. The study demonstrates the positive impacts of renal denervation on the primary endpoint of office based BP as well as an improvement of nighttime ABPM in the renal denervation group. However, the results fail to show a distinct reduction in overall ABPM and daytime ABPM.

In analyzing the results successively, we determine that the recorded reduction in **office-based BP** in renal transplanted patients is significant and moreover consistent with previous non-blinded studies of renal denervation in patients with resistant hypertension (Bhatt, Kandzari et al., 2014, Esler, Bohm et al., 2014, Kandzari, Bhatt et al., 2012).

At first sight, there was no significant decrease in overall **ABPM** after six months in our trial, which is concordant with the largest sham-controlled study, the Symplicity HTN-3 trial (Bhatt, Kandzari et al., 2014, Kandzari, Bhatt et al., 2012). The baseline ABPM levels of our entire cohort are lower compared to previous trails because of severe blood pressure limit in CKD patients, resulted from the enrollment process with lower exclusion limits for ABPM than for office BP. Apparently, the differences between ABPM and office BP in kidney transplant patients appear to be more distinct than in other hypertensive patients (Fernandez Fresnedo, Franco Esteve et al., 2012). These low baseline values in ABPM and the small number of enrolled patients might be responsible for the absence of a pronounced BP reduction in the ABPM in this trial. Hence, it should be considered to exclude patients with ABPM levels ≤130 mm Hg at baseline in future trials.

Interestingly, analyzing the difference between day and night time measurements more detailed, a substantial reduction of ABPM at nighttime was observed. Contrary, no changes could be observed during daytime recordings. In the Symplicity HTN-3 trial with kidney-healthy patients a similar effect was recognized (Bhatt, Kandzari et al., 2014, Kandzari, Bhatt

et al., 2012). Yet the reduction appears to be more pronounced in the collective of kidney transplanted patients.

Investigating the **dipping behavior** of the renal transplanted patients, the number of conversions from reverse-dipper or non-dipper at baseline to the physiological state dipper after six months was significantly higher in the ablation group. Comparable results were published recently by Schlaich et al. (Schlaich, Bart et al., 2013) who observed comparable dipping conversions already in chronic kidney diseases patients after RDN. Also in the Symplicity HTN-3, transformation from non-dippers to dippers was also higher in the denervation group but not significantly (Bakris, Townsend et al., 2014). In kidney transplant recipients and CKD patients these effects could be explained by the higher value of sympathetic-overactivity in persistent hypertension (Hausberg, Kosch et al., 2002, Nakano, Oshima et al., 2001).

It was also shown that the re-establishment of renal function through a kidney transplantation does not simultaneously normalize muscle sympathetic nerve activity which is associated with resistant hypertension, if the native kidneys remain in situ. Only kidney transplantation combined with bilateral nephrectomy enables the state of normalized sympathetic nerve activity (Converse, Jacobsen et al., 1992, Hausberg, Kosch et al., 2002). It is assumed that the increased sympathetic nerve activity appears to be conveyed by signals in the native kidneys (Hausberg, Kosch et al., 2002). In 1992, Converse et al. (Converse, Jacobsen et al., 1992) could already observe similar results for patients who suffered server CKD and did not yet have a kidney transplant. They determined a 2.5 times higher mean rate of sympathetic-nerve discharge in the patients receiving hemodialysis but who did not undergo a bilateral nephrectomy treatment.

To evaluate the effects on **sympathetic nerve activity** of a neurofunctional nephrectomy by catheter ablation the kidneys function was considered for the secondary endpoint of this trial. By analyzing baroreflex behavior as surrogate parameter, with cardiac BRS measurement it was possible to assess the autonomic nervous activity. Impaired cardiac BRS, frequent in hypertensive patients, has been associated with sympathetic overactivity (Bristow, HONOUR et al., 1969, Gribbin, Pickering et al., 1971). Furthermore, it has been shown that impaired BRS may predict response to RDN in patients with resistant hypertension (Zuern, Eick et al., 2013). It is difficult for us to issue any confident statement about whether this holds true for resistant hypertension in the certain group of kidney transplanted patients, due to the small sample size. Although, a BRS improvement after six months was recognized in the RDN group compared to no development in the control group. This observation emphasizes the pathophysiological concept that RDN of native non-functional kidneys decreases sympathetic tone in the certain group of kidney transplanted patients.

As mentioned, the impact of RDN treatment on renal function is one of the major concerns in kidney transplanted patients. Due to RDN being an invasive treatment, it is necessary for certain values of endogenous organ function to be monitored closely. In our trial, all patients' **renal function** remained in physiological range so that in this regard there was no need to take safety endpoints into consideration. The renal function is a sensitive issue especially for our specific patient collective. All patients had already experienced what it meant to live with no or almost no endogenous renal function, which is why the concern of renewed loss of kidney function was omnipresent. Therefore, we monitored renal function closely. Different to the Symplicity trials and other previous RDN trials we enrolled patients with an **eGFR** even lower than 45 mL/min/1.73m^2 but >30 mL/min/1.73m^2 (after Cockcroft-Gault (Cockcroft and Gault, 1976)) and serum **creatinine** levels up to 2.5 mg/dL. In consultation with the nephrology department of our clinic, we agreed that an eGFR level of ≥30 mL/min/1.73m^2 ensures sufficient renal function for kidney transplanted patients. The amount of contrast agent used during the interventions was as small as possible, so that the kidneys were not too strained. Patients with eGFR <30 mL/min/1.73m^2 and serum creatinine >2.5 mg/dL were excluded. After six months, we recognized a contrary result as we expected for the renal function indicator values. Changes were neither significant nor severe as on the one hand serum creatinine values increased minimally in both groups and on the other hand the eGFR values improved albeit only slightly in the ablation group but decreased in the control group. One would expect that the treated kidneys are more stressed through mechanic manipulation and contrast agent and thus consequently renal function would rather decrease instead of persist or even slightly improve. Whether, and if so under what mechanism, the eGFR values are influenced positively by the RDN procedure, was not possible for us to determine. Mahfoud et al. evaluated the renal function and hemodynamics after RDN (Mahfoud, Cremers et al., 2012). They detected that RDN reduced the BP, the renal resistive index, and the incidence of albuminuria without adversely affecting eGFR or renal artery structure within six months. A further study that investigated the success of RDN depending on the eGFR levels showed that if eGFR was >45 mL/min/1.73m^2 the responding rate was instantly higher but also for patients with eGFR <45 mL/min/1.73m^2 at enrollment a steady improvement was observed (Kiuchi, Chen et al., 2014).

For our trial, a reduction in **proteinuria** was found in the denervation group after six months. Common observations were published recently in a study on a larger group of patients that shows comparable decrease for albuminuria in hypertensive patients after renal denervation (Ott, Mahfoud et al., 2014). A further important aspect for kidney transplanted patients was published by Amer et al. (Amer, Lieske et al., 2013), who determined that lower proteinuria levels are linked to extended graft survival.

Concerning the **safety** of RDN procedures our trial was performed without any major complications. Conjuring up adverse events they include renal artery dissection and perforation, significant embolic event resulting in end-organ damage, late stenosis or promotion of artheroma in renal artery in long term, and hospitalization for hypertensive crisis not related to confirmed nonadherence with medications. Also during our follow-up period of six months no further complications occurred. Therefore, we can consider the renal denervation as a safe treatment in kidney transplanted patients. Additional available data on treated patients, with overall clinical follow-up as long as almost ten years, suggests excellent vascular safety except very few instances of fibrous stricture at the site of energy delivery or slight renal artery stenosis from renal artery atherosclerosis (Krum, Schlaich et al., 2009, Krum, Schlaich et al., 2014, Vonend, Antoch et al., 2012). It is possible that vessel spasm could appear during energy applications, however it can be reversed by nitroglycerin or verapramil. RDN remains an invasive procedure with the possible risk of injury, investigated in a study that showed the occurrence of vascular damage with radiofrequency ablation of renal nerves in pigs (Steigerwald, Titova et al., 2012). Consequentially, endothelial-intimal edemas might occur and furthermore the formation of a thrombus in renal arteries after RDN in humans has been described by optical coherence tomography, although not visible on angiography (Templin, Jaguszewski et al., 2013). To avoid this risk, our patients received preventative Heparin at a dosage of 50 – 70 IU/kg during the RDN procedure.

4.2 Not time yet to ring the death knell for RDN – Troubleshooting

At the time of the first positively implemented RDN treatments there was a lot of enthusiasm and confidence in the success of RDN. Before ringing the **death knell** on RDN now, because of not enough pronounced BP reduction, one first should consider the possible explanations for the not in this manner expected outcomes. One will notice, on the one hand arguments criticizing the method and implementation of renal denervation and on the other hand arguments supporting the use and further development of RDN. Detractors argue that previously published results have falsely misled into supposing that this novel therapy could eventually treat resistant hypertension more successfully but now in their eyes RDN is conveyed to be an ineffective method for treating (resistant) hypertension (Laffin and Bakris, 2016). In contrast, supporters argue that there is preclinical data available that shows the integration of the renal sympathetic nervous system in hypertension (Campese, Ku et al., 2011) and in heart failure (Floras, 2009), thus providing support for this treatment strategy in general, although there are necessary adjustments in the different approaches.

4.2.1 Patient enrollment

The **selection of potential patients** is a fundamental factor influencing the success of the treatment. Patients with office SBP ≥140 mm Hg and elevated SBP in ABPM despite taking at least three antihypertensive medications, of which one is a diuretic, were enrolled in our study. These values are the cut off set by the ESH for the definition of arterial hypertension (Mancia, Fagard et al., 2013). It has been shown that the higher the enrollment BP level, the higher the reduction achieved by the RDN (Krum, Schlaich et al., 2014, Lobo, Saxena et al., 2015).

Critics faulted that for the first two Symplicity HTN trials no ABPM were recorded. We considered this criticism in our trial and therefore changed the inclusion criteria, as well done in the Symplicity HTN-3 trial and in the EnligHTN-I trial. Certainly, the importance of ambulatory blood pressure monitoring cannot be underestimated. In comparison to office-based measurements, ABPM recordings reduce measuring errors, adjust observer bias, have a higher reproducibility rate, minimize the white-coat effect, and, most importantly, provide more precise prognostic information (Hansen, Kikuya et al., 2007, Salles, Cardoso et al., 2008). Moreover, the white-coat effect is a frequent source of error, emphasized by a study that determined a misallocation of 37.5% of 8295 patients classified to suffer resistant hypertension based only on office readings (de la Sierra, Segura et al., 2011). This fraction was thereupon reclassified and diagnosed with white coat hypertension after ABPM recordings were analyzed. As already mentioned, the first Symplicity trials and other earlier RDN trials did not demand a ABPM, which may have led to enrollment of individuals rather suffering secondary causes of resistant hypertension, as white coat hypertension, and as a further consequence not showing any response to RDN treatment. Considering our enrollment ABPM recordings, due to patients' appointments it was not feasible that ABPM devices were installed after all clinical investigations were completed, so that patients stayed in a clinical environment for their first recordings. Additionally, the devices could have caused a higher patients' attention to their behavior towards their blood pressure resulting in slightly different values than usual. In our study, there is the chance that in one single case the enrollment SBPs were not pronounced enough, especially in the ABPM measurements, possibly explaining the just slight to mild BP reductions.

4.2.2 Antihypertensive medication and patients' compliance

As mentioned in the introduction, post-transplant patients and patients suffering CKD are often affected by high BP values, which is linked with increased cardiovascular morbidity and mortality (Mange, Cizman et al., 2000). Over 25 – 50% of these patients are non-compliant with intermittent omission of drugs, thus leading to an increase of the likelihood of acute rejection rates, graft loss and death (Butler, Roderick et al., 2004). **Medication non-**

adherence rises with an increasing total number of drugs, complexity of the medication regimes and transplant duration (Morrissey, Flynn et al., 2007). Due to the complexity of their underlying disease, the treatment of kidney transplanted patients requires a complicated compilation of numerous different drugs, as antihypertensive and immunosuppressant drugs.

If BP values did not change as fast as the patients might have expected it to change despite antihypertensive medication, they may have lost motivation and become careless in administering their (antihypertensive) medications properly. Otherwise, it is known, that patients in clinical trials would be more focused and motivated to pay attention to their intake of antihypertensive medication, their BP levels and diet during their study participation, referred to as the Hawthorne effect (Gale, Beattie et al., 2007, McCambridge, Witton et al., 2014). The similar overall ambulatory BP decreases in the control group may be partly attributed to the Hawthorne effect, even in kidney transplanted patients with multiple medication.

Considering the **antihypertensive medication** at enrollment patients of the ablation group were administered one more antihypertensive on average (5.1 antihypertensive drugs) than the control group patients (4.3 antihypertensive drugs). However, the differences in the medication regime between the ablation group and the control group were not significant. Central acting sympatholytic agents and direct acting vasodilator drugs were higher represented in the ablation group and Angiotensin-1 antagonists in the control group.

One of the most challenging problems for the correct **antihypertensive drug regime**, besides the decrease of BP values in general, is a possible interaction between patients' concomitant diseases' medication and the collaboration of the single antihypertensive drugs. The available variety of medication enables innumerable possible combinations of the single drugs, not to mention the appropriate dose adjustment. When the most suitable combination is finally found, it is the responsibility of the patient to follow this regime and take these drugs regularly with the correct dosage. Unfortunately, not all patients stick to their drug regime. Therefore, optimization should be achieved by continuously monitoring serum and urine throughout the entire trial.

Patients' practitioners were informed of the patients' participation in this study. Therefore, unnecessary changes in the antihypertensive regime, which could falsify final results, should have been prevented for the duration of the study. In the context of our study, it is unfortunately possible that enrolled patients may have had unreported adjustments, but it is not comprehensible because of missing documentation of the practitioners practice. As in the Symplicity trials, the only way to evaluate medication compliance was by patient verbal report, because the more objective option of assessing medication compliance by checking plasma

or urine drug levels, was not conductible due to patients' denial. Regarding a further typical prescribed medication for renal transplanted patients, immunosuppressants as calcineurin inhibitors promote vasoconstriction, possibly enhance activation of renal afferents (Zhang, Li et al., 2000) and in this concern the sympathetic nervous system (Scherrer, Vissing et al., 1990). These reasons suggest that especially the group of kidney-transplanted patients is an important target audience for RDN and why further studies for improving ablation techniques are necessary.

4.2.3 Altered anatomy

One might wonder, why did previous studies on renal denervation did not take kidney transplanted patients or patients with CKD into consideration earlier, despite the high potential in these groups. The question arises, if altered anatomy is a problem for RDN treatment in kidney transplanted patients. As mentioned, the reasons for excluding these patients in earlier trials was on the one side a potential risk of deterioration in renal function and on the other side partly due to altered anatomy of renal arteries caused by degenerative processes in these patients. Due to this degeneration, the vessel caliber of the native renal arteries is often smaller than the regular requisite for catheter ablations.

As said before, the investigation of the safety and feasibility of renal denervation in RTX patients was one objective of our study. For the feasibility, exclusion could be justified due to an **altered anatomy** of the renal arteries by degenerative processes and due to a possible risk of deterioration in renal function. Recalling the reasons for exclusion: main renal arteries with <20 mm treatable length, multiple renal arteries, and history of prior renal artery stenosis. Investigating the ablation rates in this context, on average patients received 12.6 ablation treatments of a total 120 seconds each. Approximately 36% of these ablation procedures needed to be repeated because of prior abortion. Indeed, quantitative analysis of the renal arteries confirmed in almost 85% a luminal narrowing just marginal to the threshold normally accepted for RDN therapy. It stands to reason that this presumably caused an increased rate of premature termination of ablation treatments due to increasing catheter temperatures. This was possibly resolved by conducting multiple shorter ablations while recommended catheter operational parameters were not exceeded. If thereby an equal depth of RF-penetration was achieved with equivalent modulation of the sympathetic nervous system remains unclear. Despite the discontinuation, a similar BP reduction as in the Symplicity HTN-3 trial was achieved (Bhatt, Kandzari et al., 2014). Altered renal arteries anatomy could be responsible for not ensuring a sufficient blood flow necessary for cooling the catheter tip leading to an abortion of the ablation because tip temperatures reached preprogrammed limits. However, a correlation between premature abortion rate and response rate is not obvious. Schönherr et al. (Schönherr, Rehwald et al., 2016) went more précises into this matter and identified that

altered anatomy has been a problem in previous studies before. Some 46% of the patients did not match the anatomical enrollment requirements for RDN set in the Symplicity HTN-2 study. For future studies this problem could be solved by using of a cooled ablation catheter with multiple ablation electrodes.

Considering once more the number of ablations on each artery, with a mean of 12.6 total ablation attempts in our study, patients were treated with a comparable amount of ablation treatments as patients in the Symplicity HTN-1 and HTN-2 trials (Esler, Krum et al., 2012, Krum, Schlaich et al., 2014). Post-hoc analysis of Symplicity HTN-3 showed that with an even higher amount of ablation attempts (12-15 ablations) significantly pronounced reductions in SBP can be achieved (Kandzari, Bhatt et al., 2015). Furthermore, there was also a trend to a more pronounced reduction performing four-quadrant ablations, although it was not statistically significant (Mahfoud, Tunev et al., 2015). In a recent pathological study, it was shown, that the mean distance from renal artery to the nerves is least in the distal segments (Sakakura, Ladich et al., 2014). Therefore, an ablation in the distal renal artery segment might be more effective. The RDN performance was controlled by fluoroscopic guidance, however lesions might have not been placed distally enough. This adjustment needs to be considered in future studies. However, there is the chance that arterial remodeling and stiffness because of long-term hypertension maintained systolic hypertension and the assumed sympathetic overactivity has been a less significant mediator (Bhatt, Kandzari et al., 2014).

Often the anatomy of renal arteries differs in varying degrees on either side. The question rises whether a **unilateral ablation** would achieve already satisfying results in the event of abortion on just one side. This was investigated in a study on experimental hypertension that showed a unilateral denervation only lowers BP to a minimal extent (DiBona and Sawin, 2004). Further clinical registry data on unilateral denervation is unavailable until now. Otherwise, the so-called renorenal reflexes might still be influenced by a unilateral application as investigated in experimental studies (Kopp, 1992, Kopp, Smith et al., 1985). These reflexes are spinal reflexes that provide communication between the two kidneys and potentially protect against the development of hypertension, which implicates that a change in one kidney reduces sympathetic activity in the contralateral kidney because of unilateral denervation. However, until today it remains unclear as to what extent renorenal reflexes influence the patients' BP levels in the end. Therefore, if only an impeccable unilateral denervation was achieved, one should still try to complete the ablations on the opposite side in a helical pattern. Furthermore, it was found that patients with one single renal artery on either side would profit more from RDN than the ones with multiple renal arteries (Verloop, Vink et al., 2014).

4.2.4 Equipment

In troubleshooting for possible factors that may have influenced the results, one should consider the equipment used for renal denervation treatment. We used the same catheter for our patients as the one used in the Symplicity HTN-3 trials. As mentioned earlier, this Medtronic Symplicity system (Medtronic Flex™, Santa Rosa, CA, USA) consists of the Symplicity G2™ generator and a catheter that is equipped with a single electrode catheter requiring an RF application in a helical fashion to superior, inferior and lateral (anterior and posterior) walls of the renal artery. This helical application can be challenging to achieve and the fact that there is no intra-procedural marker of success impedes it even more. Furthermore, it is complicated to distinguish between an anterior and posterior position on fluoroscopy (Patel, Dhillon et al., 2014). Also, it remains unclear if the preset ablation algorithm was the best to use.

Due to these application difficulties of a single electrode system, one might assume that the use of a **multi-electrode** system for renal denervation is more successful. For this purpose, the EnligHTN I trial was the first study delivering results on the use of a multi-electrode ablation system (EnligHTN™ Renal Denervation System, St. Jude Medical, St. Paul, MI, USA) that was used in 46 patients (Papademetriou, Tsioufis et al., 2014). Unfortunately, these results were also not as convincing as hoped for. They differed, if at all, only minimally from those of the Symplicity trials. The following EnligHTN trials, in which the next generation multi-electrode ablation device with a revised generator and algorithm was used, did not show any striking BP reduction changes (Lobo, Saxena et al., 2015). Whether better results could be achieved in kidney transplanted patients using a multi-electrode ablation system, remains to be clarified, especially because the procedure in KTx patients is impeded by the native renal arteries deviations.

4.2.5 Biases

It is necessary to analyze further alterable characteristics of our study. During the analysis, we accounted vulnerabilities possibly responsible for the alleviated outcome. Amongst others biases belong to these vulnerabilities. To avoid the **bias** of different interventionists' skills the same physician performed all interventions. The physician is a skilled interventional cardiologist who had performed renal denervation procedures before executing RDN on the enrolled patients. With an increasing number of conducted interventions, potentially the physician could perform the intervention with a higher efficacy level than in the first enrolled patients. Although, our collective of patients (n=9) might have been too small for a learning curve. It is argued that this might be one of the reasons for the changes between the last two Symplicity HTN trials. There is the chance, that the US operators in the Symplicity HTN-3 trial were not able to perform renal denervation procedures as effectively as the Symplicity

HTN-2 trialists (non-US) who possibly have had more experience with renal denervation devices. Not even 25% of the interventionists in the Symplicity HTN-3 had performed ≥5 denervation procedures (Patel, Hayward et al., 2014). In fact, this suggestion was seized for the study design of the DENERHTN trial, why RDN procedures than where partly supervised by an experienced leading interventionist (Azizi, Sapoval et al., 2015). For our study the question remains, if with a larger number of enrolled patients, a learning curve would have been recognizable.

A second possible source for biases in our study is that neither the patients nor the physicians were blinded. Additionally, there was no sham procedure as there was in the Symplicity HTN-3 trial. The participation in the study and the twice-daily home BP measurement may have led to a different level of attention with respect to patients' BP, in the meaning of avoiding stress factors or reducing salt intake, and otherwise compliance in terms of following correct measuring instructions. The so-called Hawthorne effect, as mentioned earlier. For the behalf of us physicians assessing office BP after patient underwent RDN, we may have adjusted the way in how the patients measure and record BP (Howard, Cole et al., 2014). It is essential for a future trial to investigate the effect of a blinded study including a sham group. However, it remains complicated to monitor the potential patients' behavior changes relating to their BP awareness.

4.2.6 Study limitations

For **limitations** of our study one should consider the small patient collective. The estimated number of patients with sufficient statistical power for the trial was originally calculated with 20 patients per group. However, the publication of the Symplicity HTN-3 trial results (Bakris, Townsend et al., 2014) in September 2014 fueled the broad discussion about the usefulness of renal denervation. Symplicity HTN-3 was a thoroughly designed study, however failed to show significant benefit of RDN in kidney healthy patients with resistant hypertension. This complicated and impeded the achievement of the estimated sample size for our trial in this very sensitive patient population. Consequently, we decided for a premature evaluation and publication of our data (Schneider, Promny et al., 2015). Although, we acknowledge that in relation to the primary endpoint the study is underpowered for comparison between the two groups. Analyzing our **study design** once again, it was originally developed to prove efficacy and safety of renal denervation with the special emphasis for kidney transplanted patients. A blinded set up for the groups possibly shows a more pronounced validity. An even stronger significance might be achieved through a sham procedure group approach, which is to be investigated in a further study. Therefore, we concluded that it would have been inappropriate to continue the trial as planned considering the results and further

circumstances. Anyhow, as results of our prematurely terminated study are quite promising, a follow-up trial including mentioned improvements is necessary.

The **economic aspect** can eclipse the RDN procedures because at the first sight current costs are higher than for medication treatment. In case it proves that with the RDN procedure it is possible to reduce overall antihypertensive medication long-term, the financial comparison of the one-time treatment costs and the permanent costs of increased drug therapy should be taken into consideration once again.

4.2.7 Durability of achieved RDN treatment reductions

Whether a single electrode or multi electrode system is used, long-term BP **reductions** seem to **persist** (Esler, Bohm et al., 2014, Esler, Krum et al., 2012). It is of interest to review the continuous BP measurements and investigate BP trends, because renal nerve fibers might regenerate (Gazdar and Dammin, 1970, Hansen, Abildgaard et al., 1994, Mahfoud, Tunev et al., 2015). Originally, it was assumed, that after about one or two years the denervation procedure might need to be repeated and in time even performed again. Researches expected this due to the temporary lowering of surgical renal denervation effect in experimental hypertension models, when renal sympathetic nerve regrowth occurred apparently in less than six months (DiBona and Esler, 2010, DiBona and Kopp, 1997). Therefore, it was estimated that in humans suffering hypertension, the anti-hypertensive effect might also be for a rather limited time. However, with catheter-based RF denervation the BP reduction is enduring, as there occurred no loss of anti-hypertensive effect after three years of follow-up (Krum, Schlaich et al., 2014). The question arises whether this contrast in anti-hypertensive duration is a species difference (humans vs. rats) or if it is imputable to denervation methodology (RF ablation vs. surgery). A possible explanation might be that RF thermal tissue damage, compared to surgical interventions, destroys pathways extensively compared to a clean-cut edge achieved through surgery. Further, it remains uncertain, if the different available renal denervation techniques (radiofrequency using different devices, ultrasound or cryogenic) are equally effective and if reinnervation occurs are there serial procedures necessary, not known if consistent in efficacy and safety. Investigative studies are awaited.

4.2.8 Chance of prediction who and how one will profit from RDN treatment

Since the introduction of RDN, it has always been a challenge to **predict** the **patients profiting** from this certain treatment. One has misconceptions assuming, that this would be an easy task. However, previous studies (Esler, Krum et al., 2012, Hering, Lambert et al., 2013, Krum, Schlaich et al., 2009, Krum, Schlaich et al., 2014, Ormiston, Watson et al., 2013b, Worthley, Tsioufis et al., 2013) state that response rates are in the range of 50–85 %, approximately the same percentage as we achieved in our trial. Preparatory applied tests for

screening sympathetic nervous system activity were partly performed. Available tests of sympathetic activity, such as plasma and urine norepinephrine measurements, are still inaccurate. The most promising results are achieved by renal noradrenaline spillover measurements, which unfortunately are clinically impracticable (Esler, Jennings et al., 1984, Esler, Krum et al., 2010).

Hence, we additionally analyzed the **baroreflex sensitivity**, which is a noninvasive method recording the interrelation between spontaneous fluctuations of arterial BP and heart rate. Impaired cardiac BRS is a common occurrence in various diseases associated with sympathetic overactivity, including myocardial infarction (La Rovere, Bigger et al., 1998), diabetes mellitus (Barthel, Bauer et al., 2011), renal insufficiency (Tomiyama, Shiigai et al., 1980), and indeed arterial hypertension (Bristow, HONOUR et al., 1969, Gribbin, Pickering et al., 1971). Recalling the two possible approaches to measure the BRS: on the one hand, noninvasive recordings in which spontaneous variations of R-R interval and systolic BP are analyzed, and on the other hand, the invasive procedures in which prolongations of the R-R intervals to stimulated BP by vasoactive drugs are measured (La Rovere, Pinna et al., 2008). However, the noninvasive assessment of BRS is sophisticated and raises troubles during measurements. Results seem unreliable because spectral methods are highly sensitive to artifacts and ventricular premature complexes (Pinna, Maestri et al., 2005). To avoid these inaccuracies, BRS recordings were assessed by the so-called PRSA method (Bauer, Morley-Davies et al., 2010, Muller, Morley-Davies et al., 2012) that provides significantly better prognostic accuracy (Barthel, Bauer et al., 2012). Zuern et al. (Zuern, Eick et al., 2013) demonstrated that resistant hypertension suffering patients with an impaired cardiac BRS would profit from renal denervation. Considering our recorded BP qualities one by one, unfortunately we did not see a correlation between the extent of BRS results and a definitive BP trend. Similar findings were observed in a study that also investigated BRS changes after RDN in rats and humans. The researches stated that sympathetic activity did not always change analogues with BP (Hart, McBryde et al., 2013). Certainly, the analysis of baroreflex measurements helps to identify patients that may possibly benefit from renal denervation, but it will not predict which BP quality and to what extent the BP will change. Possible explanations for this could be differences in the procedure, patients' intrinsic variability of BRS_{PRSA} and BP or RDN-caused effects on BP not associated with decrease of central sympathetic activity (Zuern, Eick et al., 2013).

Due to the fact, that there was an insufficient number of VPCs measured and thus the **heart rate turbulences** could not be analyzed properly, it is not possible to make a significant statement about the results of the HRT in both groups. An explanation for the small number of VPCs and the non-meaningful HRT assessment might be the short time period (30 min) of

Holter recording (Bauer, Malik et al., 2008). Even though only a minimum of five VPC is necessary for an adequate calculation, VPCs are likely to occur quite irregularly throughout the day.

Furthermore, Esler (Esler, 2014) and his laboratory team are working on an investigative test for adequacy of RDN excretion. Instead of measurement of renal norepinephrine spillover they are examining the patients' urine for tyrosine hydroxylase fragments.

In general, the **magnitude of the blood pressure reduction** achieved with renal denervation is still rather unpredictable. It varies between individual patients. As mentioned earlier, the only consistent predictor for response is a higher baseline blood pressure (Esler, Krum et al., 2012, Krum, Schlaich et al., 2014). It is beyond dispute, that the impact of further biological factors presents in patients with resistant hypertension, for example triggered renal injury signals (especially in RTX patients), influence central sympathetic activation by renal afferent nerves (Campese and Kogosov, 1995, Converse, Jacobsen et al., 1992, Hering, Lambert et al., 2013, Schlaich, Sobotka et al., 2009a). Furthermore, it was shown that in a significant minority of patients with resistant hypertension the initial blood pressure elevation is not maintained by neural mechanisms at all (Esler, Krum et al., 2010). It is important for these patients to continue the research for a suitable solution.

Bottom line, it remains complicated to identify what kind of patient profile will profit most from renal denervation, to what extent, and which BP quality. It is still to be clarified if patients with certain antihypertensive regimes will profit with a more pronounced impact than others who are not taking these certain antihypertensive drugs. This should be investigated in further trials.

Summing up, it is not time yet to ring the **death knell** on RDN, however there is definite demand for adjustments and further investigation.

4.3 RDN treatment the new panacea for hypertension – an erroneous assumption?

The expectation of RDN to be a **panacea for patients** of all age, race, sex and disregarding further concomitant diseases was probably too simplistic. This treatment's overestimated expectancy could be justified with the still incomplete understanding of the associated mechanism of the antihypertensive effect of RDN treatment. This is illustrated by a subgroup analysis of the Symplicity HTN-3 results in which a mean difference in SBP in ABPM greater than 6 mm Hg was recognized if Black patients were excluded from the analysis. It is known that Black patients have a better response to diuretics and vasodilators than Caucasians suffering hypertension. Contrariwise, Caucasians show a better response to beta-blockers and ACE-inhibitors than Black patients (Batson, Belletti et al., 2010, Flack, Nasser et al.,

2011). Furthermore, RDN treatment does not only affect BP. Seemingly, the procedure benefits atrial fibrillation (Pokushalov, Romanov et al., 2012), diabetes (Mahfoud, Schlaich et al., 2011), obstructive sleep apnea (Witkowski, Prejbisz et al., 2011), and psychological wellbeing (Lambert, Hering et al., 2012) through central sympathetic inhibition from ablation of renal afferent nerves. The RDN treatment's potential is extensive, however, as stated before, the exact extent and application range are subject of current research.

4.4 Future prospects and development

Thinking about improvements in terms of feasibility and success of RDN with the currently available RDN devices there are certain modifications that need to be mended in **new ideal devices**. At first, it is essential that devices should provide the ability to realize complete renal nerve ablation of adventitial sympathetic nerves. It seems to prove advantageous that each renal artery be treated with a single short treatment time. Most important is the development of an immediate feedback mechanism, informing the interventionist about success or failure of the ablation. Further aspects are cooled tip catheter devices, better preselection of patients as well as a sham-control arm. It shall not be disregarded that the procedure must remain safe and only causes minimal patient discomfort.

Considering the procedural safety, new technologies being developed as an externally delivered, noninvasive, focused ultrasound device, of which early efficacy and safety data has recently been published (Sakakura, Ladich et al., 2014). Finally, there are further device-based investigational therapeutic approaches targeting the SNS. Particularly baroreceptor stimulation is a feasible option affecting hypertension by modulating the SNS activity. Carotid baroreceptors are electrically stimulated by a surgically implanted administrative device. This device works similarly to a pacemaker. The aim of these stimulations is to reduce sympathovagal imbalance by lowering the activity of the SNS while on the other hand increasing parasympathetic activity (Heusser, Tank et al., 2010, Wustmann, Kucera et al., 2009).

Future studies are necessary to integrate the ideas of improvement and avoid simple mistakes, which falsify the results. The most recent RDN study, the SPYRAL HTN Global Clinical Trial, has been designed to address the previous shortcomings of prior trials, especially the Symplicity trials. Patients are assigned to two simultaneous, randomized, blinded, sham-controlled trials, each 100 patients enrolled (Kandzari, Kario et al., 2016). The influences of the different antihypertensive agents are concerned by taking one group off antihypertensive medication (OFF-MED) and by appointing a stable and standardized drug regime for the other group (ON-MED). In this way comparing a proof-of-concept study against the efficacy of RDN in patients on a constant antihypertensive regime. This regime

consists of a thiazide-type diuretic, dihydropyridine-type calcium-channel blocker, and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, at dosage of at least 50% of the maximal recommended dose. Patients' urine and serum samples will be analyzed several times in course of the study to test for medication compliance. In both study arms patients' ablations are performed with the third-generation Symplicity Spyral™ renal denervation catheter (Medtronic Inc., Santa Rosa, CA, USA). This device is equipped with four radiofrequency electrodes, which are mounted in a way to achieve a helical pattern providing automated four quadrant ablation treatments (Figure 34).

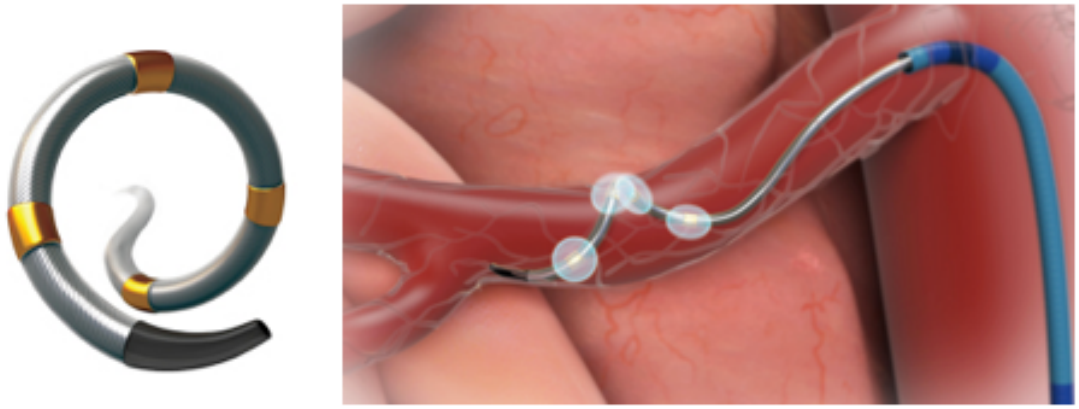


Figure 34 Medtronic Symplicity Spyral™ renal denervation catheter*. (Left) Catheter tip, (Right) catheter placement. Printed with permission by Medtronic GmbH. © Medtronic 2016*

In conclusion, as the burden of hypertension increases worldwide, focus should be on appropriate lifestyle modification and improvement of patients' medication compliance. Ongoing research on the underlying neurogenic component of hypertension encouraged the concept of interventional therapeutic approaches modulating autonomic mechanism to improve BP control. Although the initial enthusiasm has been tempered by the Symplicity HTN-3 results, the different techniques are still in developing stages. Our trial proofed RDN feasibility and safety in kidney transplanted patients with a pronounced decrease in office BP values, although missed out to show distinct BP reduction in ABPM. So, it is not time yet to call the death knell. Furthermore, renal denervation is worth to investigate further, as it remains an alternative to lifelong polypharmacy therapy for hypertension.

However, the sympathetic control of BP seems to be more complex than primarily thought. The absence of pronounced results can partly be explained by inaccurate patient selection, procedural and technical inadequacy, and individual altered anatomy.

While further adjustments will be realized, it remains to be seen to what extent RDN will influence and change hypertension treatment with a sophisticated technology in the future. Looking ahead, there are randomized, sham controlled, double-blind clinical trials

investigating the approach of multi-electrode catheter or non-invasive ultrasound underway. These studies are supposed to address the limitations noticed in previous trials. Preliminary results are promising. Until achieving the point of obtaining predictable and sustainable renal denervation, that reliably results in reduction of renal sympathetic output, it is still a laborious but fascinating journey. We are not there yet, but we are on the right track.

5 SUMMARY

5.1 English

The genesis of arterial hypertension is multifactorial, including lifestyle, dietary, metabolic, and genetic factors (Aucott, Poobalan et al., 2005, Bramlage, Pittrow et al., 2004, Parati and Esler, 2012). Hypertension in patients after kidney transplantation is common and a major risk factor for graft failure and atherosclerotic cardiovascular disease, which present the leading cause of premature death (Mange, Cizman et al., 2000, Shirali and Bia, 2008). Many of these patients are affected by the status of resistant hypertension (Guidi, Menghetti et al., 1996).

Furthermore, in post-transplant hypertension a rise of the sympathetic nerve activity in the native kidneys can be seen (Hausberg, Kosch et al., 2002). Catheter-based radiofrequency renal denervation of sympathetic nerve fibers is a promising treatment for resistant hypertension (Krum, Schlaich et al., 2009). Until today, this treatment was not investigated in kidney transplanted patients. Therefore, this trial investigated the feasibility and efficacy of catheter-based bilateral renal denervation for the treatment of resistant hypertension in kidney transplanted patients.

18 patients with resistant post-transplant hypertension were enrolled and randomized 1:1 to receive RDN or medical treatment. The primary efficacy end point was the change in office SBP and ABPM measurements at 6 months. Changes in renal function or renovascular complications were set for safety end points.

A significant reduction of 23.3 ± 14.5 mm Hg (P=0.001 for change difference between groups) was observed for the office blood pressure measurements in the denervation group compared to the control group at 6 months follow-up. The change in ABPM recordings was not as pronounced. However, analyzing the measurements closely, there was a reduction of 10.38 ±12.8 mm Hg (P=0.06) determined in the nocturnal values of the RDN group, whereas no changes were realized during daytime. Furthermore, the recordings showed a significant higher conversion rate for the dipping behavior of the ablated patients. No adverse safety events were observed.

In conclusion, this trial is one of the first to focus on the influence of renal denervation in kidney transplanted patients. It confirmed the feasibility and safety in this group of patients. However, it is necessary to identify the reasons for the differences in office BP recordings compared to ABPM measurements. Therefore, larger sham controlled studies are required, as further trials investigating new improved devices to achieve the full potential of renal denervation, not only in kidney transplanted patients.

5.2 German

Die Thematik Hypertonie stellt trotz der Entwicklung der vergangenen Jahre und des stetigen Fortschritts in der pharmakologischen Therapie eine große Belastung für die Gesundheitssysteme dar. Schätzungsweise versterben jährlich fast 10 Millionen Menschen weltweit an Bluthochdruck und dessen Folgen, was etwa der gesamten Todeszahl aller Infektionskrankheiten gemeinsam entspricht (Lim, Vos et al., 2012). Bluthochdruck entsteht durch ein Zusammenspiel multipler Faktoren, zu denen unter anderem Lebensstil, Diät, Stoffwechsel und genetische Faktoren zählen (Aucott, Poobalan et al., 2005, Bramlage, Pittrow et al., 2004, Parati and Esler, 2012).

Eine Patientengruppe die besonders häufig betroffen ist, sind nierentransplantierte Patienten. Diese leiden oft an Hypertonie, häufig bereits vor der Transplantation. Die Mehrzahl der nierentransplantierten Patienten ist trotz regelrechter und regelmäßiger Therapie von sogenannter resistenter Hypertonie betroffen (Guidi, Menghetti et al., 1996). Zudem kann bei diesen Patienten eine Überaktivität des sympathischen Nervensystems beobachtet werden, die eben unter anderem die Regulation von Blutdruckwerten beeinflusst (Hausberg, Kosch et al., 2002). Hypertonie ist einer der Hauptrisikofaktoren für Transplantatverlust und kardiovaskuläre Morbidität (Mange, Cizman et al., 2000, Shirali and Bia, 2008).

Neben medikamentösen Therapiemöglichkeiten ist die renale Denervation ein katheterbasiertes Verfahren, welches bis dato vielversprechende Ergebnisse zeigt. Diese Therapieoption setzt an dem zuvor genannten sympathischen Nervensystem an (Schlaich, Sobotka et al., 2009a). Die zuletzt veröffentlichen Forschungsergebnisse betonen, wie wichtig es ist, den zu Grunde liegenden Mechanismus der renalen Denervation auszumachen und Patienten zu identifizieren, die von dieser speziellen Therapie profitieren.

Diese randomisierte Studie überprüfte daher die Durchführbarkeit und Wirksamkeit dieses Verfahrens bei nierentransplantierten Patienten mit resistentem Bluthochdruck. Hierfür wurden die 18 Studienteilnehmer 1:1 in eine Denervationsgruppe und eine Kontrollgruppe eingeteilt. Analysiert wurden der Ausgangs Office-Blutdruck und 24 Stunden-Blutdruckwerte, sowie Verlaufswerte nach einem Monat, nach drei Monaten und nach sechs Monaten.

In Zusammenschau der Ergebnisse der Denervationsgruppe zeigte sich nach sechs Monaten eine signifikante Reduktion von 23.3 ± 14.5 mm Hg (P=0.001) in den Office-Blutdruckwerten in der Denervationsgruppe im Vergleich zu der Kontrollgruppe. In der 24-h Blutdruckmessung fielen die nächtlichen Werte im Ausmaß von 10.38 ±12.8 mm Hg (P=0.06), wohingegen keine Veränderungen während des Tages festzustellen waren. Zudem konnte in den Messungen häufiger eine Veränderung des Dipping-Verhaltens in der abladierten

Gruppe erfasst werden. Unerwünschte Nebenwirkungen wurden über den gesamten Zeitraum nicht beobachtet.

Zusammenfassend ist die Studie eine der ersten, die die Wirkung von renaler Denervation in nierentransplantierten Patienten untersucht. Die Ergebnisse der Studie bestätigen die Durchführbarkeit und Wirksamkeit von renaler Denervation in diesem speziellem Patientenkollektiv. Weiterhin ist es jedoch notwendig, die Ursachen für die Unterschiede in den jeweiligen Office-Messungen bzw. 24-Stunden Aufzeichnungen zu identifizieren. Demnach besteht weiterhin der Bedarf nach zusätzlichen umfassenderen Studiengruppen, als auch die Untersuchung von neuen technischen Geräten, um das gesamte Potential von renaler Denervation zu erreichen.

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7 ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
ASBP	Ambulatory systolic blood pressure
ACE	Angiotensin-converting-enzyme
ACEi	Angiotensin-converting-enzyme inhibitor
AHA	American Heart Association
ARB	Angiotensin-receptor blockers
AT1	Angiotensin 1
BNP	Brain natriuretic peptide
BP	Blood pressure
Ca	Calcium
CAD	Coronary artery disease
CKD	Chronic kidney disease
Corp.	Corporate (business)
DBP	Diastolic blood pressure
dL	Deciliter
eGFR	Estimated glomerular filtration rate
ESH	European Society for Hypertension
ESRD	End stage renal disease
Fr	French (French catheter scale, 1 Fr = 1/3 mm)
FU	Follow-up
GFR	Glomerular filtration rate
HbA1c	Hemoglobin A1c
HRT	Heart rate turbulence
Inc.	Incorporation (business)
IQR	Interquartile range
IU	International units
KDIGO	Kidney Disease: improving global outcomes
kg	Kilogram
KTx	Kidney transplantation
Ltd.	Limited company (business)
m^2	Square meter
MAE	Major adverse events
mg	Milligram
MI	Myocardial infarction
mL	Milliliter

Mm	Millimeter
mm Hg	Millimeter of mercury
ms	Milliseconds
Na^+	Sodium
NHANES	National Health and Nutrition Examination Survey
OSBP	Office systolic blood pressure
RBF	Renal blood flow
RDN	Renal denervation
RF	Radio frequency
RHTN	Resistant hypertension
RTx –	Renal transplantation
s	Second(s)
SABPM	Systolic ambulatory blood pressure monitoring
SBP	Systolic blood pressure
SD	Standard deviation
SNS	Sympathetic nervous system
TIA	Transient ishemic attack
VPC	Ventricular premature complex
W	Watt

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9 PUBLICATION

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*Contributed equally to this work.