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Novel Approaches in Hypertension Treatment - Modulation of the Sympathetic Overactivity

Sebastian A. Potthoff, Lars-Christian Rump and Oliver Vonend
Department of Internal Medicine / Nephrology, Medical Faculty,
Heinrich-Heine-University Duesseldorf,
Germany

1. Introduction

Arterial hypertension is the leading cause of mortality in the world [1]. It is estimated that 25 to 35 % of modern populations suffer from this condition [2-4]. Hypertension is the major risk factor for the most common cardio vascular diseases which are a major cause for morbidity and mortality. Depending on the stage of hypertension, it dramatically increases the individual risk for heart failure, heart attack, stroke or chronic kidney failure if not treated adequately [5]. Since hypertension is usually not directly linked to specific symptoms, it is one of the most insufficiently treated diseases in the population with only 10-20 % of patients with controlled blood pressure levels [4]. It is estimated that the prevalence of hypertension is going to increase within the next decades. Aging populations contribute significantly to this trend [6]. Due to its impact on public health, it already is a major burden for modern societies [7].

New strategies and treatment options have to be evaluated in order to slow or prevent the rise in hypertension related morbidity and mortality. This chapter focuses on the role of the sympathetic nervous system in the pathogenesis of hypertension. After almost half a decade with only minor advancements in this field, sympathetic overactivity has been recognized as a major contributor to hypertension [8]. Many secondary causes can increase sympathetic activity which can lead to hypertension. Beyond the initial contribution, sympathetic overactivity can sustain hypertension. Therefore the sympathetic nervous system plays a role in the acute and chronic pathogenesis of hypertension. Understanding the mechanisms involved in the regulation of the sympathetic nervous system is currently leading to novel approaches in hypertension treatment.

2. Anatomy of the sympathetic nervous system

2.1 Efferent sympathetic neurons

Sympathetic innervation origins from the intermediolateral cell column of the spinal cord. Preganglionic neurons range from the thoracic to the lumbar parts (T1-L2). These short neurons usually travel to the paravertebral ganglia where they connect to the postganglionic neurons. Those postganglionic neurons sympathetically innervate most organs such as heart, kidney and blood vessels (Fig. 1). Sympathetic nerve endings release a variety of neurotransmitters notably norepinephrine, neuropeptide Y (NPY) and adenosine triphosphate (ATP) [9, 10].

Sympathetic overactivity is a major contributor to arterial hypertension which is one of the leading causes of stroke, chronic kidney failure, left ventricular hypertrophy and sudden cardiac death.
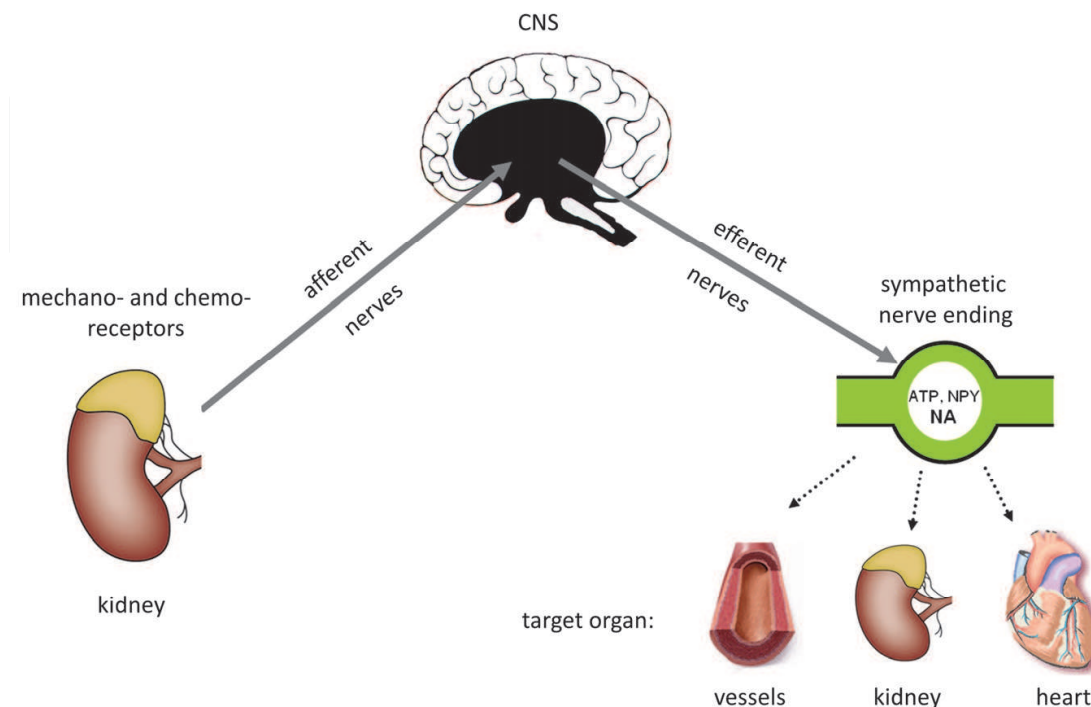

Fig. 1. Schematic of sensory, afferent and sympathetic efferent neurons and target organ innervation.

One of the distinct features of the sympathetic nervous system is the immediate regulation of peripheral vascular resistance through adaptation of the vascular tone. Besides this immediate action on blood pressure control through vasoconstriction, release of sympathetic neurotransmitters contribute to adaptive mechanisms through regulation of cell proliferation, transformation and apoptosis which are blood pressure independent [11-14].

2.2 Afferent sympathetic nerve activity

Besides the efferent innervation, sensory afferent neurons travel from target organs to the sympathetic nuclei of the central nervous system (CNS). These afferent nerves have been extensively described for the kidney but can also be found in the heart [15]. The pathogenesis of this sympathetic activation was elucidated in several animal models [16]. Afferent nerves are activated by baro- or chemoreceptors in ischemia or inflammation [17]. They travel along the renal artery and insert the posterior horn of the spinal cord at the level of TH6-L3 from where they travel to the sympathetic nuclei of the CNS (Fig.1). Neurotransmitters of these afferent neurons are ATP, substance P and calcitonin-gene related peptide (CGRP)[18].

The renin-angiotensin-aldosterone system (RAAS) contributes to the central nervous feedback in sympathetic activation. Especially angiotensin II and nitric oxide (NO) are important effectors of this system [19]. Inhibition of the RAAS leads to a decrease in efferent sympathetic activity in chronic kidney disease patients [18]. Not all inhibitors of the RAAS can penetrate through the blood-brain barrier, therefore peripheral actions of angiotensin II are likely to affect afferent signal transduction.

Renal ischemia leads to a release of adenosine as a paracrine transmitter. This leads to a potent activation of afferent neurons [17]. Interestingly, in an animal model, already minor kidney injury through local injection of phenol leads to a permanent neurogenic hypertension [20]. Severing afferent and efferent sympathetic nerve fibers prevents hypertension in an animal model of chronic kidney injury [21]. Independent from CNS-effects, chronic kidney injury leads to an increase of presynaptic norepinephrine release in the heart and kidney. This might be due to an increase in angiotensin II through RAAS activation [22-24]. However, it is still unclear which renal mechanisms contribute to a sustained activation of renal afferent neurons.

3. Detection of increased neuronal activity

3.1 Microneurography

Microneurography has been established at the university of Uppsala (Sweden) by Karl-Erik Habbarth und Åke Vallbo [25]. The sympathetic nerve activity can be measured by insertion of a micro electrode into a peripheral nerve (mostly peroneal nerve) [26].

Patient with kidney graft

before   after

nephrectomy of recipient kidneys

Sympathetic nerve activity (MSNA in burts/min)	39	18
Creatinine (mg/dl)	0.9	1.2

Control Patient

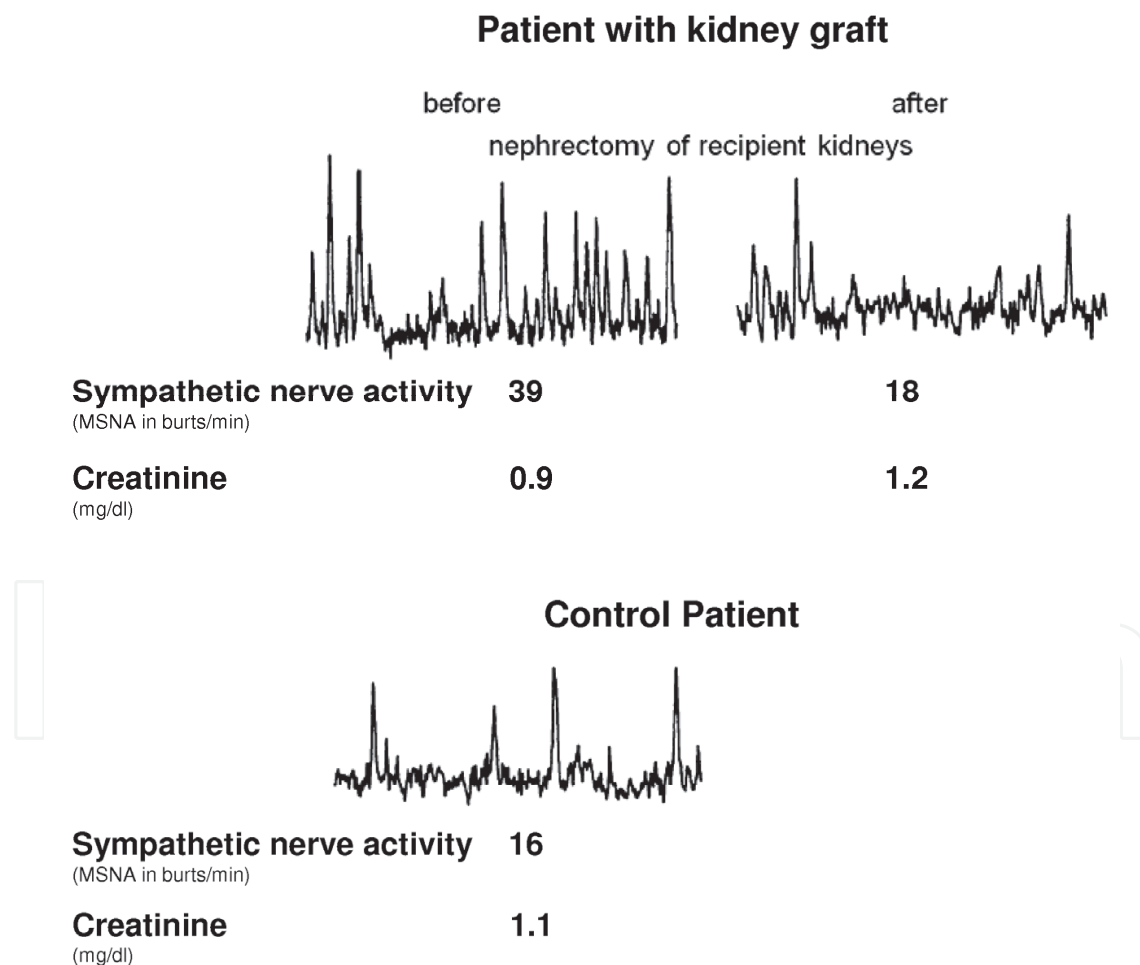|	
Sympathetic nerve activity (MSNA in burts/min)	16
Creatinine (mg/dl)	1.1

Fig. 2. Multiunit activity sympathetic nerve activity (MSNA) of the sural nerve. Kidney transplant patients show an increased sympathetic nerve activity despite normal serum creatinine levels. Only nephrectomy of the native kidneys is able to normalize the activity compared to healthy controls (modified from [28]).

Multiunit activity sympathic nerve activity (MSNA) is equivalent to the sympathetic activity. This activity is measured as "bursts" per minute. Using this method, the concept of the kidney as a pacemaker of sympathetic activity could be very well established. Converse et al. analyzed the sympathetic activity in dialysis patients vs. healthy controls [27]. Interestingly, in kidney transplant patients with normal serum levels of creatinine and urea, the sympathetic overactivity persisted. Only bilateral nephrectomy was able to abolish the pathologic sympathetic overactivity (Fig. 2) [28].

3.2 Norepinephrine release

Besides microneurography, norepinephrine release can be used to estimate the activity of the sympathetic nervous system. This concept has been established by Murray Esler from Melbourne, Australia [29]. Norepinephrine can be measured in blood samples. Also local norepinephrine release can be quantified in tissue samples from kidney and heart.

The heart is an important target organ of sympathetic activity. Especially patients with end stage renal disease show a dramatic and early increase of cardiovascular events. Zocalli et al. could demonstrate that norepinephrine and NPY serum levels correlate with the patient mortality (Fig. 3) [30, 31].
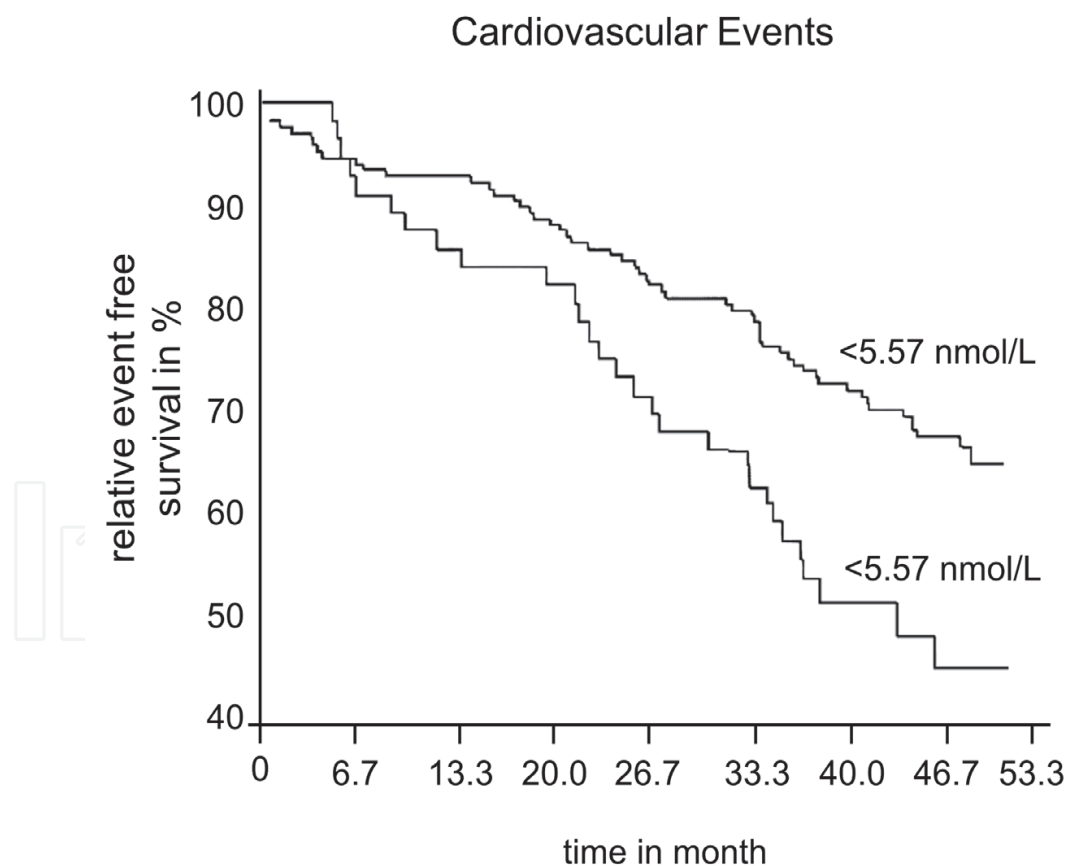

Fig. 3. Serum norepinephrine levels correlate well with the incidence of cardiovascular events in end stage renal disease patients (n = 228 patients on haemodialysis). Kaplan-Meier survival curves for cardiovascular events (fatal and nonfatal) in patients below and above 75th percentile of serum norepinephrine (5.57 nmol/L) (from [30]).

3.3 Modulation of sympathetic activity

The sympathetic nervous system allows for rapid adaptation of the body to current events. Orthostatic reaction is a well examined example of immediate activation of the sympathetic nervous system [32]. Besides pain, stress and urgency, changes in temperature, blood oxygenation and ambient sound level lead to a change in sympathetic activity [15, 32].

Instead of immediate alterations of sympathetic activity, it appears feasible that long-term change in sympathetic activity is the underlying mechanism which contributes to the development of hypertension. Aging people show an increase in sympathetic activity with an increase of MSNA of 1 burst/min per year [33]. Although female subjects are characterized by a lower MSNA, they exhibit a more significant annual increase [34]. It is likely that the increase in MSNA contributes to the development of hypertension in the aging population, since the prevalence of hypertension increases with age. There is a tight correlation between blood pressure and MSNA in subjects older than 40 which does not occur in younger patients (Fig. 4.) [34]. This might be due to diminished compensatory mechanisms in the elderly population (endothelial dysfunction, diminished baroreflex, etc.). Sympathetic overactivity is the pathogenic link between hear failure, sleep apnea, metabolic syndrome and hypertension.
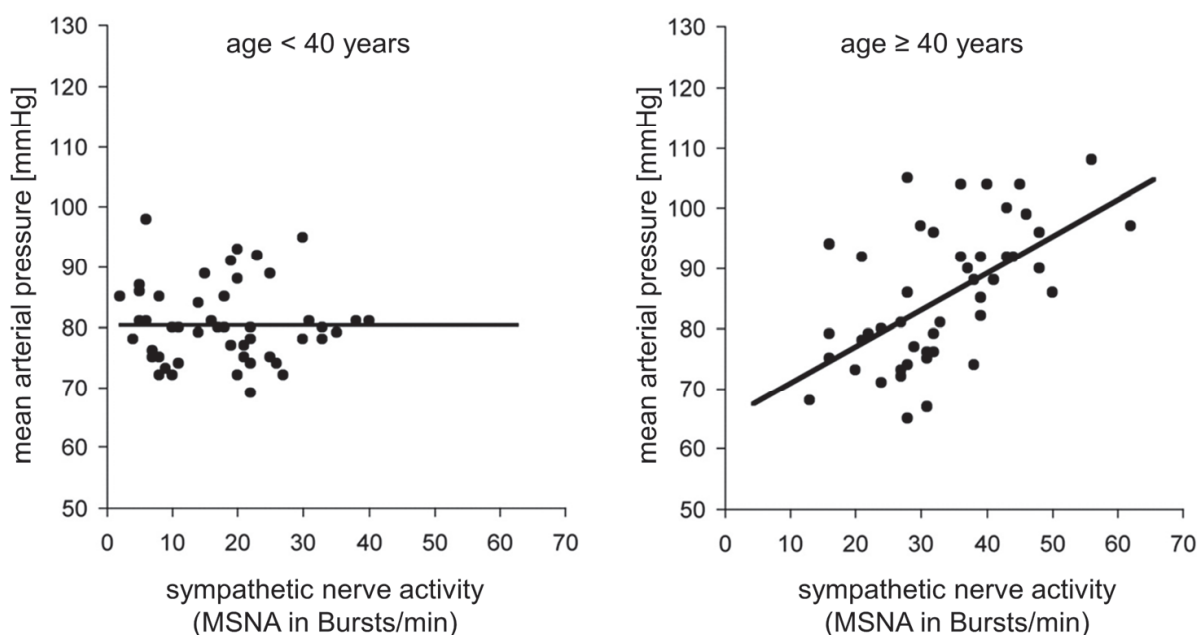

Fig. 4. Correlation between MSNA and mean arterial blood pressure in female subjects <40 and ≥ 40 years of age. A correlation between blood pressure and MSNA cannot be found until the age of 40 (modified from [34]).

3.4 Sympathic overactivity in chronic heart failure

Chronic heart failure is associated with an increased sympathetic activity [35]. There is a tight correlation between severity of heart failure and MSNA. However, MSNA does not allow direct conclusion on the degree of heart failure. Due to different mechanisms of sympathetic activation, high MSNA can also be found in patients with only mild to moderate heart failure [36].

The rise in MSNA causes an increase of norepinephrine release in the myocardium. The increased release of norepinephrine contributes to the increased risk of arrhythmogenic cardiac events and left ventricular hypertrophy.

In an animal model with genetically determined sympathetic overactivity (α2-adrenoceptor knockout - decreased adrenergic auto inhibition), increase of left ventricular mass and heart failure can be observed [37].

Hypernatremia is a common finding in severe chronic heart failure. This leads to an activation of the RAAS and sympathetic nervous system. However, the increase in sympathetic activity can already be observed in mild to moderate chronic heart failure. The underlying cause is not well understood. This might be linked to a change in baroreflex sensitivity or a maladaptation of the cardiopulmonary reflex [35].

A left ventricular systolic dysfunction with an increase of cardiopulmonary filling pressure can trigger sympathetic activity. Obesity and sleep apnea add to this condition.

Therefore, a goal in chronic heart failure has to be the inhibition of the self-sustaining pacing of sympathetic activity, in order to reduce the cardiovascular mortality.

3.5 Sympathetic overactivity in sleep apnea

Sleep related respiratory dysfunction is much more common in patients with hypertension compared to the common population [18]. Some authors estimate that every second patient with hypertension is prone to sleep related respiratory dysfunction [38]. An increase in blood pressure is almost always observable in sleep apnea patients. Apnea causes an immediate increase in sympathetic activity which is the underlying cause of the increase in blood pressure [39]. Chemo-receptors within the carotid body (glomus caroticum) are activated due to hypoxia. Those chemo-receptors can directly activate the sympathetic nervous system. [18].

In chronic sleep apnea, this activation of the sympathetic nervous system persists during daytime which results in increased MSNA and norepinephrine release [40]. Intermittent hypoxia leads to a sustained increase in blood pressure in an animal model. Denervation of the carotid body abolishes the blood pressure increase after hypoxia [41]. Desensitizing chemo-receptors through respiration of 100 % oxygen leads to a decrease in sympathetic activity, heart rate and blood pressure in wake sleep apnea patients but not in healthy controls [42]. Apparently, a sustained activity of chemo receptors contributes to the stimulation of the sympathetic nervous system while awake which is leading to hypertension.

Despite chemoreceptors, baroreceptors play a central role in regulation of the cardiovascular system. A dysfunction of baroreceptors can be observed in sleep apnea patients similar to chronic heart failure patients. In a canine animal model of sleep apnea, the baroreflex is adjusted to higher blood pressure levels [43]. Obstruction of the respiration at night leads to a sustained hypertension at daytime [44]. Continuous Positive Airway Pressure (CPAP) therapy is able to abolish or reduce sleep apnea. Night- and day-time sympathetic overactivity can be significantly reduced through this therapy [40].

3.6 Sympathic overactivity in metabolic syndrome

The increased sympathetic activity in metabolic syndrome patients contributes to the increased cardiovascular risk in this patient group [45]. In overweight patients, sympathetic overactivity appears to be linked to a dysfunction of the baroreflex [46]. This is also linked to the distribution of body fat mass. Accumulation of visceral fat is characterized by an increase in MSNA and cardiovascular risk [45].

Compared to healthy individuals, overweight people suffer significantly more often from hypertension and show an increased risk for the development of type 2 diabetes. An increased MSNA can also be observed in patients with type II diabetes [47].

The underlying cause for this interacting pathogenesis is unknown. Hyperinsulinemia appears to play an important role. For instance, administration of insulin in an increasing dose was able to increase MSNA in euglycemic individuals [48].

3.7 Sympathic overactivity in hypertension

Almost all studies measuring microneurographic sympathetic nerve activity in hypertensive patients could demonstrate the central role of sympathetic overactivity [49]. Smith et al. was able to show that especially in patients with observable target organ damage MSNA increase is more pronounced [50] (Fig. 5).
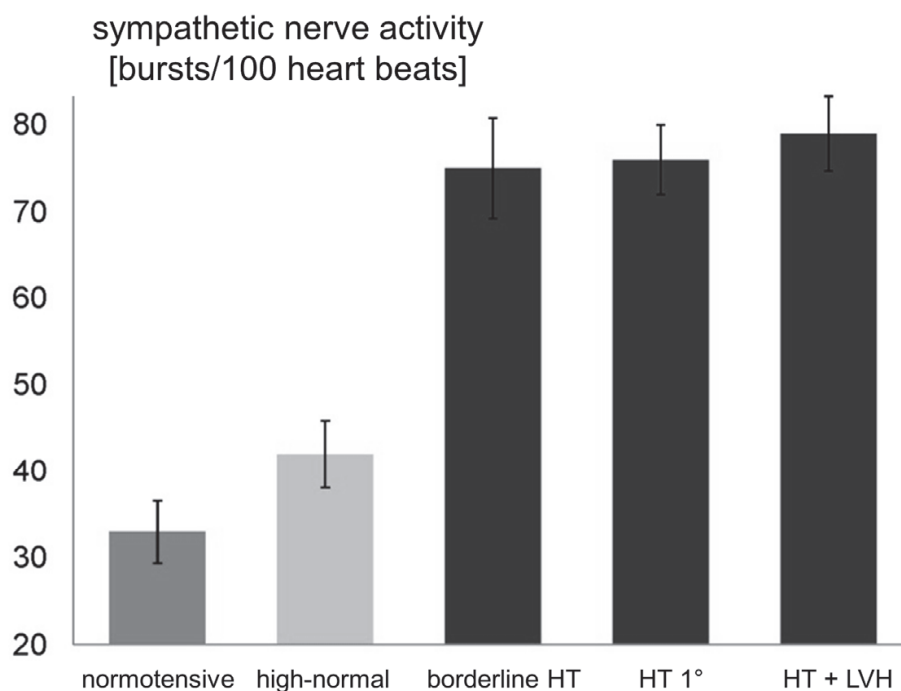

Fig. 5. Microneurographic measurements confirm a significant increase in sympathetic nerve activity (MSNA) in patients with hypertension (HT) compared to healthy individuals. An increased MSNA can already be found in high-normal blood pressure patients (130-139/85-89 mmHg) (modified from [50]).

The underlying conditions of sympathetic overactivity in hypertension are often linked and cannot be distinguished from each other. These conditions among others include chronic kidney disease, heart failure, obesity and sleep apnea. However, there is evidence that sympathetic reactivity might be genetically determined. Children of hypertensive individuals show normal MSNA-levels. When subjected to mental stress these children show a significantly increased MSNA if compared to children of non-affected parents [51].

Other hypertensive conditions such as preeclampsia [52] or pulmonary arterial hypertension [52] show an increased burst activity in microneurography.

Today, we have a distinct understanding of the pathogenesis of hypertension induced by chronic kidney injury. As seen in figure 1, activation of afferent neurons in the injured kidney leads to an increased sympathetic activity through central nervous mechanisms. It is

well established that increase of serum norepinephrine levels can indicate chronic kidney failure [53]. However, this finding is mostly based on reduced norepinephrine clearance in the kidney. Recently, it has been discovered that the kidney also releases a soluble monoamine-oxidase (Renalse) which degrades circulating catecholamines and thereby might regulate blood pressure [54]. Renalase serum levels are significantly decreased in chronic kidney failure. If Renalase actually plays a significant role in hypertension in chronic kidney failure patients has not been proven yet.

As stated above, bilateral nephrectomy is able to normalize MSNA. This can be reproduced in an animal model by renal denervation or selective dorsal rhizotomy [55]. Beside increased catecholamine levels, increased MSNA is an additional finding in renovascular hypertension [56]. The underlying mechanism for renovascular hypertension in renal artery stenosis is increased renin release which is dependent on renal innervation. Increase in blood pressure can be abolished in a Goldblatt-hypertension animal model ("2 kidney 1 clip") if the affected kidney is denervated [57]. Interestingly, denervation of the non-affected contralateral kidney also abolishes hypertension in this model [58].

4. Therapeutic approach in sympathetic overactivity

4.1 Pharmaceutical approach

In patients with chronic renal failure, the degree of the disease correlates very well with the sympathetic activity [59]. An increase of MSNA of 10 burts/min increases the event rate by 60 %. Concordantly, adverse cardiovascular events are also increased in these patients (Fig. 6.).
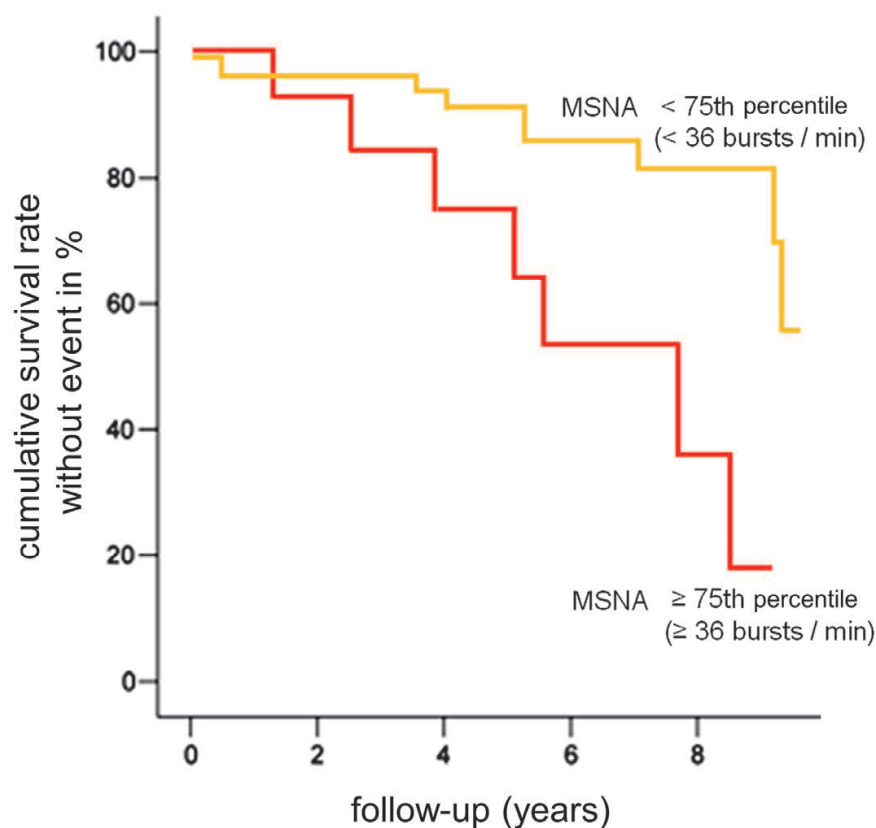

Fig. 6. Kaplan-Meier curve for adverse cardiovascular events in dependence of MSNA above (≥ 36 bursts/min) and below (< 36 bursts/min) the 75th percentile (modified from [59]).

RAAS blockade, through ACE-inhibitors or AT1-blockers, leads to a reduction in the efferent sympathetic activity [60, 61]. However, normalization of sympathetic activity can only be achieved if a central sympatholytic drug (moxonidine) is added to this treatment [62]. Moxonidine has been shown to have renoprotective properties in chronic renal failure and to reduce MSNA [63, 64]. This effect was independent from blood pressure reduction. In an animal model of chronic kidney failure, monoxidine is able to significantly improve histomorphologic and functional renal outcome. It is able to reduce albuminuria and the degree of glomerulosclerosis [65]. This might be dependent on an alteration of gene expression [14]. Adrenergic receptor activation (α- and β-receptors) is involved in this pathogenesis [66]. Therefore it appears feasible that adrenergic receptor inhibitors might be beneficial.

In patients with resistant hypertension, the suggested blood pressure goal of below 140/90 mmHg cannot always be achieved using oral antihypertensive medication. Therefore, there has been extensive research on alternative approaches for blood pressure control. Due to the pivotal role of sympathetic activity in the pathogenesis of hypertension, novel treatment strategies have focused on the alteration of sympathetic overactivity in order to control blood pressure and reduce overall cardiovascular risk.

There have been two major advancements in the field of non-pharmaceutical intervention: baroreflex activation therapy at the caroid body and catheter-based renal denervation. Each of these strategies significantly reduces sympathetic activity and controls blood pressure beyond pharmaceutical intervention.

4.2 Baroreflex activation therapy

As described above, dysfunction of the baroreceptor reflex causes an increase in sympathetic activity in a variety of diseases such as sleep apnea and chronic heart failure. In a canine animal model, Lohmeier et al. could demonstrate that activation of the baroreflex at the carotid artery by implanted pacemaker was able to reduce blood pressure as well as serum catecholamine levels [67, 68]. This approach is currently in clinical evaluation for resistant hypertension [69]. Promising data from a clinical trial for baroreflex activation therapy has been published recently. In this study, baseline mean blood pressure was 179/105 mmHg and heart rate was 80 beats/min, with a median of 5 antihypertensive drugs. After 3 months of device therapy, mean blood pressure was reduced by 21/12 mmHg. This result was sustained in 17 subjects who completed 2 years of follow-up, with a mean reduction of 33/22 mm Hg. The device exhibited a favorable safety profile [70].

In the Rheos Pivotal Trial, preliminary results (2010) also show similar results in blood pressure control [71]. In this study, subjects were enrolled if systolic blood pressure (SBP) was > 160 mmHg, 24-hour ambulatory SBP > 135 mmHg and they were on at least 3 antihypertensive drugs at maximum doses including a diuretic. 2010, 45 of 55 roll-in subjects have reached 6 months follow-up: Prior to baroreflex activation therapy mean blood pressure was 178/102 mmHg and post baroreflex activation therapy mean blood pressure was 144/87 (p<0.001). A reduction of > 20 mmHg was achieved in 69 % and > 30 mmHg in 58 % of subjects. In this study, antihypertensive medication remained unchanged during the follow-up period.

There are some issues of concern regarding this intervention. Previously, baroreflex activation therapy required bilateral carotid preparation and implantation of electrodes and the corresponding pacemaker aggregate. Due to the approach of bilateral activation, battery power of pacemakers lasts only for two years with the need of replacement after this period. However, advancements regarding baroreflex activation therapy are made. Recently, a

single side baroreflex activation device has been introduced which is currently investigated in clinical trials.

4.3 Renal denervation therapy

As stated above, renal denervation in animals leads to a reduction of MSNA and blood pressure. In 1923, sympathectomy was performed for the first time in order to treat hypertension with stenocardia [72]. In 1935, Page and Heuer at the Rockefeller institute published data on surgical sympathectomy on blood pressure and renal function [73].

In 1953, a large study of 1266 cases was published on lumbal sympathectomy. However, this procedure was linked with severe side effects such as voiding dysfunction, intestinal dysfunction, impotence and orthostatic dysregulation [74]. Due to pharmaceutical alternatives, surgical sympathicolysis was replaced by antihypertensive drugs.

Recently, a novel, minimal-invasive, catheter-based approach is available which selectively severs renal nerve fibers at the site of the renal artery [75]. This renal denervation strategy can significantly reduce blood pressure in resistant hypertension (Fig. 7) [76]. In a multicentre, prospective, randomized trial, patients who had a baseline systolic blood pressure of 160 mmHg or more (≥150 mmHg for patients with type 2 diabetes) and were treated with at least 3 antihypertensive drugs were enrolled. After a 6-month follow-up period after renal denervation, office-based blood pressure measurements in the renal denervation group reduced by 32/12 mmHg (SD 23/11, baseline of 178/96 mmHg, $p<0.0001$) without significant side effects. Patients with a glomerular filtration rate of < 45 ml/Min/1.73 m^2 (MDRD) or renal artery abnormalities were excluded from the study.

Due to the pathogenesis of sympathetic overactivity in chronic kidney failure, it is feasible that this novel approach might also be beneficial in this patient group.
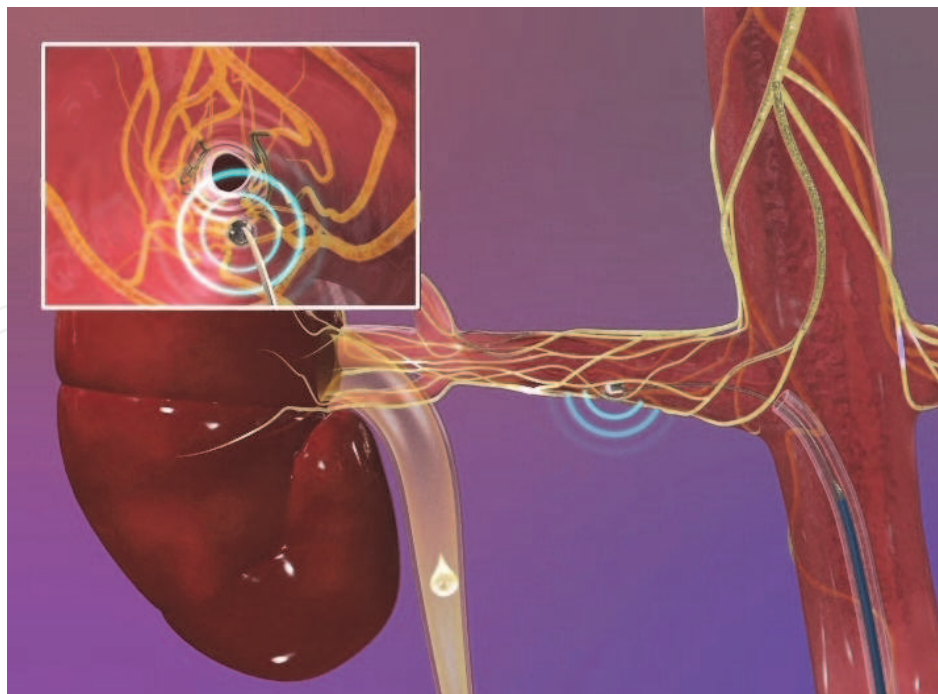

Fig. 7. Schematic of renal nerve fibres along the renal artery. Renal denervation is achieved by ablation using a catheter which is connected to a radiofrequency generator (picture by Ardian/Medtronic).

In a preliminary study, renal norepinephrine release was measured. There was a significant mean reduction of 47 %. Exemplary, MSNA was measured in a patient before and after renal denervation. A marked reduction in nerve activity could be demonstrated (Fig. 8) [77].
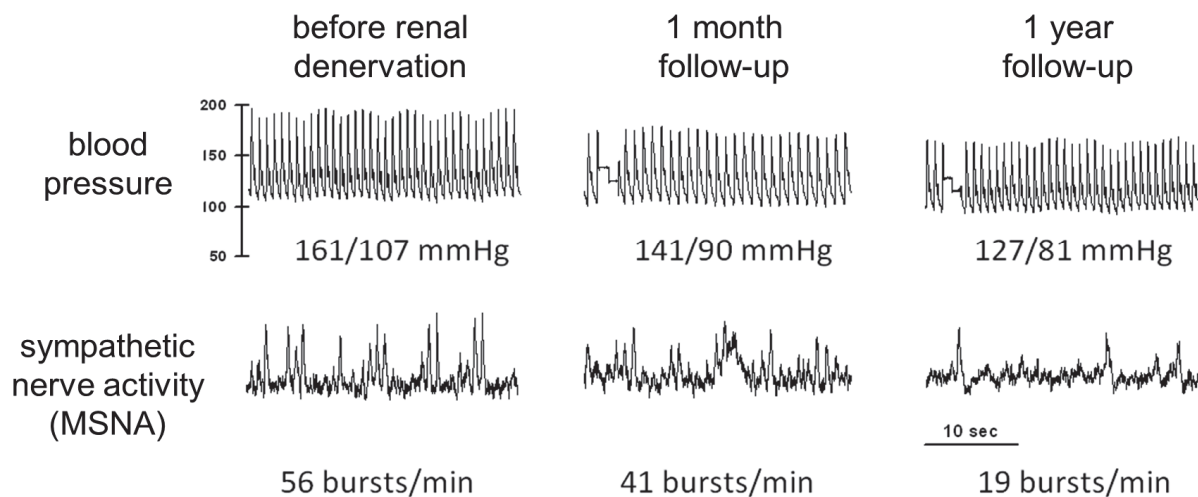

Fig. 8. Exemplary blood pressure and MSNA in a patient before and after renal denervation. There is a significant reduction in blood pressure and burst activity (modified from [77]).

5. Summary

Hypertension is the most significant health burden in modern societies. 25 to 35 % of the population suffers from this condition. Due to increasing age, the incidence of hypertension will increase in the future.

Overactivity of the sympathetic nervous system is a striking feature of a variety of cardiovascular and renal diseases. There is a distinct correlation between sympathetic activity, stage of disease and hypertension. Almost every hypertensive subject shows sympathetic overactivity. It correlates well with the cardiovascular event rate (heart failure, myocardial infarction, and stroke).

The kidney plays a pivotal role in the control of sympathetic nerve activity. Baro- and chemoreceptors which activate afferent sensory nerves travel from the kidney to the sympathetic nuclei of the central nervous system. This can lead to an increase in sympathetic activity which leads to an increase of neurotransmitter release in the target organs. This axis is especially pronounced in patients with chronic kidney disease. But also chronic heart failure, sleep apnea and obesity increase sympathetic nerve activity which can be measured by microneurography.

Pharmaceutical intervention can be achieved with RAAS-blockade (Renin- or ACE-inhibitors, or AT1-blockers) and peripheral adrenergic receptor antagonists and centrally acting sympatholytic drugs.

If pharmaceutical therapy fails in achieving target blood pressure levels, novel approaches in hypertension treatment such as baroreflex activation or renal denervation therapy are promising strategies for future treatment which directly inhibit the pacing of sympathetic activity.

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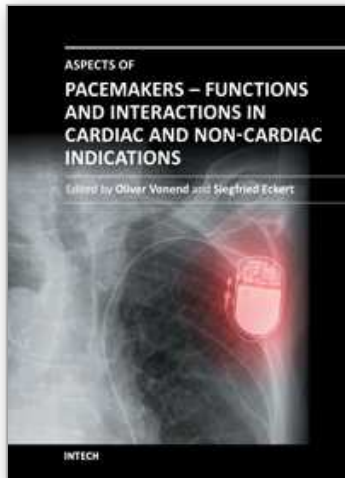
Aspects of Pacemakers - Functions and Interactions in Cardiac and Non-Cardiac Indications

Edited by Dr. Oliver Vonend

Outstanding steps forward were made in the last decades in terms of identification of endogenous pacemakers and the exploration of their controllability. New â€œartificalâ€ devices were developed and are now able to do much more than solely pacemaking of the heart. In this book different aspects of pacemaker â€“ functions and interactions, in various organ systems were examined. In addition, various areas of application and the potential side effects and complications of the devices were discussed.

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