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THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE PATHOMECHANISM AND THE THERAPY OF HYPERTENSION

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Ph.D. Thesis

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LIST OF FULL PAPERS THE THESIS IS BASED ON

I. **Légrády Péter,** Vörös Erika, Bajcsi Dóra, Sonkodi Sándor, Barzó Pál, Ábrahám György: Neurovascular pulsatile compression and neurosurgical decompression of the rostral ventrolateral medulla in medically resistant hypertensive patients. Kidney Blood Press Res 2008; 31: 433-437. Impact factor: 1.268

II. **Légrády Péter,** Bajcsi Dóra, Fejes Imola, Vörös Erika, Barzó Pál, Ábrahám György: Effect of left-sided brain stem decompression on blood pressure and short-term cardiovascular regulation in resistant hypertension. Hypertens Res 2012; 35: 1118-1119. Impact factor: 2.791

III. **Légrády Péter,** Bajcsi Dóra, Lengyel Csaba, Várkonyi T Tamás, Fejes Imola, Kempler Péter, Ábrahám György: Investigation of cardiac autonomic and peripheral sensory neuropathy in diabetic and nondiabetic patients with hypertension. Clin Exp Hypertens 2013; 35: 465-469. Impact factor: 1.276

IV. **Légrády Péter,** Vörös Erika, Bajcsi Dóra, Fejes Imola, Barzó Pál, Ábrahám György: Observations of changes of blood pressure before and after neurosurgical decompression in hypertensive patients with different types of neurovascular compression of brain stem. Kidney Blood Press Res 2013; 37: 451-457. Impact factor: 1.596

V. **Légrády Péter,** Bajcsi Dóra, Lengyel Csaba, Várkonyi Tamás, Hajszán Nikoletta, Kempler Péter, Ábrahám György: Cardialis autonóm és perifériás sensoros neuropathia vizsgálata cukorbeteg és nem cukorbeteg hypertoniás betegekben. Diabet Hung 2007; 15: 271-280.

VI. **Légrády Péter,** Barzó Pál, Vörös Erika, Bajcsi Dóra, Sonkodi Sándor, Ábrahám György: A rostrális ventrolaterális medulla neurovaszkuláris pulzatilis kompressziója

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VII. **Légrády Péter,** Barzó Pál, Vörös Erika, Bajcsi Dóra, Fejes Imola, Ábrahám György: Bal oldali agytörzsi dekompresszió hatása a vérnyomásra és gyors kardiovaszkuláris adaptációra. Magy Belorv Arch 2012; 65: 69-74.

VIII. **Légrády Péter,** Nagy Ferenc T, Thury Attila, Bajcsi Dóra, Fejes Imola, Simon Judit, Nagy Endre, Ungi Imre, Ábrahám György: Mindkét oldali renalis artéria rádiófrekvenciás ablációjának hatása a vérnyomás, a terápia és a baroreflex szenzitivitás alakulására terápiarezisztens hypertoniás beteg esetében. Hypertonia és Nephrologia 2012; 16: 148-152.

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I. Tóth Ferenc, Várkonyi Tamás, Kiss József Géza, Róvó László, Lengyel Csaba, **Légrády Péter,** Jóri József, Czigner Jenő: Brainstem auditory-evoked potential examinations in diabetic patients. Scand Audiol 2001; 30 (Suppl 52): 156-159. Impact factor: 0.652

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III. Sonkodi Balázs, Fodor JG, Ábrahám György, **Légrády Péter,** Ondrik Zoltán, Lencse Gerda, Sonkodi Sándor: Hypertension screening in a salami factory: a worksite hypertension study. J Hum Hypertens 2004; 18: 567-569. Impact factor: 1.93

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V. **Légrády Péter,** Lengyel Csaba, Várkonyi Tamás, Paprika Dóra, Szili-Török Tamás, Rudas László, Kempler Péter, Ábrahám György: A rövid időtartamú vérnyomás-variabilitás vizsgálata cardialis autonóm és perifériás sensoros neuropathiával szövődött normotensiv 1-es típusú diabeteses mellitusos betegekben. Diabet Hung 2008; 16: 7-17.

VI. Fejes Imola, **Légrády Péter,** Bajcsi Dóra, Farkas Katalin, Ábrahám György: A vizsgaidőszak mint stressz-szituáció hatása a cardiovascularis paraméterekre egészséges egyetemi hallgatókban. Magy Belorv Arch 2012; 65: 179-184.

VII. Sonkodi Balázs, Sonkodi Sándor, Steiner S, Helis E, Turton P, Zachar P, Ábrahám György, **Légrády Péter,** Fodor JG: High prevalence of prehypertension and hypertension in a working population in Hungary. Am J Hypertens 2012; 25: 204-208. Impact factor: 3.665

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LIST OF ABBREVIATIONS

ABPM =	ambulatory blood pressure monitoring
AHA =	American Heart Association
ANOVA =	one-way analysis of variance
ATRAMI =	Autonomic Tone and Reflexes After Myocardial Infarction
BRS =	baroreflex sensitivity
BRSL =	baroreflex sensitivity in the lying position
BRSS =	baroreflex sensitivity in the standing position
BP =	blood pressure
BMI =	body mass index
C =	healthy nondiabetic normotensive controls
CAN =	cardiac autonomic neuropathy
CPT =	current perception thresholds
CRT =	cardiovascular reflex test
CV =	cardiovascular
DBP =	diastolic blood pressure
DHT =	type 2 diabetic patients with hypertension
DM =	diabetes mellitus
ECG =	electrocardiogram
ESC =	European Society of Cardiology
ESH =	European Society of Hypertension
F =	female
eGFR =	estimated glomerular filtration rate
HbA1c =	glycated haemoglobin A1c
HT =	hypertension
HR =	heart rate
JNC 7 =	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
M =	male
MRA =	magnetic resonance investigation combined with angiography
MRFIT =	Multiple Risk Factor Intervention Trial
NDHT =	nondiabetic patients with hypertension
NE =	norepinephrine
NS =	non-significant
NTS =	nucleus tractus solitarius
NVD =	neurosurgical neurovascular decompression

NVPC = neurovascular pulsatile compression
PA = primary aldosteronism
PICA = posterior inferior cerebellar artery
PP = pulse pressure
PSN = peripheral sensory neuropathy
RAAS = renin-angiotensin-aldosterone system
RBF = renal blood flow
RDN = renal denervation
RHT = resistant hypertension
RRI = interval between ventricular depolarizations
RVLM = rostral ventrolateral medulla
SNA = sympathetic nerve activity
SBP = systolic blood pressure
SD = standard deviation
SNS = sympathetic nervous system
TOD = target organ damage
VA = vertebral artery

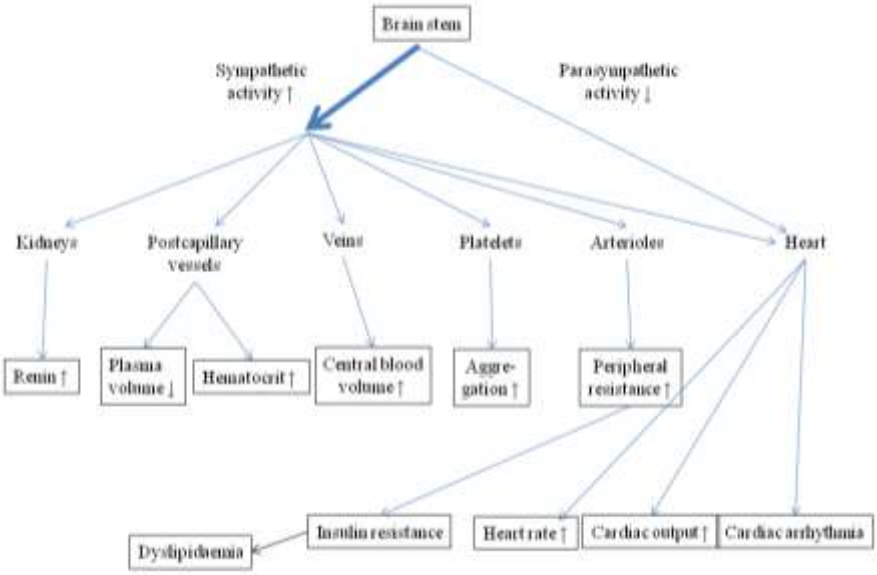
1. INTRODUCTION

1.1. The sympathetic nervous system and cardiovascular diseases

CV diseases are the leading causes of death almost all over the world. Increased SNA is associated with higher CV risk.

The SNS has an important role in the pathogenesis not only of HT and DM, but also of the metabolic syndrome, congestive heart failure, and renal insufficiency. It is the main regulatory element for the CV system. Neurons located in the RVLM of the brain stem play the central role for SNA. These neurons have a basic, so called tonic SNA that maintains a basic peripheral vascular tone. The SNA generated in the brain stem is modulated by arterial baroreceptors, cardiopulmonary mechanoreceptors, chemoreceptors, and more centrally by limbic centers, the hypothalamus and the cerebral cortex (1). The effects of SNA are summarized in Figure 1.

Figure 1 *The effects of sympathetic activation (2).*



1.2. The epidemiology of hypertension

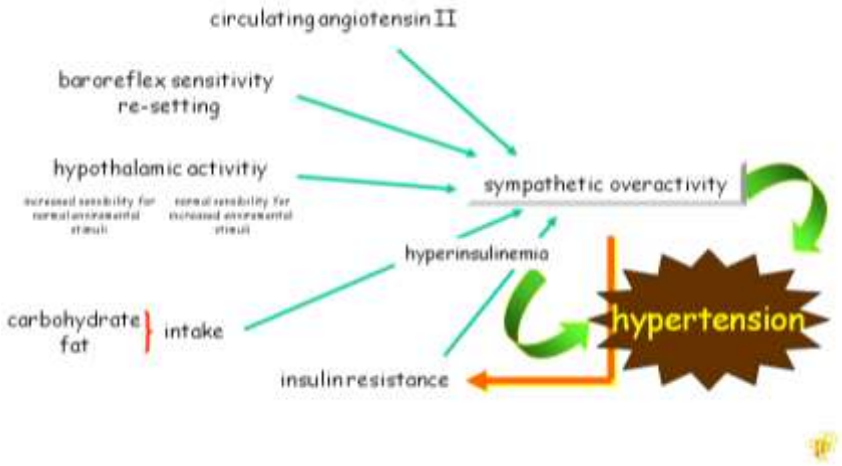
HT is one of the most important CV risk factors and it is can be controlled. The newer classifications of HT try to describe both its complex and progressive modality. According to

these newer concepts HT is a syndrome involving discrete BP thresholds, the assessment of an individual's risk for CV events and the TODs (3). There is a linear association between the BP values and CV risk and the risk of CV diseases doubles with each increment of 20/10 mmHg, beginning at 115/75 mmHg (4). Individuals who are normotensive at 65 years of age and their expected residual lifetime is 20 years have a 100% risk for developing HT (5). HT is more prevalent in developed countries; in European countries the prevalence is around 44%, and in North-American countries 28% (6). HT is more common in economically developed countries (37.3%) compared to developing ones (22.9%) (7). Overall the prevalence of HT is about 30–45% of the general population (8). The prevalence of HT in Hungary, according to Sonkodi et al. is approximately 25.7% (9). The estimated total number of HT patients in 2000 was 972 million, and the prognosis is an increase by 60% to a total number of 1.56 billion by 2025. About 29% of the worldwide adult population will be affected. HT therefore poses great public health and economical challenges worldwide.

1.3. The role of the sympathetic nervous system in the pathogenesis of hypertension

The pathogenesis of HT is of highly sophisticated complexity, but increased SNA plays a major role. There are many mechanisms related to SNA that may lead to HT not only peripheral resistance and heart rate (Figure 2).

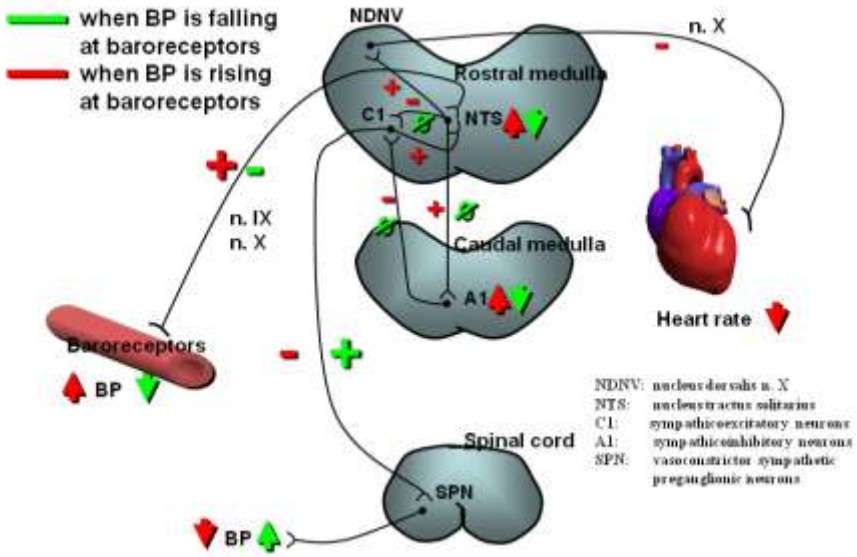
Figure 2 *Mechanisms that lead to sympathetic overactivity and hypertension.*



1.3.1. The sympathetic and parasympathetic regulation of blood pressure

The RVLM located in the brain stem is the center for the neuronal regulation of BP and HR. There is a sympathico-excitatory group of neurons (the so called C1 neurons) in the RVLM about 1 mm below the surface of the brain stem. This group of neurons is an integral part of baroreflex pathway. Cranial nerve IX (the glossopharyngeal nerve) carries afferent impulses from the aortic arch and cranial nerve X (the vagus nerve) does the same from the carotid sinus, baroreceptors are located there. The left nerve X also carries afferent signals from the mechanoreceptors in the left atrial wall (10). The stimulus for baroreceptor activity is the distension of the arterial wall. The afferent impulses from baroreceptors activate the NTS which inhibits the C1 neurons and activates inhibitory A1 neurons located in the caudal ventrolateral medulla (the so called depressor region). The final result of this is a parasympathetic activation and a decrease of tonic SNA. Efferent fibres lead from the C1 neurons into the preganglionic sympathetic neurons located in the intermediolateral column of the thoracic spinal cord. Discharge of these C1 neurons increases systemic SNA (11). An activation of the C1 neurons elevates the BP, whereas its deactivation decreases the BP (12, 13) (Figure 3).

Figure 3 *The baroreflex mechanism.*



The SNS modulates the heart rate (via β1-receptors) and resistance vessels (via α1-receptors) positively. The parasympathetic nervous system mainly affects the heart rate negatively. In HT the increased SNA is associated with decreased parasympathetic activity (1).

There is a positive feedback mechanism between the SNS and the RAAS. The SNS increases RAAS activity and, in turn, angiotensin II stimulates the adrenergic centers so that a vicious circle develops.

1.3.2. Baroreflex sensitivity

The baroreflex is one of the most important mechanisms for preventing excessive changes in BP.

The changes of BP wave amplitudes lead to prompt modulation of HR via the baroreflex mechanism. The BRS is an index of the sensitivity of arterial baroreflex modulation of HR but it has a wide range of variability in a healthy population. In healthy individuals the BRS decreases after standing up compared to a lying position because of an increased sympathetic tone suppresses the vagal cardiac efferent tone (14). In primary HT there is an increased SNA, the set point of the baroreflex is displaced upwards and the BRS is decreased. The arterial BRS is a marker for parasympathetic activity which is responsible for short-term CV regulation. The BRS may be useful as a risk marker for CV diseases (15). Decreased vagal BRS is suggested to be an independent predictor of poor survival following an acute myocardial infarction even 28 days later, according to the results of the ATRAMI study (16). In heart failure, decreased BRS is associated with the severity of the disease and it is an independent predictor of long-term survival (17). BRS decreases with the higher grade of HT and is related to several CV risk factors (15). Impaired BRS is also associated with diastolic dysfunction in HT patients (18) and the BRS is also suggested to be a sensitive early marker in diabetic neuropathy (19). Decreased spontaneous BRS were observed in HT (20), and with elevated pulse wave velocity (21, 22).

1.3.3. Evidence for increased sympathetic activity in patients with hypertension

Tachycardia is a simple but significant indicator of SNA and it is often related to hyperkinetic circulation in borderline HT. Furthermore tachycardia is an important marker of CV risk (23, 24). Tachycardia is associated with significantly higher BP (25).

In the Goldstein meta-analysis of 32 studies, NE levels were higher in HT patients (26). Compared to normotensive individuals the total NE spillover was only approximately 20-25% higher in HT patients, but the regional NE spillover was about 150% higher in HT patients (27).

Using microneurography the muscle SNA was higher in patients with HT compared to normotensives (28, 29) but skin SNA was not elevated, indicating that increased SNA is not a general, whole body phenomenon (30).

In the early stage of HT the SNA mainly increases cardiac output, while in the late stage it increases the peripheral resistance (31).

1.4. Hypertension and diabetes mellitus

HT is common feature of both type 1 and typically type 2 DM. Office BP readings are in the normal range for a long time in DM, and usually it is the nocturnal BP which increases first. Therefore monitoring 24-h ambulatory BP in apparently normotensive patients with DM is a useful prescribed diagnostic procedure (8).

HT is more common in individuals with type 2 DM compared to the general population; the prevalence is about 60-70% of the type 2 diabetic population (32). In HT patients, type 2 DM develops 2.5 times more frequently (33). In type 1 DM, HT appears after the development of diabetic nephropathy (34). The development of HT accelerates the course of micro- and macrovascular complications in diabetic patients. In the MRFIT Study coronary artery disease mortality was 2-3-times higher among HT diabetic patients (35).

The CV morbidity and mortality in DM is 2.5-7.2 times higher compared to the general population (33).

In 1999 the AHA, examining the CV complications of DM, made the statement that, from the point of view of CV medicine, it may be said: “diabetes mellitus is a CV disease.” (36).

1.4.1. Diabetic polyneuropathy

The diabetic polyneuropathy has 3 types as classified by Dyck et al. (37). The most common and, in terms of the prognosis, the most important complications of DM are the autonomic and sensorimotor neuropathies, which have been subjected to intensive research over the past decades (38).

1.4.1.1. Cardiac autonomic neuropathy

The CAN may cause symptoms ranging from resting tachycardia to sudden cardiac death. A disturbance of the sympatho-vagal balance leads to deficient reductions in HR and BP during the night, resulting in the "non-dipper" phenomenon. The early parasympathetic damage may lead to a relative sympathetic overactivity with the development of an increased HR before HT has appeared (39).

1.4.1.2. Peripheral sensory neuropathy

The PSN, which can be characterized quantitatively, is considered as the most important pathogenetic factor for the development of the diabetic foot syndrome, a condition mostly responsible for lower-extremity amputations. The EURODIAB IDDM Complication Study, involving 3250 insulin-dependent diabetic patients, identified well-known and new risk factors for the development of PSN. Significant correlations were demonstrated between the PSN with age, duration of diabetes, diabetic retinopathy and high-density lipoprotein cholesterol, presence of CV disease, elevated DBP, triglyceride, cigarette smoking, height, ketoacidosis, retinopathy, microalbuminuria, and metabolic control (40). There are likewise

associations between HT and PSN in type-1 and type-2 DM and in elderly nondiabetics (41, 42). The role of HT in the development of PSN is not well understood, although a positive correlation in nondiabetics also has been described (42). On the contrary, there are results showing that HT might be protective against the development of PSN, mainly in the elderly patients, with or without DM (43, 44).

1.5. The resistant hypertension

HT is poorly controlled not just in Hungary, but also in Europe and worldwide. In Hungary in 2007 the BP of 46% of the nondiabetic HT population and only 8.5% of the diabetic HT population was in the goal range (45).

In 2013, according to the ESH and the ESC, HT is defined as therapeutically resistant when an appropriate lifestyle modification with a triple antihypertensive drug combination (a diuretic and two other antihypertensive drugs belonging to different classes but not necessarily including a mineralocorticoid receptor antagonist) at adequate doses fail to lower SBP and DBP values to <140 and 90 mmHg (8). But there are some other frequently used definitions of RHT (Table 1) (46).

The real prevalence of RHT is not known, it varies over a wide range depending on the definition and goal BP values used at different data collection locations, the population examined and the level of medical screening (etc. work place, general practitioner office, hospital, clinic, HT center, and so on). The prevalence in general practitioner offices is suggested to be less than 5% of the overall HT population, while in clinical trials 10-20% and in HT centers (47).

According to an ESH Newsletter, published in 2011, the prevalence of RHT is 2.9-43% (48).

The prevalence of TODs such as left ventricular hypertrophy, retinopathy, microalbuminuria and thicker arterial intima-media layer are higher in true RHT by a 50-100% range compared to well-controlled hypertensives. The risk of CV diseases is also 2.5-5 times higher (49, 50).

Table 1 The frequently used definitions of resistant hypertension.

2003 ESH-ESC guidelines (51)
Hypertension may be termed resistant to treatment, or refractory, when a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs in adequate doses has failed to lower systolic and diastolic blood pressure sufficiently.
2007 ESH-ESC guidelines (52)
Hypertension is usually defined resistant or refractory to treatment when a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs (including a diuretic) in adequate doses has failed to lower systolic and diastolic blood pressure to goal.
JNC 7 (2003) (4)
Resistant hypertension is defined as the failure to achieve goal BP in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic.
AHA 2008 (53)
Resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose amounts.

The increased SNA has a key role in generating and sustaining primary, true RHT. The TODs of HT may also come with increased SNA leading to further progressions. The possible causes of RHT are summarized in Table 2.

In RHT, the prevalence of so called identifiable causes is fourfold higher than in non-RHT (54). Pseudoresistant and secondary RHT forms are usually tractable, and they can convert to be controlled or well-controlled HT.

1.5.1. Pseudoresistant hypertension

One of the most important and most common causes of RHT in primary care concerns problems with BP measurement. The technical issues involved here are the improper cuff (e.g., usually smaller-than-required in obese patients, inaccurate manometer), the lack of a

few-minutes (e.g., usually 5 minutes) rest prior to measurement, and markedly atherosclerotic arteries causing so called pseudohypertension (10-15 mmHg higher pressure is needed to compress the cuff compared to intra-arterial pressure). A positive Osler manoeuvre and the presence of calcified brachial arteries by radiography can support the pseudohypertension (55).

Table 2 Possible causes of resistant hypertension (56).

1. Pseudoresistant hypertension		
	Improper blood pressure measurement technique	
		Improper cuff
		Missing rest prior to measurement
		Difficulty to compress atherosclerotic arteries
	"White-coat effect"	
	Poor patient adherence and/or compliance	
2. Secondary resistant hypertension		
	Co-morbidities and conditions	
		Obesity
		Excess alcohol consumption
		Chronic pain
		Obstructive sleep apnoea syndrome
		Depression
	Drugs, health products, poisoning	
		Non-steroid anti-inflammatory drugs
		Excess glucocorticoid activity
		Sympathomimetics
		Oral contraceptives
		Sibutramine
		Cocaine, amphetamine, „crack” „speed”
		Erythropoietin
		Cyclosporine
		Tricyclic antidepressant drug
		Lead, mercury
	Secondary hypertension	
		Primary aldosteronism
		Chronic kidney disease
		Renal artery stenosis
		Pheochromocytoma
		Cushing's syndrome
		Hyperparathyroidism

The "white-coat effect" means that office BR readings are high while home BP reading are within goal values. This white-coat effect can be suspected if HT-related TODs are less severe than could be expected from the office BP. The prevalence of the white-coat effect is approximately 20-30% (54). The white-coat effect is very probable if the office BP is 140/90 mmHg and the mean BP of 24 home measurements per 7 days is less than 125/75 mmHg. The patients showing the “white-coat effect” have a lower CV risk and TOD compared to true RHT patients (57).

Non- or poor adherence to prescribed drugs and/or non-compliance make it more difficult to reach the goal BP of HT patients. The non-compliance prevalence is higher (50%) in primary care than in centers specialized on HT (16%) (53, 58). Non- or poor adherence usually can be due to intolerance (objective and/or subjective ones) (54). Its diagnosis is quite difficult, because the sensitivity of methods such as a personal interview with the patient, the so called „clinical experience” or the counting of tablets is about 50% effective, although their specificity is over 85% (58, 59). Non-adherence may be related to the level of patient education and/or accomplishment, complexity of the regimen, anticipated or actual side effects, or interestingly the idea that „drugs are poisons”.

1.5.2. Secondary causes of resistant hypertension

After excluding all the pseudoresistant causes and revealing co-morbidities, drugs and health products in a case of suspected RHT the final step is to look for possible secondary causes.

PA is a common form of endocrine HTs and is the most important in RHT. The inappropriate production of aldosterone results in sodium retention and suppression of renin. It is usually caused by an adrenal adenoma on one side or bilateral hyperplasia of the adrenocortical zone glomerulosa.

Classically PA is featured with hypokalemia, but according to newer data of the ESH hypokalemia is only presented in 9-37% of the all PA cases (60). The prevalence of PA is 15-20% in RHT and less than 1% in the general HT population. By applying the plasma aldosterone level/plasma renin activity ratio as a screening test in HT patients, regardless of the presence or absence of hypokalemia, a much higher prevalence of PA was found, 12%

(60). But 77% prevalence in secondary HT has also recently been published (61). In an endocrine guideline screening for PA the RHT patients is recommended (62).

In RHT pheochromocytoma as a secondary cause should be suspected if high BP appears in attacks with palpitation, headache, becoming pale, sweating, angina, arrhythmia, pulmonary edema, loss of weight. The typical triad is paroxysmal headache, palpitation and sweating. The incidence of pheochromocytoma is very low, 2-8 patients per 1 million people (63) and in the HT population the prevalence is about 0.2% (61). Catecholamine-secreting tumors arise from chromaffin cells, and the term „pheochromocytoma" in clinical practice covers both the adrenal (true) pheochromocytomas and the extra-adrenal sympathetic paragangliomas. These tumors have similar symptoms (63). The most sensitive and specific method for screening for pheochromocytomas is the measurement of metanephrine and normetanephrine levels from a 24-hour urine sample or from a plasma sample. The older method of determining vanillyl mandelic acid in a 24-hour urine sample is not specific. If a screening is positive, then an imaging technique is required to localize the tumor. If two of the typical triad are presented then screening for pheochromocytoma is markedly advised.

1.5.3. Resistant hypertension and the kidney

The kidney is also involved in the autonomic regulation of BP. On the one hand it partially generates, and on the other hand it receives impulses that force the development of, and sustain, sympathetic overactivity. Animal studies have indicated that the kidney contains different afferent nerves which may cause reflex SNA and so give rise to systemic BP (64, 65).

Renal nerves arise from T10-L2 spinal segments, arborize around the renal artery and primarily lie within the adventitia. All the major renal structural elements are innervated, including vascular smooth muscle cells (including pre- and postglomerular arterioles), tubules, mesangium and renin-secreting cells (66). The juxtaglomerular apparatus, including the renin-containing granular cells is also innervated (67).

Kidney function is independent from tonic renal SNA, after a renal denervation there no changes in RBF and GFR have been found (68). It has also been confirmed after kidney

transplantations that the renal vascular and tubular function is independent from neural control (69).

The RBF autoregulation has two components: a slower tubuloglomerular feedback and a faster myogenic one (70). In normal conditions there is a tonic renal SNA that increases renal tubular sodium reabsorption and renin secretion, but it does not have a vascular effect (70).

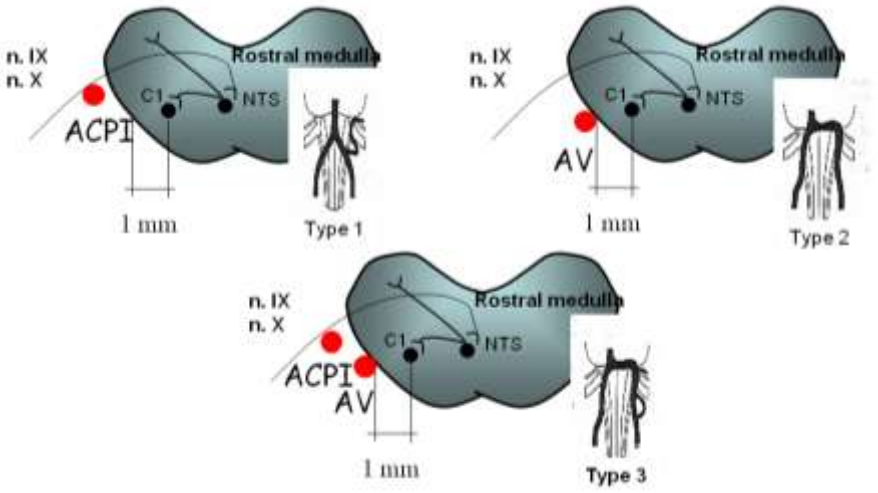
Low-intensity (frequencies ≤ 1.0 Hz) stimuli of renal nerves result first in an increase of renin secretion and then in tubular sodium reabsorption with no change in the GFR and/or RBF. High-intensity (frequencies ≥ 1.0 Hz) stimuli will cause decreased RBF and GFR in addition to increased renin secretion and sodium reabsorption (70, 71).

Physiologically the stimulation of afferent sensory renal nerves inhibits the sympathetic efferent renal nerves, resulting in natriuresis (renorenal reflex). However, in HT animal models this negative feedback is impaired and stimuli from afferent sensory nerves cannot decrease or further increase the renal SNA (72, 73).

1.5.4. Neurovascular pulsatile compression of the brain stem

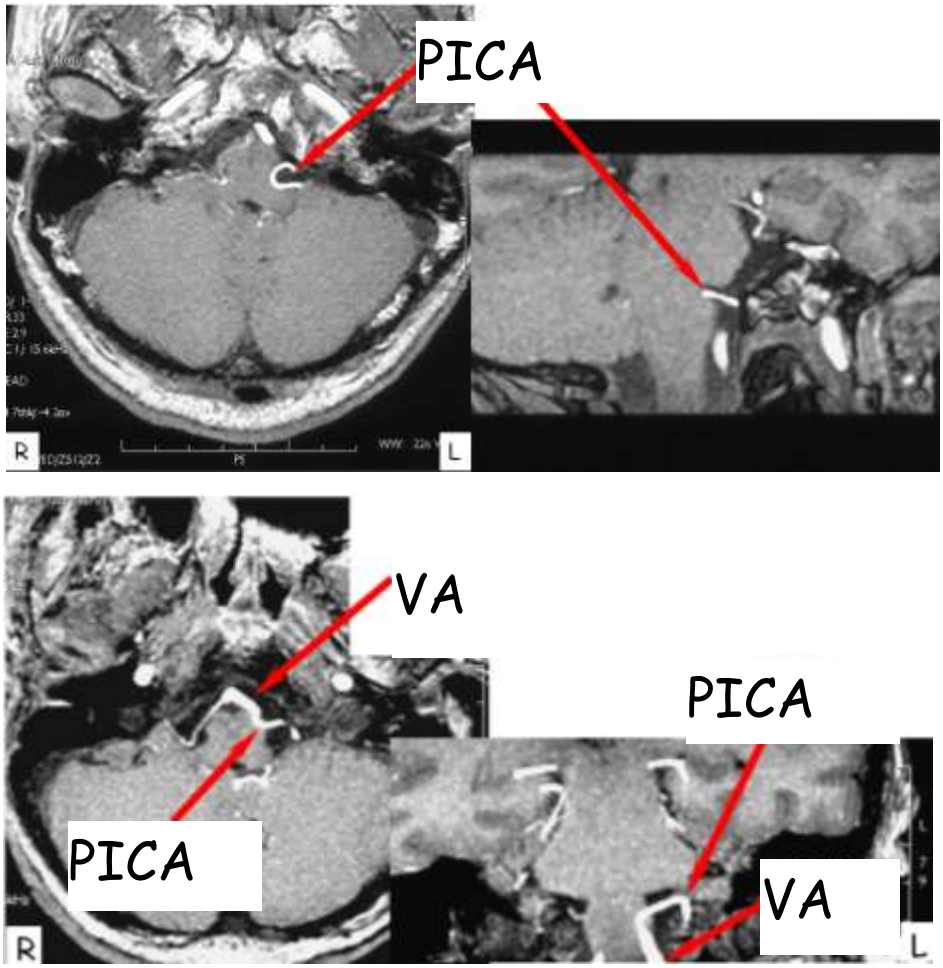
Trigeminal, glossopharyngeal neuralgias and hemifacial spasm are caused by arterial compression, referred to as NVPC, by elongated and/or not typically placed arteries. About forty years ago it was reported for first time by Jannetta and his colleagues that NVPC of the RVLM also can be behind arterial HT. The PICA and/or the VA can compress the root-entry zone of cranial nerves IX and X and/or the C1 neurons containing the retro-olivary sulcus near to the root-entry zone on the left side (Figure 4) (74, 75, 76, 77, 78).

Figure 4 *Types of neurovascular pulsatile compression.*



An MRA can evaluate the diagnosis of NVPC (Figure 5). Without angiography just an MRI is not so sensitive for evaluating any compression.

Figure 5 MRA images of neurovascular pulsatile compression.



1.5.5. Non-pharmacological, non-lifestyle based therapy for hypertension

There are many novel technologies for non-pharmacological, non-lifestyle based therapy for HT. They have in common the attempt to reduce the sympathetic overactivity instrumentally. They are summarized in Table 3.

Non-selective surgical sympathectomy effectively already decreased the BP in ’30s and ’50s of the last century. However this technique unfortunately had severe side effects, causing significant worsening of the quality of life (79, 80, 81).

Table 3 Different non-pharmacological, non-lifestyle based therapies for hypertension.

- Renal denervation
- Baroreceptor activation therapy
- Iliac arteriovenous fistula
- Carotid body ablation
- Deep brain stimulation
- Decompression of the rostral ventrolateral medulla
- Device-guided respiration
- CPAP (in OSA)
- Stent repair of aortic coarctation
- Endovascular repair of renovascular disorders
- Surgical therapy for endocrine HT (adrenalectomy, paraganglionectomy)

The development of endovascular catheter technology in our day permits selective RDN in the adventitia of the renal arteries. The radiofrequency energy is a heat energy that is delivered directly to the nerves in the adventitia and destroys them while preserving other structures of the arterial wall. It may be that renal nerves much more sensitive to heat energy and vibration than other tissues close to them (82). This is a relatively new technology but it also has many different forms (Table 4).

Table 4 Technologies to achieve selective renal sympathectomy.

- Radiofrequency ablation
  - generation 1: unifocal
  - generation 2: multifocal
- Ultrasound therapies
  - endoluminal: high intensity non-focused
  - external: low intensity focused
- Microinjection of neurotoxin
- Cryotherapy

In case of NVPK of the RVLM on the left side, an NVD can significantly decrease both the SBP and the DBP and can improve the sensitivity to drug treatment (83, 84, 85).

2. AIMS

1. To investigate PSN in HT patients without DM and also to evaluate PSN, CAN and BRS in HT patients associated with DM. Additionally, to look for associations between the duration of HT, the duration of DM, the BP values and the severity of any CAN and PSN.

2. To retrospectively collect and analyze the BP levels and the therapy of patients with or without NVD of NVPC over a 2–year period.

3. To retrospectively investigate whether there is an association between the types of NVPC and the SBP and DBP before and after NVD and/or between the types and the changes of BP after NVD.

4. In one case there was an opportunity to monitor the changes of sympathetic and parasympathetic activity before and after an NVD.

5. To observe the changes of BPs and SNA before and after RDN of 4 RHT patients.

3. PATIENTS AND METHODS

3.1. Cardiac autonomic neuropathy

In the first part of this investigation 18 NDHT, 10 DHT, and 11 C individuals were enrolled. An oral glucose tolerance test was performed in all nondiabetic individuals in order to exclude DM and impaired glucose tolerance. Impaired fasting glucose levels were excluded from

fasting plasma glucose measurements. In the second part of this investigation 22 NDHT, 18 DHT and 15 C individuals were enrolled.

Subjects with arrhythmias, bundle-branch block, congestive heart failure, valvular disease, acute myocardial infarction, coronary heart disease, cardiomyopathy, electrolyte disturbances, renal failure, or any other condition causing autonomic and/or sensory neuropathy in the history were excluded from the study. For at least 12 hours before the examination, the patients did not drink coffee or alcohol, did not smoke, and did not perform any strenuous physical activity.

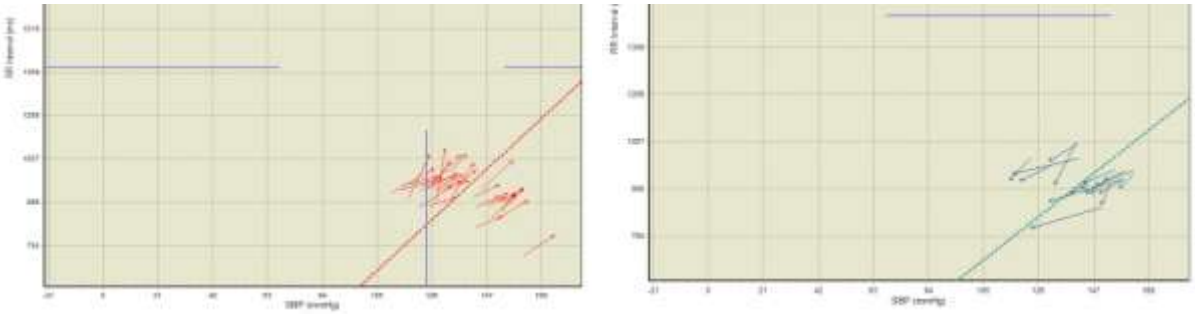
The CAN was assessed by means of the five standard CRTs proposed by Ewing et al. (86). The parasympathetic function was characterized via the changes in HR in response to deep breathing, to the Valsalva manoeuvre, and to standing up (30/15 ratio). The sympathetic function was characterized via the SBP changes in response to standing up and via the DBP changes in response to a sustained handgrip. In all tests, normal values were scored 0, borderline values 1, and abnormal values 2. The sum of the scores gave the total CAN score. A patient was considered as CAN-positive if the score was 2 or higher (at least 2 tests with borderline or 1 test with abnormal values). A score of 0–1 was taken as normal, 2–3 as mild, 4–6 as moderate, and 7–10 as severe CAN.

3.2. Baroreflex sensitivity

Spontaneous BRS was calculated in 10 minutes lying and 10 minutes standing positions via a sequence (time-domain) method using a software package for BRS analysis (Nevrokard BRS 5.1.3; Medistar) (Figure 6).

BRS calculation by sequence method is based on the quantification of sequences of at least three beats in which SBP consecutively increases or decreases, which is accompanied by changes in the same direction of the RRI of the subsequent beats. The software scans the RRI and SBP records, identifies sequences and calculates the linear correlation between RRI and SBP for each sequence.

Figure 6 *The time-domain baroreflex sensitivity by Nevrokard software.*



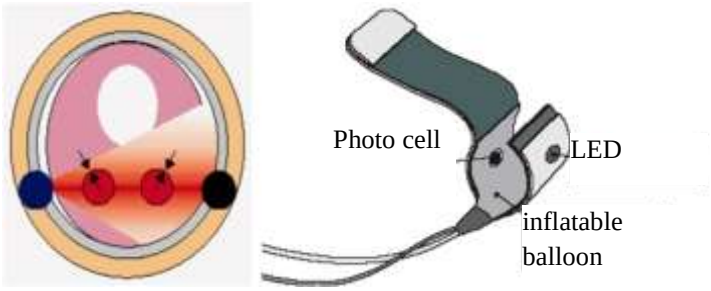
The SBP and RRI files were generated via the beat-to-beat data acquisition system by finger photoplethysmography (Finometer, TPD Biomedical Instruments, Finapres Medical Systems B.V., Amsterdam, The Netherlands) at 200 Hz combined with an ECG (Figure 7 and 8).

Figure 7 *Measurement with Finometer.*

The photoplethysmography technique was developed by Peñáz in 1973 (87). Based on it the continuous beat-to-beat measurement of the arterial BP in a finger and producing a real-time display of the arterial pressure waveform with Finapres was introduced in the early 1980s. The Finometer is a newer generation based on this prelude; it is a non-invasive built-in-one computerized device to measure the brachial arterial pressure using a pneumatic inflatable finger cuff. The brachial arterial BP wave is reconstructed in waveform and level. For this purpose an upper arm cuff return-to-flow systolic pressure determination is used and analysed by an appropriate algorithm. This reconstruction procedure runs fully automatically, which is a default setting of the Finometer (88).

In the wall of the inflatable finger cuff is a photo-electric, infrared plethysmograph, which measures the real time blood volume of the finger (Figure 8). The changes of the blood volume in the finger are modulated by the changes of the systemic arterial BP associated to cardiac cycles. The elasticity of the vessel wall means resistance inverse to blood volume therefore transmural pressure of the arterial wall should be settled up. A fast pneumatic servo system and a dynamic servo set point adjuster assure arterial unloading at zero transmural pressure and consequent full transmission of arterial BP to cuff air pressure (89). The pressure inside the cuff represents the intra-arterial finger pressure with a minimal delay (90).

Figure 8 *The pneumatic inflatable finger cuff.*



3.3 Peripheral sensory neuropathy

The peripheral sensory function was characterized via the CPTs as measured with a Neurometer (Neurotron Inc., Baltimore, MD, USA) (Figure 9). Median and peroneal nerves (digital branches) were assessed. The intensity of the current issued by the device ranged between 0.01 and 9.99 mA. For both the median and the peroneal nerves, the CPTs were measured at 2000, 250, and 5 Hz in order to assess large and small myelinated, as well as small unmyelinated, sensory nerve fiber function, respectively (91, 92, 93).

Figure 9 *The Neurometer device.*

The data obtained on the control patients and the patients treated for HT were compared statistically by parametric ANOVA or nonparametric ANOVA (Kruskal–Wallis). Pairwise comparisons were made using the Student-Newman-Keuls test. The relationships between the results of the examinations and the various patient data were analyzed using Pearson's correlation and multiple linear regression tests. A probability value of <0.05 was considered as significant. Means ± SD are reported.

3.4. Neurovascular pulsatile compression

Between 2000 and 2004, using a neurosurgical database, an MRA was performed in 50 resistant primary HT cases. The criterion for MRA was the prior exclusion of all the possible secondary causes of RHT.

For the MRA a 1T Sigma Horizont LX General Electric device with a 3D spoiled gradient echo /3D time-of-flight technique was used. The volume thickness was 60-70 mm and the slice thickness was 1 mm. The time of echo was 2.9 msec, the time of repetition was 33 msec and the flip angle was 20 degrees. The maximum intensity projection was reconstructed in an optional plane. The requirement for a positive MRA finding was a touch between the looping arteries and the surface of the RVLM at the root entry-exit zone of nerves IX and X, or between the looping arteries and the cranial nerves IX and X on the left side. All the MRA readings were done by the same expert radiologist.

Based on possible anatomical variations according to MRA, different groups were formed. In group BS the NVPC affected only the brain stem (on right side: BSR, on left side: BSL, on both sides: BSB). In group N the NVPC affected only the nerves IX-X (on right side: NR, on left side: NL, on both sides: NB). In group D dual NVPC could be observed affecting both the brain stem and the nerves (on right side: DR, on left side: DL, on both sides: DB).

NVDs were performed under anaesthesia. Following a retromastoidal suboccipital craniotomy on the left side, identifying the anatomical structures a tissue-friendly haemostatic sponge (Spongostan^{TM}) was placed between the arteries and the nerves or the surface of the RVLM. All the procedures were performed in the Department of Neurosurgery in Szeged by the same neurosurgeon.

BP readings were recorded at the time of the last visit, a few days before the NVD, and at the end of 1st postoperative week in the 1st Department of Internal Medicine in Szeged which is one of the Excellence Centers of the ESH. BP readings were performed by manual sphygmomanometer. Means of two measurements were calculated.

To follow-up the changes of BP values the data of control examinations performed 1, 3, 6, 12 and 24 months after the intervention or after MRA in the non-operated cases were analyzed. During the control consultations, physical examination, BP measurement and checks on the therapy were carried out.

Data were compared statistically by means of parametric ANOVA. The relationships between the types of the compressions and the BP levels were analyzed with Pearson's correlation test. Probability levels $p<0.05$ were taken as significant. Means ± SD are reported.

The CAN, the BRS and the plasma NE were estimated in a case of a 57-year-old white woman with HT resistant to 10 different antihypertensive agents (Table 23). The duration of her HT was 36 years. She had impaired glucose tolerance, her BMI was 26.33 kg/m^2 and her GFR was 79.5 ml/min. She had TOD of mild left ventricular hypertrophy (the posterior wall was 10 mm, and the interventricular septum was 11 mm) and Keith–Wagener–Baker grade II hypertensive retinopathy. There were no trigeminal neuralgia or hemifacial spasms in her case history. After excluding all of the possible secondary causes, an MRA was performed as detailed above.

The spontaneous BRS, via a sequence method, were calculated from ECG and BP data recorded by a Finometer device on the day of NVD, just prior to the procedure, and on postoperative day 9. The technique is detailed above.

The NE was quantitatively determined in plasma by a competitive enzyme immunoassay in a microtiter plate format (2-CAT RIA, DIAsource Immuno-Assays S.A., Louvain-La-Neuve, Belgium). Samples for NE were collected on the day of NVD just prior to the procedure and on postoperative days 1 and 9.

Before and after NVD of this woman, a 24-hour ABPM was performed with an ABPM-04 device (Meditech Ltd., Budapest, Hungary).

3.5. Transcatheter renal denervation

Four validated RHT patients agreed to RDN. Their parameters are summarized in Table 5. Before RDN and after it, on the post-procedure day 1, a 24-hour ABPM was performed in every case (ABPM-04 device, Meditech Ltd., Budapest, Hungary). Mean SBP and DBP values were analyzed in this work. The spontaneous BRS via a sequence method were calculated from ECG and BP data recorded with a Finometer device on the day before RDN and on post-procedure day 1. The technique is detailed above.

Table 5 Clinical parameters of patients undergoing renal denervation.

Patients	**52 year old woman**	**50 year old woman**	**39 year old woman**	**62 year old man**
BMI (kg/m^2)	39.1	29.5	32.8	39.9
co-morbidities, TOD	obesity, hyperlipidemia LVH, HF (NYHA I) hypertensive angiopathy st. II	hyperlipidemia, LVH, mitral insuff. I-II, aortic insuff. I , hypertensive angiopathy st. II	obesity, hyperlipidemia, T2DM LVH, PSVT (RF ablation), HF (NYHA I), NVD (24 March 2010)	obesity, hyperlipidemia, IGT LVH, atrial fibrillation, HF (NYHA I), OSAS hypertensive angiopathy st. II, NVD (10 Feb 2010)
antihypertensive medications prior to RDN	valsartan 2x160 mg amlodipine 2x10 mg nebivolol 2x5 mg doxazosin 2x6 mg indapamide 2x1 tbl. clopamide 20 mg urapidil 3x90 mg spironolactone 50 mg dihydralazine 3x12.5 mg minoxidil 1x5 mg	valsartan 2x80 mg hydrochlorothiazide 2x12.5 + 25 mg perindopril 2x10 mg amlodipine 1x10 mg indapamide 1x2.5 mg urapidil 3x90 mg prazosin 3x6 mg doxazosin 2x4 mg carvedilol 1x6.25 mg dihydralazine 2x25 mg amilorid 1x50 mg	valsartan 2x160 mg doxazosin 2x4 mg urapidil 3x90 mg carvedilol 2x25 mg amlodipine 2x5 mg spironolactone 2x25 mg indapamide 2x1.5 mg dihydralazine 3x50 mg rilmenidine 2x1 mg guanfacine 2x1 mg	perindopril 2x5 mg amlodipine 2x10 mg indapamide 2x1.5 mg urapidil 3x90 mg doxazosin 2x6 mg metoprolol 3x25 mg dihydralazine 3x25 mg spironolactone 1x50 mg guanfacine 2x1 mg

RDNs were performed by the joint guidance of the Symplicity^{TM} Catheter System producing Medtronic Inc. and Krum et al. who first described it in 2009 (93). An invasive cardiologist performed the RDNs, but the first time an interventional radiologist also

cooperated in the process. The alprazolam pre-medication and the intraoperative analgesia with propofol-fentanyl combination were provided by an anaesthesiologist.

All the RDN procedures were performed in the Division of Invasive Cardiology, Second Department of Medicine and Cardiology Center, University of Szeged using an Innova 2000™ (GE Healthcare) x-ray machine with angiography. The RDN procedure using a Symplicity^{TM} Catheter System was performed via a femoral approach (6F femoral guide) after an intra-arterial nitro-glycerine administration in analgosedation. The catheter was connected to a radiofrequency generator. The anatomical eligibilities - defined as ≥4 mm diameter, ≥20 mm length, not more than one main renal artery, no significant renal artery stenosis, and/or previous renal artery intervention – were confirmed via renal CT angiography in all cases. Participants were given heparin – average 5000 IU – intravenously to achieve an activated clotting time of more than 250 s. Hydration and acetyl salicylic acid also were applied for all participants. After the confirmation of a proper wall-contact from distal to proximal five-to-six discrete, low-power radiofrequency treatments were applied separated rotationally and longitudinally along the length of renal arteries separately. Each low-power radiofrequency treatment lasted ≤2 minutes with only a 6 Watt energy. During the procedure the system calculates the radiofrequency energy delivered to the nerves by the impedance and the heat was detected via an electrode at the catheter tip. There were no acute vascular complications after the RDN procedure (94).

All the investigations were approved by the local Human Investigation Review Board, University of Szeged (31/2006, 2/2007, 109/2011), and all patients provided written informed consent.

4. RESULTS

4.1. Neuropathies in hypertension and diabetes mellitus

All the HT patients were treated with multiple combinations of antihypertensive drugs, but the two HT groups did not differ significantly in the number of combinations (NDHT 4.44 ± 0.37, DHT 4.2 ± 0.33). Table 6 and Table 7 summarize the types and frequencies of

antihypertensive medications used by the patients in the first and second part of investigations.

Table 6 Frequency of use of antihypertensive drugs in the two patient groups in the first part of investigation.

	NDHT (n=18)	**DHT (n=10)**	*p*
Angiotensin-converting enzyme inhibitor	15/18	6/10	NS
Angiotensin receptor blocker	1/18	3/10	NS
Beta-blocker	6/18	5/10	NS
Dihydropyridine calcium channel blocker	17/18	10/10	NS
Non-dihydropyridine calcium channel blocker	1/18	1/10	NS
Imidazoline I-1 receptor agonist	5/18	6/10	NS
Alfa-1-blocker	2/18	1/10	NS
Alfa-1-blocker + beta-blocker in fixed combination	6/18	1/10	NS
Alfa-1-blocker-alfa-2-agonist	5/18	1/10	NS
Thiazide diuretics	14/18	7/10	NS

Table 7 Frequency of use of antihypertensive drugs in the two patient groups in the second part of investigation.

	NDHT (n=22)	**DHT (n=18)**	*p*
Angiotensin-converting enzyme inhibitor	17/22	14/18	NS
Angiotensin receptor blocker	5/22	3/18	NS
Beta-blocker	8/22	5/18	NS
Dihydropyridine calcium channel blocker	20/22	17/18	NS
Non-dihydropyridine calcium channel blocker	1/22	1/18	NS
Imidazoline I-1 receptor agonist	4/22	6/18	NS
Alfa-1-blocker	4/22	2/18	NS
Alfa-1-blocker + beta-blocker in fixed combination	8/22	4/18	NS
Alfa-1-blocker-alfa-2-agonist	5/22	2/18	NS
Thiazide diuretics	18/22	15/18	NS

In the first part of the investigation, of the DHT patients 1 was on premix insulin and 1 received only dietary treatment at the time of the investigations, the others were on oral antidiabetics. In the second round, 1 patient was on oral antidiabetics + insulin therapy, 6 patients received only dietary treatment, and the others were on oral antidiabetics.

In the first part of the investigation the two HT groups did not differ significantly in BMI or treated SBP or DBP, but these parameters were significantly higher in both of them than in

group C (Table 8). The clinical parameters for enrolled individuals in the second part are summarized in Table 10.

Table 8 Clinical parameters of investigated groups in the first part of investigation. (*$p < 0.05$ NDHT *vs.* C and DHT vs. C; †$p < 0.05$ DHT *vs.* C and NDHT)

	C (n=11)	NDHT (n=18)	DHT (n=10)
Gender	5 M, 6 F	8 M, 10 F	4 M, 6 F
Age (yr)	44.9±7.3	54.4±13.9	51.0±8.6
Duration of HT (yr)	-	10.6±9.8	12.3±9.9
Duration of DM (yr)	-	-	6.1±7.7
BMI (kg/m^2)	23.7±4.0	28.2±4.7*	28.5±2.8*
SBP (mmHg)	116.8±11.7	134.9±18.0*	131.6±12.5*
DBP (mmHg)	64.1±6.2	84.2±11.8*	85.6±8.3*
Blood glucose (mMol/L)	4.8±0.6†	5.16±0.7†	8.2±3.1
HbA1c (%)	5.3±0.4†	5.7±0.3†	6.8±1.3

Table 9 Clinical parameters of investigated groups in the second part of investigation. (*$p <$ 0.05 DHT *vs.* C)

	C (n=15)	NDHT (n=22)	DHT (n=18)
Gender	5 M, 10 F	5 M, 17 F	6 M, 12 F
Age (yr)	50.2±5.9	57.2±5.5	57.8±4.7
Duration of HT (yr)	-	8.7±5.2	15.0±11.7
Duration of DM (yr)	-	8.4±7.9	-
BMI (kg/m^2)	26.4±3.7	29.1±3.1	30.9±4.6
SBP (mm Hg)	123±6.0	129±13.8	137±19.1*
DBP (mm Hg)	71±8.0	75±9.2	72±10.0*
Blood glucose (mMol/L)	4.6±1.4	5.1±1.1	6.7±3.7
HbA1c (%)	4.5±1.1	4.7±1.2	6.2±2.7

Table 11 lists the means of the CRTs. In group DHT, one patient did not have CAN with a normal value in the reflex tests and in group NDHT, two patients did not have CAN, but both had borderline value in the reflex tests. The CAN score did not differ significantly between the HT groups (NDHT 4.6 ± 2.5; DHT 3.9 ± 1.96). Group C was free of autonomic neuropathy. There were no patients with sympathetic neuropathy alone either in the DHT or in the NDHT group. Two patients had parasympathetic neuropathy alone both in the DHT

(2/10) and in the NDHT (2/18) groups. In group DHT, 7 patients and, in group NDHT, 14 patients had sympathetic plus parasympathetic neuropathies together.

Table 11 Results of cardiovascular reflex tests in the first part of investigation. (*$p < 0.05$ NDHT *vs.* C and DHT *vs.* C)

	C (n=11)	NDHT (n=18)	DHT (n=10)
Deep breathing (beat/min)	24.8±7.1	13.2±7.6*	16.7±8.9*
Valsalva manoeuvre	1.7±0.3	1.4±0.2*	1.4±0.4*
30/15 ratio	1.2±0.1	1.0±0.1*	1.0±0.1*
Standing up (mmHg)	7.7±8.8	19.8±8.8*	13.5±6.6
Sustained handgrip (mmHg)	26.4±8.7	20.4±11.2	18.8±12.8

The CRT results are presented in Table 12. In group NDHT, 2 patients did not have CAN, 6 patients had mild, 6 patients had moderate, and 4 patients had severe CAN. In group DHT, 1 patient did not have CAN, 2 patients had mild CAN, 7 patients had moderate CAN, and none had severe CAN. In group C, no CAN has been observed at all.

Table 12 Distribution of cardiovascular reflex tests in hypertensive groups in the first part of investigation.

	Number of patients					
	Abnormal (2 points)		Borderline (1 point)		Normal (0 point)	
	DHT	NDHT	DHT	NDHT	DHT	NDHT
Deep breathing	3	8	2	3	5	7
Valsalva manoeuvre	0	3	4	1	6	14
30/15 ratio	6	12	0	2	2	4
Standing up	0	2	7	13	3	3
Sustained handgrip	4	6	1	1	5	11

Data on sensory nerve function are shown in Table 13. The CPTs on the peroneal nerve at 250 Hz in group NDHT and at 250 and 5 Hz in group DHT were higher compared with group C, but the differences were not significant. All the CPTs of the CAN-free patients were within the normal range.

In group NDHT, we found a positive correlation between the severity of CAN and the known duration of HT ($r = 0.64$, $p = 0.008$). In group DHT, there was no correlation between the duration of HT and the severity of CAN. In group DHT, there was a positive correlation

between the duration of HT and the CPTs measured on the lower extremities at 250 Hz (r = 0.68, p = 0.04) and 5Hz (r = 0.68, p = 0.04). The duration of DM also showed a positive correlation with the CPTs measured on the lower extremities at 250 Hz (r = 0.8, p = 0.01) and 5 Hz (r = 0.74, p = 0.02). Such a correlation was not found in group NDHT. When multiple linear regression test was used, in group NDHT there was a correlation between the age and the HR changes in response to deep breathing (t = -2.72, p = 0.02) and to standing up (t = 2.61, p = 0.03). Furthermore, in group NDHT there was a correlation between the BMI and the SBP changes in response to standing up (t = -2.39, p = 0.04). In group DHT, with a multiple linear regression test we found a correlation between age and the SBP changes in response to standing up (t = -3.19, p = 0.04).With a multiple linear regression test in group C, age correlated with the HR changes in response to deep breathing (t = -3.81, p = 0.02), while the BMI correlated with the SBP changes in response to standing up (t = 2.78, p = 0.01). Moreover, in group C, the SBP values correlated with the HR changes in response to deep breathing (t = 4.3, p = 0.01) and with the HR changes in response to the Valsalva manoeuvre (t = -4.48, p = 0.01). In the group C, the DBP values also correlated with the HR changes in response to the Valsalva manoeuvre (t = -3.68, p = 0.01).

Table 13 Current perception thresholds in the first part of investigation.

		Current perception threshold (mA)				*p*
	Hz	**NDHT (n=18)**	**DHT (n=10)**	**C (n=11)**	**Normal range**	
Median nerve	2000	2.55±2.3	1.94±1.2	2.77±0.7	1.20-2.98	NS
	250	1.16±0.9	1.12±0.8	1.03±0.4	0.22-1.80	NS
	5	0.66±0.6	0.52±0.4	0.59±0.2	0.16-1.01	NS
Peroneal nerve	2000	3.06±2.8	3.46±3.2	3.38±0.8	1.87-5.16	NS
	250	2.38±2.9	2.22±2.8	1.51±0.7	0.46-1.90	NS
	5	1.24±1.7	1.74±2.9	0.73±0.3	0.18-1.70	NS

In group DHT, a positive correlation was found between the severity of CAN and the CPTs measured on the median nerve at 250 Hz (r = 0.69; p = 0.02) and 5 Hz (r = 0.74; p = 0.01).

The SBP and DBP values did not correlate either with the severity of CAN or with the severity of PSN. We did not investigate heart rate variability.

The second part of investigation was planned to calculate BRS against CAN score. All the BRS values decreased after standing up in all groups, and they were highest in group C and lowest in group DHT (Table 14) All the patient groups were CAN positive (mean CAN scores: group C 1.0, group NDHT 3.64, group DHT 4.1). The CRT results are in Table 15.

Table 14 The changes of baroreflex sensitivity (ms/mmHg) values in the second part of investigation. ($^{*}p < 0.05$ standing *vs.* lying, $^{\dagger}p < 0.05$ DHT *vs.* NDHT)

	upBRSL	**downBRSL**	**allBRSL**	**upBRSS**	**downBRSS**	**allBRSS**
DHT (n=18)	6.69±4.3	8.34±6.4	7.99±4.8	4.82±2.5*	4.43±2.4*†	4.42±1.8*†
NDHT (n=22)	9.87±5.3	9.7±6.5	10.04±5.0	6.69±4.3*	7.54±4.7	7.31±4.4*
C (n=15)	10.31±6.1	9.98±4.6	10.93±4.2	5.64±2.3*	6.51±2.5*	6.13±2.3*

Table 15 Results of cardiovascular reflex tests in the second part of investigation. ($^{*}p < 0.05$ NDHT *vs.* C and DHT *vs.* C)

	C (n=15)	**NDHT (n=22)**	**DHT (n=18)**
Deep breathing (beat/min)	20.0±7.1	15.35±6.3	13.17±6.2*
Valsalva manoeuvre	1.41±0.3	1.27±0.2	1.38±0.4*
30/15 ratio	1.18±0.5	1.1±0.3	1.18±0.2
Standing up (mmHg)	8.73±4.0	15.55±13.13	21.6±11.34*
Sustained handgrip (mmHg)	24.67±9.7	18.73±8.1	14.56±8.9

In NDHT group there was a positive correlation between the 30/15 ratio and the upBRSS (r = 0.64, $p = 0.0013$), the downBRSS (r = 0.68, $p = 0.0005$) and the allBRSS (r = 0.65, $p = 0.0009$).

4.2. Neurovascular decompression

According to the MRA from the 50 patients no kind of NVPC was found in 6 cases. Left-sided neurovascular contact was found in 43 cases, and right-sided contact in 1 case. Fifteen patients had type BS, 12 patients had type N and 17 had type D compression (Table 16).

Table 16 Distribution of types of neurovascular pulsatile compression among all the 50 patients by magnetic resonance investigation combined with angiography. Six patients had no NVPC.

Type BS (n=15)			**Type N (n=12)**			**Type D (n=17)**		
BSL	**BSR**	**BSB**	**NL**	**NR**	**NB**	**DL**	**DR**	**DB**
n=12	n=0	n=3	n=12	n=0	n=0	n=15	n=1	n=1

NVD was recommended for severe primary HT patients with neurovascular contacts only on the left side. In the cases of left-sided neurovascular contact with only mild-to-moderate increased BP level the NVD was not recommended. NVDs were performed on the 18 patients who agreed to surgery. Only 13 of these were patients of the Szeged 1st Department of Internal Medicine and the others were only sent for the surgical procedure from other hospitals, therefore data concerning them could not be collected retrospectively. All the 13 patients (Table 17) followed up in the 1st Department of Internal Medicine came back to the visit month 1, 10 of them to the visit month 3, 10 of them to the visit month 6 and the same 9 of them to the visit month 12 and 24. The two-year data of these 9 patients were analyzed, because they were the same at all visits (age: 43.7 ± 9.0 years, BMI: 28.5 ± 4.5 kg/m^2, duration of HT: 14.2 ± 9.3 years).

In the 1st Department of Internal Medicine NVD was recommended not just in a case of severe HT but a positive family history of fatal or non-fatal cardio-/cerebrovascular complications was also required. Of course all possible secondary causes were excluded in all cases prior to MRA.

Only in 7 non-operated cases the follow-up was continuous and could be collected the 24 monthly data (age: 40.0 ± 19.3 years, BMI: 29.4 ± 5.5 kg/m^2, duration of HT: 6.1 ± 7.3 years). Many of the remaining 25 non-operated patients did not come back to visits at all or just irregularly. Five operated patients were only sent for NVD from different hospitals and

outpatient clinics, 2 operated patients did not come back to visits at all and 2 operated patients only a few times. In this retrospective work I did not investigate the history of these patients. Further I did not investigate why the patients did not come back to visits.

Table 17 Data of 13 operated patients.

Gender	Age (years)	Time of HT (years)	BMI (kg/m^2)	BP before NVD (mmHg)	BP after NVD (mmHg)	PP before NVD (mmHg)	PP after NVD (mmHg)	N° of comb. before NVD	N° of comb. after NVD
F	52	16	29.9	190/120	156/100	70	56	8	4
F	45	5	26.5	220/125	150/80	95	50	4	3
M	50	5	29.0	190/105	130/75	85	55	5	5
M	31	18	23.1	210/100	130/80	110	50	4	4
F	47	15	22.8	280/150	140/80	130	60	6	3
M	53	15	29.4	240/150	120/80	90	40	3	1
F	47	12	no data	240/145	145/90	95	55	6	4
F	40	10	35.4	200/120	170/120	80	50	6	5
F	35	5	33.6	160/100	140/90	60	50	6	4
F	33	13	22.0	300/140	143/92	160	51	4	4
F	55	35	27.1	200/110	154/90	90	64	7	5
F	50	17	28.9	200/100	120/80	100	40	7	4
F	34	14	25.5	200/140	140/80	140	60	4	4

In the course of the 18 NVD procedures, the MRA findings were confirmed in all but one case using the neurosurgical database. In this case, the MRA indicated NVPC of the root-entry zone of cranial nerves IX and X and of the RVLM caused by the PICA and the VA on the left side. However, NVD revealed only NVPC of the RVLM caused by the VA.

Among the 7 non-operated patients, the MRA pointed to NVPC of the RVLM in 4 cases and of the root-entry zone of cranial nerves IX and X in 3 cases, all on the left side. In these cases there were no double contacts.

Both the SBP and the DBP levels were significantly higher in the operated group before the NVD, as did the PP and all decreased significantly after the NVD. Although there were mild increases in BP during the 2 years, they remained below the BP levels recorded before the NVD (Tables 18 and 19). In the non-operated group, the BP did not change significantly during the 2 years (Table 18).

Table 18 The systolic, the diastolic blood pressure and the number of antihypertensive agents during the 2 years. (*$p < 0.05$ *vs.* the preoperative level, **$p < 0.05$ non-operated *vs.* operated)

		At operation or MRA	Month 1	Month 3	Month 6	Month 12	Month 24
Non-operated (n=7)	**SBP (mmHg)**	156±36**	141±22	161±32	151±37	158±34	142±26
	DBP (mmHg)	85±24**	87±15	96±21	85±21	85±24	76±15
	№ of agents	4.3±2.6	5.1±2.3	5.1±2.3	5.3±2.4	5.1±2.3	5.1±2.3
Operated (n=9)	**SBP (mmHg)**	211±40	147±13*	153±18*	161±21*	152±29*	148±32*
	DBP (mmHg)	116±17	91±13*	99±15	97±13	94±11*	95±18
	№ of agents	5.9±1.4	4.7±0.9*	5.0±1.1	5.2±1.1	5.4±0.9	5.7±1.0

The significance of differences of mean BP values before and after the NVD only derived from the significant differences observed in group DL. The decreases of BP were not statistically significant in other groups and subgroups (Table 20).

All the NVDs were successful, no serious complications or death connected with it, were observed. Only transient vertigo appeared in some cases after the decrease of BP levels.

No correlation was found between either the types of NVD and the pressure or the number of antihypertensive agents. However the change of BP after NVD was only significant in cases of dual NVPC on the left side. The absolute BP values of these patients did not differ significantly from the others.

The need for the antihypertensive medication was calculated as the sum of the number of different drugs administered. It also decreased in most of the cases after NVD (Table 21).

The type D NVPC was observed most frequently among the 13 operated patients, 6 of them on the left side and 1 on both sides. However in the latter case NVD was performed only on the left side (Table 22).

Table 19 The blood pressure of the operated patients during the 2 years.

		At operation	Month 1	Month 3	Month 6	Month 12	Month 24
Patient 1	**SBP (mmHg)**	190	156	156	185	165	160
	DBP (mmHg)	120	100	100	108	96	110
Patient 2	**SBP (mmHg)**	190	130	153	142	124	140
	DBP (mmHg)	105	75	109	99	89	100
Patient 3	**SBP (mmHg)**	210	130	160	138	130	112
	DBP (mmHg)	100	80	110	80	100	80
Patient 4	**SBP (mmHg)**	240	145	160	146	150	155
	DBP (mmHg)	145	90	90	92	90	100
Patient 5	**SBP (mmHg)**	200	170	180	200	220	220
	DBP (mmHg)	120	120	130	120	120	130
Patient 6	**SBP (mmHg)**	160	140	130	150	130	110
	DBP (mmHg)	100	90	80	90	80	70
Patient 7	**SBP (mmHg)**	300	143	122	170	145	139
	DBP (mmHg)	140	92	87	90	88	81
Patient 8	**SBP (mmHg)**	200	154	150	148	151	148
	DBP (mmHg)	110	90	92	88	89	95
Patient 9	**SBP (mmHg)**	200	158	165	168	150	148
	DBP (mmHg)	100	80	95	108	90	95

In the case of a 57-year-old white woman with RHT, the MRA showed mild compression on the left anterior surface of the RVLM at the level of the PICA. In June 2009, neurosurgical NVD was performed under anaesthesia. A tissue-friendly haemostatic sponge was placed between the cranial nerves and the PICA.

Table 20 Blood pressure and pulse pressure values in operated patients by neurovascular pulsatile compression subgroups. (*$p < 0.05$ after *vs.* before; **$p < 0.01$ after *vs.* before)

	SBP (mmHg)		DBP (mmHg)		PP (mmHg)	
	Before NVD	After NVD	Before NVD	After NVD	Before NVD	After NVD
DL	201±11	**137±5	116±7	*87±4	85±7	*50±2
BSL	240±40	147±7	130±20	85±5	110±20	62±2
NL	225±50	143±21	125±19	93±19	100±43	50±8
DB	240	145	145	90	95	55

Table 21 The number of drugs in combination of the operated patients during the 2 years.

	Number of drugs in combination					
	At operation (n=13)	Month 1 (n=13)	Month 3 (n=10)	Month 6 (n=10)	Month 12 (n=9)	Month 24 (n=9)
Patient 1	8	4	5	6	6	7
Patient 2	5	6	6	6	5	5
Patient 3	4	6	3	4	4	4
Patient 4	6	4	5	4	5	6
Patient 5	6	5	5	5	6	6
Patient 6	6	4	4	4	5	5
Patient 7	4	4	5	5	5	5
Patient 8	7	5	7	7	7	7
Patient 9	7	4	5	6	6	6

Table 22 Distribution of types of neurovascular pulsatile compression among the operated 13 patients.

Type BS (n=2)			Type N (n=4)			Type D (n=7)		
BSL	**BSR**	**BSB**	**NL**	**NR**	**NB**	**DL**	**DR**	**DB**
n=2	n=0	n=0	n=4	n=0	n=0	n=6	n=0	n=1

During the NVD procedure, the MRA finding was confirmed. NVD was successful, and no serious complications of the intervention were observed. Both SBP and DBP decreased after NVD, as measured with the ABPM-04. During the active period, the mean BP was 163/73 mmHg before and 115/62 mmHg after NVD. During the passive period, the mean BP was 130/60 mmHg before and 113/50 mmHg after NVD. The hyperbaric time index decreased from 76.63/7.61% to 8.47/0.0%. Less antihypertensive medication was needed within a short period after NVD; only five different drugs were needed from approximately postoperative day 8 (Table 23).

Table 23 The change of the antihypertensive therapy before and after the neurovascular decompression.

Before NVD	After NVD
• dihydralazine 0-3-2-1 tab. • doxazosin 4 mg 2x1 tab. • metoprolol 50 mg 2x1/2 tab. • indapamide at lunch 1 tab. • urapidil 90 mg 3x1 cap. • guanfacine2x1 tab. • isosorbid mononitrate 60 mg at morning 1 caps. • amlodipine 5 mg 2x1,5 tab. • losartan 100 mg 2x1 tab. • moxonidine 0.4 mg 0-1-1 tab.	• metoprolol 50 mg 2x1/2 tab. • indapamide at lunch 1 tab. • isosorbid mononitrate 60 mg at morning 1 caps. • amlodipine 5 mg 2x1 tab. • losartan 50 mg ½-0-1 tab.

Normally, the spontaneous BRS decreases after standing up, and this dynamic was also preserved after NVD. In the supine position, the BRS was 5.62 ms/mmHg before and 7.51 ms/mmHg after NVD. In the standing position, the BRS was 3.29 ms/mmHg before and 5.57 ms/mmHg after NVD. The BRS increased after NVD in both positions.

The sum of the CAN scores did not change; it remained 3. However, the decrease in BP after standing up decreased to half of the value detected before NVD (Table 24).

The plasma NE level decreased to almost half of the level measured before NVD (421 pg/ml *vs.* 282 pg/ml, before *vs.* after).

Table 24 Changes of the cardiac autonomic neuropathy before and after neurovascular decompression.

	Change of HR (beat/min)	Valsalva ratio	30/15 ratio	Test Handgrip (mmHg)	Orthostatic hypotension (mmHg)	CAN score
Before NVD	19	1.66	1.03	35	46	3
After NVD	15	1.21	0.97	20	23.14	3

4.3. Transcatheter renal denervation

Both the SBP and the DBP decreased in all cases after the RDN. The changes of mean BP values after the successful RDN are summarized in Table 25.

Table 25 Characteristics of renal denervations and changes of blood pressure after renal denervations in four resistant hypertensive patients.

Patients	52-year old woman	50-year old woman	39-year old woman	62-year old man
N° of ablation sites (right)	5	5	5	5
N° of ablation sites (left)	6	5	5	5
Complications	post-procedure headache, vomiting	no	no	no
BP (mmHg) prior to RDN	204/105	183/111	161/92	166/104
BP (mmHg) after RDN	111/50	160/95	134/77	132/83
BP (mmHg) 1 month later	156/73	177/101	140/84	119/72
Anti-HT therapy change after RDN	2 stopped 2 elevated	2 elevated 3 decreased	4 stopped, 1 decreased	3 stopped 4 decreased

BRS was calculated only in the case of the 52-year old woman (Table 26). Unfortunately ECG and BP data recordings were unsuccessful in other cases because of finger cuff failure of the Finometer device.

Table 26 Changes of baroreflex sensitivity after renal denervation in a 52-year old woman.

	upBRSL (ms/mmHg)	**upBRSS (ms/mmHg)**	**downBRSL (ms/mmHg)**	**downBRSS (ms/mmHg)**	**allBRSL (ms/mmHg)**	**allBRSS (ms/mmHg)**
Before RDN	3.21	2.53	3.53	2.31	3.36	2.65
After RDN	11.26	5.05	5.48	4.48	8.69	4.85

5. DISCUSSION

In severe diabetic CAN characterized by CRTs, the 5-year mortality exceeds 50%; more than half of these cases were cardiac (86). In a meta-analysis, the mortality of diabetics with CAN after 5.8 years was 29%, whereas for diabetics without CAN the mortality was just 6% (95).

In diabetic patients with CAN, the parasympathetic dysfunction appears first and is associated with sympathetic overactivity, especially during the night. An increase in the sympathetic activity and/or a decrease in the parasympathetic tone encourage the development of malignant ventricular arrhythmias (96). In diabetic patients with parasympathetic CAN, the orthostatic hypotension is less expressed because of the sympathetic overactivity (97). Mostly, the response to the handgrip-test from the sympathetic CRTs is abnormal (97). In our study among the sympathetic CRTs the response to the handgrip-test was mostly abnormal in both HT groups. The SBP changes in response to standing up were generally borderline and only in a few cases abnormal. We did not find any relationship between the basic SBP and the SBP changes in response to standing up. From our data, there is a connection between the duration of the HT and the severity of autonomic neuropathy. Although most of the hypertensive patients displayed sympathetic and parasympathetic neuropathies, the parasympathetic dysfunctions (38.1%) predominated over the sympathetic dysfunctions (21.43%).

It is well known that effective BP control reduces the cardiovascular risk in diabetic and nondiabetic hypertensive patients (35, 98, 99). In our study, DM associated with HT did not enhance the prevalence of neural dysfunctions, and the two HT groups did not differ

significantly in BP values. These data might suggest that the effective BP control might have contributed to the lack of difference in the severity of neuropathy between the two patient groups. Interestingly, in the diabetic group, the extent of hypaesthesia of the small fibres correlated positively with the severity of the CAN on the upper extremities. Moreover, in the diabetic group, there was a positive correlation between the severity of hypaesthesia of the small fibres on the lower extremities and the documented duration of DM and HT. In the NDHT group, we found an association between the orthostatic hypotension and the hypaesthesia of the large and the small fibres on the lower extremities. In the diabetic group, there was a negative correlation between the HR changes in response to standing up and the hypaesthesia of the large and the small fibres on the lower extremities. These observations might indicate that vascular factors may play a role in the development of PSN. Our observation that all the CPTs of the CAN-free patients were within the normal range might confirm the association between the autonomic and peripheral sensory neuropathy.

The association between the duration of diabetes and the presence of diabetic peripheral neuropathy has already been described (40), and is also supported by our data. Furthermore, we found correlation between the duration of HT and the severity of autonomic and peripheral sensory neuropathy. There are some limitations to this study. This is a small study with a low number of enrolled patients. The potential effect of the antihypertensive medication on the autonomic function cannot be excluded completely, but it is unlikely because there was no significant difference between the antihypertensive medications of the treated groups. Furthermore, some of the agents amend while some of them worsen the autonomic function.

The sympathetic nervous system may produce selective changes in efferent outflow to different organs. The output to different sympathetic preganglionic neurons depends on the central autonomic nervous system organization including relative contributions of a wide range of brain nuclei and on the inputs to those nuclei (from baroreceptors, chemoreceptors, somatic receptors and from all areas of the brain). Although in RHT the SNA is increased the sympatholytic drug therapy, usually in a multiple combination, is not enough to reach the goal BP.

The cranial nerve IX carries afferent signals from the aortic arch, whereas cranial nerve X does so from the carotid sinus. The left nerve X also carries afferent signals from the mechanoreceptors in the left atrial wall (10). The sympathico-excitatory catecholamine

synthesizing C1 neurons are situated in the RVLM, probably 1 mm below the surface of the brain stem. These catecholaminergic C1 neurons have an important role in maintaining resting sympathetic vasomotor tone and arterial HT. Efferent fibres lead from there into the preganglionic sympathetic neurons located in the intermediolateral column of the thoracic spinal cord. The discharge of these neurons increases the SNA (12). Stimulation of the C1 neurons with glutamate elevates the BP, whereas cooling or destruction of this region decreases the BP, as does stimulation with gamma-amino butyric acid (13, 100, 101).

The NVPC at the root-entry zone of cranial nerves IX and X can cause a temporary oxygen deficiency, which blocks signal transmission into the NTS. Therefore it will not be activated and the C1 neurons released from the physiological inhibition caused by the NTS (101). According to another theory, direct excitation of the C1 neurons by arterial pulsation can surpass the inhibitory signals from the NTS, causing a permanent discharge of the excitatory neurons (102).

Microanatomical investigations performed by Naraghi et al. of samples from cadavers of HT patients did not reveal either demyelinization or degeneration provoked by NVPC (101). In that work they described 3 types of NVPC: type I (monovascular): compression by only the VA or only the PICA; type II (vertebral): compression by only the VA; and type III (combination): compression by both the VA and the PICA. Our grouping was similar to theirs.

In a recent Japanese study it has been reported, similar to many previous studies, that prevalence of NVPC of the RVLM was significantly higher in the group of patients with primary HT (35%) than in the normotensive group (13%) ($p < 0.05$) (100, 101, 102-106). A recent study using high-resolution MRI scans with 1 mm slices showed that the frequency of NVPC of the RVLM was clearly and significantly higher in patients with primary HT (73.5%) than in patients with secondary HT (12.5%) (107).

Since Jannetta's papers many studies have confirmed that an NVD of the RVLM on the left side decreases the BP value, even lasting for many years (10, 13, 108, 109). Among others Sasaki et al. reported successful NVD in cases of 4 refractory HT patients (110). Three of them had hemifacial spasm. Our patients did not show any symptoms of cranial rhizopathies. In a previous work we described that 2 years after a successful NVD the BP values and the therapeutic efforts were decreased compared to the pre-operative period (111).

In primary HT patients with NVPC on the left side of the RVLM there is a significantly increased plasma NE level confirming the elevated SNA (88, 89). More evidence for increased SNA is the increased muscle SNA in primary HT patients with NVPC of the RVLM (112).

German authors have presented their results of 14 HT patients with more than 3 antihypertensive drugs who underwent NVD procedure. Not only the BP but also SNA decreased after NVD (113).

A Japanese team have reported a case of a patient, with RHT and NVPC of the RVLM on the left side, who experienced notable BP reduction by clonidine therapy (114). However, unfortunately not all the NVPC HT patients react to central-acting antihypertensive agents; otherwise discussion about a possible beneficial neurosurgical procedure would not be necessary.

It is still not clear why NVPC only on the left side causes HT, and does not on the right side, though some study groups have reported NVPC with the same frequency on both sides (101, 106).

According to the literature NVD is usually performed in HT patients with at least 3 different antihypertensive drugs. In our cases the mean number of antihypertensive agents were 5.

The lower plasma NE level and higher BRS values after NVD confirm that there is a sympathetic overactivity in RVLM pulsatile compression. The efficacy of NVD confirms that C1 neurons may have an important role in the maintenance of this sympathetic overactivity. After NVD, the repetitive discharge of C1 neurons was halted. As a part of CAN, the degree of orthostatic hypotension decreased, which can also be explained by the improvement in short-term CV regulation. In this case, after NVD, the BRS, BP and the need for antihypertensive medication also improved.

The slightly elevation of the BP levels and the increase of the need for antihypertensive therapy may be caused by the target organ damage of HT. The NVD may be most beneficial if both the BP levels and the medication also decrease after it, but it is still beneficial if the BP levels decrease with sustained or just slightly improved need for antihypertensive medication.

Non-selective surgical sympathectomy/denervation was effectively used to decrease the BP in severe hypertension before antihypertensive drugs became generally available. But

unfortunately side effects arising from the non-selective aspect significantly worsened the quality of life of HT patients (79, 80, 81).

Development of endovascular catheter technology enables selective denervation of the kidney, with radiofrequency energy delivered in the renal artery lumen, accessing the renal nerves located in the adventitia of arteries. The first-in-man, non-randomized cohort of patients with RHT (SBP ≥160 mm Hg on ≥3 anti-HT drugs, including a diuretic; eGFR ≥ 45 ml/min) was published by Krum et al. in 2009. In five centers 45 RDNs were performed and the mean BP decrease was -27/-17 mm Hg by the end of 12 months follow-up (94).

This cohort was expanded in the Symplicity HTN-1 trial. This was a multicentre safety and proof-of-principle cohort with 153 RHT patients. The mean baseline BP was 176/98 ± 17/15 mmHg, and the mean number of antihypertensive drugs were 5.0 ± 1.4. Bilateral RDN were performed in all cases. No major complications were observed and only 4 minors ones: 1 renal artery dissection during catheter delivery (prior to RF energy) and access site complications. One, 3, 6, 12 and 24 months after the RDN the BP values were decreased by 20/10, 24/11, 25/11, 23/11, 26/14 and 32/14 mmHg in order (115).

After it a multicenter, randomized, controlled clinical trial was planned named Symplicity HTN-2. RDN was performed in cases of 52 RHT patients with mean baseline BP 178/96 mmHg and more than 3 antihypertensive medications. The BP reduction was 20/7, 24/8 and 32/12 mmHg in order 1, 3 and 6 months after RDN. No serious device or procedure related adverse events were observed. The 6-month renal imaging showed no vascular abnormality at any RDN treatment site (82).

The RDN reduces the sympathetic activity in OSAS (116), the insulin resistance (117), the plasma renin activity, the left ventricular mass and improves the renal blood flow and the BRS (118).

All the RDNs were technically successful in this observation and BP values also decreased. Although the reduction of antihypertensive medication was not the objective of any RDN treatment, in all cases in this work the medication decreased by 1 or 2 drugs. Of course it is a very important aspect of improving the adherence and compliance of patients. In the case of a 52-year old woman after the RDN the BRS increased both in lying and standing position. More mechanisms could explain this improvement of BRS. One is the decrease of SNA, but perhaps as independent factors the decrease of BP or the arterial stiffness may resulted in

increase of BRS. From a decrease of SNA decreased CV morbidity and mortality could be expected as a long-term conclusion.

6. SUMMARY

In the first study reported in this thesis we hypothesized that the complications generally attributed to DM only may also appear in NDHT. In our work both CAN and PSN could be observed together in NDHT and their severity did not differ significantly from that in DHT. It may further support the view that vascular factors may play an essential role in the development of neuropathy. The duration of the HT rather than the BP values themselves might be an important risk factor for the development of autonomic and peripheral sensory neural dysfunctions. Our results provide further support for parasympathetic dysfunction enhancing SNA in HT and DM. The BRS decreased in both lying and standing positions in diabetic and nondiabetic HT groups, but it was lowest in the diabetic group, supporting the idea that DM and HT together may multiply the CV risk. Our results may suggest that poorly healing ulcers of the lower extremities, due to microvascular complications and often leading to amputation based on PSN, threaten not only diabetic patients but also NDHT. These observations might be essential for the development of risk reduction strategies among NDHT to avoid or postpone the development of neuropathy.

In the second work of this thesis we collected retrospective data about invasive treatment methods of RHT, focusing on NVD of the brain stem. In the cases of severe primary RHT, without any possible so-called conventional secondary causes, not responding to multiple combinations of therapy, NVPC of the brain stem should be considered and MRA performed. If NVPC is confirmed by MRA, successful neurosurgical NVD of the brain stem on the left side can guarantee a BP reduction with less or same need for antihypertensive medication. From our results NVPCs on the left side of the brain stem may relate to HT, but the type of the NVPC does not correlate with the BP values. Therefore, perhaps, neither the location nor the number of NVPCs on the left side affects the degree of the SNA. From this point of view the fact of NVPC on the left side is the most important not its type. A continuous pulsatile stimulation of the RVLM on the left side may lead to a tonic increase in SNA and HT, but it

cannot explain all the refractory HTs. A new question arises here: if NVD may affect the BP and the SNA, is it really a case of a primary HT or is it a case of an unconventional secondary form? More data are needed to decide this. Further, our results – MRA findings compared to intraoperative observations - may confirm that MRA slice thickness 1 mm is necessary for successful identification of an NVPC.

Before any invasive treatment of RHT the pseudoresistant HT, the "white-coat effect", the conventional secondary causes and other patient- and/or therapy-related causes should be excluded. After confirming the primary RHT it is important to optimize the medical antihypertensive treatment. Is RDN the appropriate next step? If the office BP is sustained >160/ mmHg with eGFR >45 ml/min/1.73 m^2 and the anatomy of renal artery is suitable then the answer is "yes". Compared to NVD, the RDN is an easier invasive technique with fewer possible side effects and a shorter procedure time.

7. CONCLUSIONS (NEW OBSERVATIONS)

- There is an increased sympathetic nerve activity in hypertension not just because of the pathogenesis of primary hypertension, but because of parasympathetic dysfunction based on possible microvascular complications.

- Peripheral sensory neuropathy also can be observed in hypertension without diabetes mellitus.

- In resistant hypertension a neurovascular pulsatile compression of the brain stem on the left side may cause sustained sympathetic overactivity leading to increased blood pressure.

- At least 1 mm MRA slice thickness is required to indentify the possible neurovascular contacts.

- In resistant hypertension with neurovascular pulsatile compression of the brain stem on the left side a neurovascular decompression may be prescribed because subsequently the arterial systolic and diastolic blood pressure and sympathetic nerve activity may decrease permanently.

- The baseline blood pressure is independent of the type of the neurovascular pulsatile compression of the brain stem on the left side, but in a case of double compression on the left side after a decompression there is a bigger reduction of blood pressure.

- The transcatheter renal radiofrequency denervation may lead to a significant decrease of blood pressure and sympathetic nerve activity.

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