INTRODUCTION

Due to higher cardiovascular risk, resistant hypertension is serious and requires special diagnosis and treatment of multidisciplinary team of hypertension specialist, nephrologist, interventional cardiologist or radiologist and nurse. It is very important that patients understand the rationale for adherence to antihypertensive therapy. Poor adherence is a major cause of lack of blood pressure control and it can be misleading in further diagnostics and treatment with detection of drugs in blood and/or urine. New devices like renal denervation were developed to interrupting the cardiovascular disease continuum, the leading cause of death globally (1). Arterial hypertension is a permanent increase of systolic blood pressure values above >140 mmHg and diastolic blood pressure values above >90mmHg. It is a very important modifiable risk

RENAL DENERVATION: AN EARLY DECREASE IN AMBULATORY AND HOME BLOOD PRESSURE

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The primary goal of the hypertension specialist is to determine which patients with resistant hypertension require renal denervation procedure. We investigate the characteristics of early changes of blood pressure in true resistant hypertension patients undergoing renal denervation and the predictors of ambulatory blood pressure monitoring response and home blood pressure measurements early after procedure. From a total of patients in Hypertension unit, only patients with refractory resistant hypertension (10.4%) were included in study, from which 12% have criteria for new method. All subjects have ambulatory blood pressure measurement before and after renal denervation. Patients age were 60±6 years, 6.7±1 for number of antihypertensive drug classes included spironolactone use in doses from 50-100 mg, BMI 36±3 kg/m², estimated GFR CKD-EPI was 63±28 ml/min-1 1.73m². Arterial stiffness was determined using pulse wave velocity in patients with resistant hypertension, evaluated using the noninvasive Agedio B900 device from Germany. Renal denervation significantly reduced continuously 24 h blood pressure measurement from maximum value 252/142 mmHg (average 169/103 mmHg) to minimal value 131/78 (average 144/91mmHg) 24 h after procedure (p<0.001). Significant reduction was found in continuously blood pressure measurement 24 h after (-21/12 mmHg) and home blood pressure measurements (-23/11 mmHg) 72 h after renal denervation in patients with normal (p<0.001) or moderate (p<0.05) elevated pulse wave velocity (for age 55-65y normal value is 6.5-7.7m/s). The mean value of the total measured pulse wave velocity value was higher than reference for age in older and diabetics and was 8.14 m/s. There was no deterioration in kidney function after renal denervation with follow up of one year. Renal denervation is an innovative procedure designed to achieve a reduction of blood pressure of 10 mmHg in a short period of time. The purpose is not a complete cessation of antihypertensive medication but lowering the cardiovascular risk and mortality. In choosing patients for renal denervation is to determine arterial stiffness using pulse wave velocity measurements as a predictor of cardiovascular mortality, associating elevated pulse wave velocity that reference value for age, with poorer response to renal denervation procedures.

Key words: renal denervation, resistant hypertension

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factor connected with heart disease, cerebrovascular incident, chronic kidney failure and premature mortality and disability and is one of the most important world health problems of today (2). Studies show that cardiovascular risk is doubled with every increase of blood pressure values by 20/10 mmHg and every reduction of systolic blood pressure value by 10 mmHg proportionally lowers the incidence of major cardiovascular disease events (stroke, heart failure, coronary disease) and reduces the all-cause mortality by 13% (3). Resistant hypertension (RH) is diagnosed when it is not possible to achieve recommended blood pressure values of <140/90 mmHg even after implementing the required lifestyle changes and incorporating at least three different antihypertensive drugs in treatment, including a diuretic (4). Cardiovascular morbidity and mortality are a lot higher among RH population when compared to the population suffering from arterial hypertension (4). Renal denervation is one of the methods used for the treatment of RH. Many studies confirm that RDN is effective in lowering BP in patients with RH with additional positive effects on blood glucose levels, OSA and multi-organ failure caused by hypertension (5-9).

The primary goal of the hypertension specialist is to determine which patients with resistant hypertension (RH) require renal denervation (RDN) procedure (1). New innovative devices therapies create an additional novel pathway of blood pressure lowering procedures and should be prescribed by a specialist hypertension clinic. In this study we investigate the characteristics of early changes of blood pressure (BP) in RHpt undergoing RDN and the predictors of Ambulatory Blood Pressure Monitoring (ABPM) response and home blood pressure measurements (HBPM) early after RDN at University Hospital Merkur.

**PATIENTS AND METHODS**

From a cohort of 80 resistant patients in Hypertension unit, only refractory RHpt (10.4%) were included in study, from which 12% have criteria for RDN. Resistant hypertension was confirmed with 24h ABPM according to European Society of Cardiology and European Society of Hypertension guidelines. In standardized stepwise screening protocol we selected patients with refractory RH (10). Approximately 30 % patients have severe OSA sy treating with CPAP, 35% were older>65 years and 45% diabetics. Exclusion criteria were patients with kidney transplantation, pseudoresistance, inaccurate measurement techniques, nonadherence to treatment and a suboptimal medication regimen. Secondary causes of hypertension, hospitalisation due to a hypertensive emergency in this year, renal diameter <4mm and renal artery length < 20mm were exclusion criteria. Patients that presented with the anatomy of renal arteries incompatible with the procedure (multiple renal arteries), GFR <45/ml/min/1.73m², diabetes type 1 or type 2 with HbA1C >7.5% were excluded from the study.

All participants with office BP >160 mmHg were prescribed three or more different antihypertensive drugs, including a diuretic, in maximally tolerated dosage. The following classes of medications were angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs) and diuretics. Around 75% patients had combinations like ACEI+CCB+diuretic, 45% beta blockers, 40% sympatholytics, potassium sparing diuretic in 30 %.

All subjects measured 24 hours (h) BP monitoring (ABPM) to rule out white coat hypertension, and to confirm the RH, before selecting patients for RDN. Patients were aged 60±6 years, 6.7±1 for number of antihypertensive drug classes included spironolactone use in doses from 50-100 mg, body mass index (BMI) was 36±3 kg/m², estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with eGFR 63±28 ml/min-1 1.73m².

Arterial stiffness was determine in all 80 patients with RH and in part of patients after RDN using pulse pulse wave velocity (PWV, m/s), evaluated using the noninvasive Agedio B900 device (Germany) (11). We used brachial pressure waveforms of superficial arteries and this arm cuf based method makes use of a transfer function like method with the ARC Solver algorithm built in the Mobil-o-graph (11). An appropriate cuf-size we used to avoid poor blood pressure measurement after rest of 5 minutes. We measured PWV several times in an ideal environment (patients were calmly in quietly room).

Adherence was assessed through patient interview. We keep the regimens for the resistant hypertension management as simple as possible. We selecting optimal medication combinations at the most effective dosages based on the patient’s conditions to improve blood pressure control.

This study was conducted in accordance with the amended Declaration of Helsinki. The study was approved by the hospital ethics committee and all participants gave their informed written consent.

**Statistical Analysis**

The data were processed in the software program SPSS. Statistical analysis of a data was performed using descriptive statistics. Paired sample t-test were applied...
for comparison of results. The level of statistical significance was set at p<0.05.

RESULTS

A minority of RH patients (27, 35%) were male and were younger than their female counterparts (53.9 years). The difference between sex was statistically significant for PWV (M/F= 8.1/9.2 m/s, p>0.01).

Primary endpoint of study was to evaluate efficacy and safety of early effect after RDN. Renal denervation significantly reduced continuously blood pressure measurement from maximum value 252/142 mmHg (average 169/103 mmHg) to minimal value 131/78 (average 144/91 mmHg) 24 h after procedure (p<0.001).

Significant reduction in continuously blood pressure measurement 24h after renal denervation (-21/12 mmHg) and home blood pressure measurements (-23/11 mmHg) 72 h after renal denervation was found in patients with normal (p<0.001) or moderate (p<0.05) elevated pulse wave velocity (for age 55-65y normal value is 6.5-7.7 m/s).

The mean value of the total measured pulse wave velocity value was higher than reference for age in older and diabetics and was 8.14 m/s.

There was no deterioration in kidney function after renal denervation with follow up of one year. Reported rates of renal events were 0% for new renal artery stenosis.

DISCUSSION

Resistant hypertension patients often have comorbid cardiorenovascular conditions, such as heart failure, atrial fibrillation or chronic kidney disease (4). The diagnosis of hypertension and treatment are based usually on daytime clinic blood pressure measurements. Evidence is that the asleep blood pressure better predicts cardiovascular events than the awake or 24 h blood pressure mean (4). Therapeutic restoration of normal physiologic blood pressure reduction during night-time sleep (circardial variation) is the most significant independent predictor of decreased cardiorenovascular risk and the basis for the chronotherapy. Although chronotherapy is not uniformly recommended in the treatment of resistant hypertension, it is a cost-effective strategy for reducing cardiovascular risk and we have showed than circadian rhythm of blood pressure restoration and nephrotic proteinuria alleviation in a patient with chronic kidney disease after renal sympathetic denervation in real life exist (9). We have previously proved for the first time that RH patients have higher PWV (than according to age), and this research confirmed the difference between sex (11). In this study we have showed that PWV could be predictor after RDN procedure. What about real position and new date with RDN?

The results of early studies of renal denervation success were quite promising, but were lacking in sham-control which allows assessment of blood pressure reduction due to effects unrelated to renal denervation. SYMPLICITY HTN-3 in 2014, the first large prospective, randomised, double-blinded and sham-controlled study was did not meet its primary goal to prove significant blood pressure reduction between the RDN group and sham-control. That caused a huge step back for RDN (12). However, many oversights have been found after detailed analysis and revision of the study: the first one is the inexperience of the operators, 31% of all 111 operators had only performed one procedure before they were included in the study. Furthermore, the number of ablations differed from centre to centre. It is also estimated that approximately ¾ of patients did not receive ablations in all four quadrants of the renal arteries. In addition, a quarter of participants were of Afro-American heritage. Renal denervation has been found ineffective among these patients due to their beta-1 adrenergic receptor polymorphism and lower renin plasma levels. The Afro-American population is frequently prescribed vasodilators for hypertension which have been connected with a lower response to RDN. Moreover, patients were randomised only two weeks after the adjustment of their antihypertensive medication. In that time the maximal effect of the administered drugs was not achieved and could have interfered with the results. During the study period, 39% of patients had some changes in their prescribed antihypertensive medication (12).

The study recognised that the younger and older population (<65 and >65) responded differently to the procedure (12). It is considered that isolated systolic hypertension (ISH), a dominant phenotype of hypertension among elderly population, is connected to reduced response to RDN when compared to population with combined systolic-diastolic hypertension (13). These patients have increased vascular stiffness, elevated pulse pressure and increased risk for stroke or myocardial infarction (13).

Another benefit of the study is that the patients with OSA have been identified as low responders to RDN (13). Because polysomnography was not performed before the randomisation, all data about OSA was self-reported by participants (14).
Despite many limitations, RDN is once again confirmed as safe method with minimal number of reported side effects (13,14). Despite the disappointing results, many saw the potential of RDN and kept up with further research in that field (13-17).

The results of SPYRAL HTN-OFF MED, a multi-centric, randomised, sham-controlled study in 2017 with multi-electrode catheter (which contains four electrodes and allows the administration of the radiofrequency energy in all four quadrants of the renal artery, and are able to reach accessory branches of the renal artery with the diameter <1 mm, which previous ablation systems were incapable of doing) finally proved that RDN indeed causes a statistically significant reduction of blood pressure in patients off any antihypertensive medication. Confounding factors, identified in Symplicity HTN-3 study, have been eliminated in this study: patients were diagnosed with mild to moderate hypertension (SBP >150 mmHg and <180 mmHg, DBP >90 mmHg, mean 24-h ambulatory SBP >140 mmHg and <170 mmHg), patients with ISH, that have been identified as low-responders, were completely excluded and all procedures were done by highly experienced operators.

The key feature of the study is that the patients had to be off any antihypertensive medication 3 to 4 weeks prior to and during the study period. Liquid chromatography and mass spectroscopy of urine and plasma was done at baseline and 3 months in the study to ensure patients compliance with the absence of medication. Patients that presented with SBP >180 mmHg that persisted for 72 h or more, were given antihypertensive treatment and were eliminated from the study. Patients were enrolled at 21 centres in USA, Japan, Australia and Europe (UK, Germany, Greece, Austria) (15). This diversity makes the results of the study applicable to the global population. The results confirm a statistically significant reduction of SBP -10 mmHg (-15.0 do -4.9 mmHg, p<0.0004), DBP -5.3 mmHg (-7.8 to -2.7 mmHg, p<0.0002) and 24h ambulatory BP -5.5/-4.8 mmHg in RDN arm of the study when compared to sham control. Lower risk of cardiovascular mortality, coronary death and stroke were connected with the reduction of BP of this extent. That discovery has brought back faith in the efficacy of RDN in treating hypertension (15).

SPYRAL HTN-ON MED study is another international, randomised, single-blind, sham-controlled study conducted to prove efficacy and safety of RDN in patients on standardised antihypertensive therapy consisting of up to three different antihypertensive medications - thiazide diuretic, dihydropyridine calcium-channel blockers, ACEI/ angiotensin receptor blockers or a β blocker with doses ≥50% of the maximum manufacturer’s recommended dosage. Exclusion criteria include inappropriate renal artery anatomy, GFR<45mL/min, DM1 or poorly controlled DM2, one or more episodes of orthostatic hypotension, chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for OSA, primary pulmonary hypertension, pregnancy, nursing or planning to become pregnant, chronic NSAID treatment (excluding aspirin), the history of myocardial infarction, unstable angina pectoris, syncope or cerebrovascular incidents within 3 months of screening, atherosclerosis, with documented intravascular thrombosis or unstable plaques and night shifts. Drug adherence was assessed with liquid chromatography and mass spectroscopy of urine and plasma at baseline and 1, 3 and 6 months post-procedure (16). Findings show a significant reduction of mean 24-hour ambulatory SBP for -7 mmHg (-12 to -2,1 mmHg, p=0,0059) and DBP for -4,3 mmHg (-7,8 to -0,8 mmHg, p=0,0174) compared to sham control. Adherence with prescribed medication was 60%. In a period of 6 months after the procedure was done no major adverse effects were registered.

The Swedish registry for RDN is endorsed by the Swedish Society of Hypertension, Stroke and Vascular Medicine and it contains data about procedures and patient history as well as follow-up information for all RDN procedures done from 2011 to 2015: the RDN study was successfully performed in 252 patients (97%). Six different ablation systems were used for the procedure - Symplicity Flex, Symplicity Spyrall, EnligHTN, Paradise, OneShot and Vessix. Only 7% patients presented with adverse effects (two renal artery dissections, one femoral artery dissection, one retroperitoneal bleeding, four localised hematomas and nine cases of minor adverse effects) (17). The reduction of office SBP ≥10 mmHg was achieved in 58% of the participants, while 53% showed a decline in mean ambulatory BP ≥5 mmHg, 33% responded in both office and ambulatory BP. There were no registered changes in adjustment of medication as well as a decrease in GFR or signs of deterioration of renal function in predisposed patients (17). Renal denervation is proved effective in reduction of BP, but different population groups respond differently to treatment. For the RDN procedure to achieve its maximal success, it is necessary to determine the truly eligible population and therefore correct inclusion criteria. ISH, therapy of mineralocorticoid receptor agonists or direct vasodilators, number of ablations per artery, the level of eGFR and obesity have already been determined as predictors of BP changes after RDN (14). Other factors that influence procedure success need to be identified in the future, like PWV (18).

The efficacy and the consequences of redoing the procedure remain unknown. The correct inclusion criteria
for patients undergoing RDN needs to be determined in the future. Due to many important advancements and discoveries in the field of RDN, it is only natural to assume that the procedure will become a part of a routine treatment of RH. The nonpharmacologic and pharmacologic management of resistant hypertension is largely based on consensus recommendations by experts. Algorithm-based approaches, such as renin profiling to guide drug selection, require further validation.

In terms of costs, there is no question pharmacoeconomically that effective blood pressure control in resistant hypertension with drugs and new innovative devices therapies is cheaper than treating the consequences of hypertensive target organ damage. However, further trials are needed to confirm these findings in patients with hypertension and in those with resistant hypertension. Due to higher cardiovascular risk, resistant hypertension is serious and requires special diagnosis and treatment by a multidisciplinary team. It is of high importance that the evaluation of a patient with RH includes 24-hours monitoring of blood pressure, home blood pressure (HBPM) and measurement of PWV as a predictor of RDN response.

LIMITATIONS OF THE STUDY

The limitation of the analysis include the single centre study, lack of an untreated control group and lack of drug adherence testing.

CONCLUSION

Renal denervation is an innovative procedure designed to achieve a reduction of BP (≥10 mmHg) in a short period of time. The purpose of RDN is not a complete cessation of antihypertensive medication. RDN lowering the cardiovascular risk and mortality. Home blood pressure monitoring improve adherence to medications by increasing patients involvement. In choosing patients for RDN is to determine arterial stiffness using PWV measurements as a predictor of CV mortality, associating elevated PWV with poorer response to RDN procedures. We have now entered a new era of renal denervation, where the primary question has shifted from “Does renal denervation actually lower blood pressure?” to “What is the appropriate application of renal denervation to reduce blood pressure and cardiovascular risk within the enormous hypertensive population.”

REFERENCES

Probir bolesnika koji će imati najviše koristi od dodatne metode liječenja rezistentne hipertenzije denervacijom bubrežnih arterija, kojom se smanjuje tonus simpatičkog živčanog sustava selectivnom ablacijom živčanih ogranaka u stijени bubrežnih arterija, iznimno je bitan. Cilj studije je bio utvrditi rani učinak denervacije bubrežnih arterija na sniženje krvnog tlaka unutar 24 sata (kontinuirano mjerenje) kao i na kućno mjerenje tlaka 72 sata poslije denervacije bubrežnih arterija. Od ukupnog broja bolesnika 10,4 % je imalo kriterije za rezistentnu hipertenziju a od njih svega 12 % za liječenje denervacijom bubrežnih arterija. Kod svih bolesnika s rezistentnom hipertenzijom učinjeno je mjerenje krutosti žila neinvazivnim mjerečem (Agedio B900, Njemačka). Za statističku analizu korišten je program SPSS, uz razinu značajnosti \( p < 0,05 \). Nakon denervacije bubrežnih arterija dolazi do značajnog ranog sniženja tlaka mjereno kontinuiranim mjerečem: s prosječnog 169/103 mm Hg prije na 144/91 mm Hg 24h nakon denervacije bubrežnih arterija (\( p <0,001 \)). Značajno rano sniženje uočeno je u holteru tlaka (za -21/12 mm Hg) nakon 24h i kućnom (-23/11 mm Hg) mjerenju nakon 72 sata od denervacije bubrežnih arterija, i to posebno u bolesnika s normalnim (p<0,001) ili blago povišenim (p<0,05) nalazom krutosti žila (referentna vrijednost za dob 55-65 godina 6,5-7,7 m/s). Unutar 6 mjeseci prosječan broj antihipertenzivnih lijekova ostao je nepromijenjen (važno da se objektivizira učinak denervacije bubrežnih arterija). Nije zabilježeno neposrednih komplikacija denervacije bubrežnih arterija, bubrežna funkcija bila je stabilna. Povišena krutost žila mjerenia neinvazivnim mjerenjem povezana je sa slabijim ranim sniženjem krvnog tlaka nakon postupka denervacije bubrežnih arterija. Prigodom odabira bolesnika za postupak denervacije bubrežnih arterija mjerenjem krutosti žila dobiva se dodatna informacija koja može doprinijeti prigodom izbora bolesnika koji će imati najviše koristi od denervacije bubrežnih arterija.

**Ključne riječi:** renalna denervacija, rezistentna hipertenzija