

## РЕНАЛНА ДЕНЕРВАЦИЯ В КЛИНИЧНАТА ПРАКТИКА: ЛЕЧЕНИЕ НА ПАЦИЕНТИ С ВИСОК СЪРДЕЧНО-СЪДОВ РИСК

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## RENAL DENERVATION IN CLINICAL PRACTICE: TREATING PATIENTS WITH HIGH CARDIOVASCULAR RISK

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### Abstract.

**Introduction:** Arterial hypertension is the most common correctable risk factor for death worldwide. Achievement of therapeutic goal is hampered by multiple factors including non-adherence to drug therapy and individual physiological resistance. **Objective:** We aimed to determine the efficacy of renal denervation in lowering SBP and DBP at 1<sup>st</sup> and 6<sup>th</sup> month, in patients at high cardiovascular risk, in whom lowering BP would possibly also result in risk reduction and lower incidence of future cardiovascular events. **Methods:** The procedure was performed in 39 patients with resistant hypertension admitted to the University Hospital „Acibadem City Clinic – Cardiovascular Center“ (Sofia) for the period January 2017–June 2020. Access was via brachial artery and the Simplicity Spiral catheters were used, at an average of 19.5 ablation points per artery. The number of complications, as well as the mean systolic and diastolic BP values at 1<sup>st</sup> and 6<sup>th</sup> month were recorded. Baseline, risk profile and follow-up medical treatment of the study group was monitored. **Results:** In the study group, the predominant risk factors were dyslipidemia, age, diabetes mellitus, with 21 patients (53.84%) already having clinically significant atherosclerosis – a realized heart attack, stroke, peripheral or coronary revascularization. At follow-up, a significant reduction in both systolic and diastolic BP (blood pressure) values was observed. At the first month, the fall in SBP (systolic blood pressure) was –17.8 mm Hg, with a persistent reduction in the range of –14.5 mm Hg at 6<sup>th</sup> month. In terms of DBP (diastolic BP), the mean reduction at the first month was –8.9 mm Hg and at the 6<sup>th</sup> month it was –7.2 mm Hg. Regarding antihypertensive treatment, there was a mild reduction in the intake of antihypertensive drugs. **Conclusion:** Substantial proportion of people with hypertension have uncontrolled hypertension (both treatment resistant and due to non-adherence to treatment or due to additional pathophysiological mechanisms). Renal denervation has proven effective and safe in patients with uncontrolled hypertension and high cardiovascular risk profile.

**Key words:** renal denervation, uncontrolled arterial hypertension, high cardiovascular risk, brachial approach

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### Резюме.

**Увод:** Артериалната хипертония е най-честият коригируем рисков фактор за смърт в световен мащаб. Постигането на терапевтичната цел е затруднено от множество фактори, включително непридържане към медикаментозната терапия и индивидуална физиологична резистентност. **Цел:** Целта е да определим ефективността на реналната денервация за понижаване на систолното и на диастолното артериално налягане на 1-ви и 6-и месец при пациенти с висок сърдечно-съдов риск, като при тях понижаването на артериалното налягане би довело и до редуция на риска и понижаване на честотата на бъдещи сърдечно-съдови събития. **Материал и методи:** Процедурата е проведена при 39 пациенти с резистентна хипертония, приети в УМБАЛ „Аджибадем сити клиник – Сърдечно-съдов център“ (София) за периода януари 2017–юни 2020 г. Достъпът е брахиален, като се използва катетър Simplicity Spiral, при средно 19.5 аблационни точки. Отчетени са броят усложнения, както и средните стойности на систолното и диастолното артериално налягане на 1-вия и 6-ия месец. Проследени са провежданото изходно и последващо медикаментозно лечение, както и рисковият профил на изследваната група. **Резултати:** В изследваната група преобладаващите рискови фактори са: дислипидемия, възраст, захарен диабет, като 21

пациенти (53,84%) са с вече клинично значима атеросклероза и реализиран инфаркт, инсулт, периферна или коронарна реваскуларизация. При проследяването се наблюдава значимо намаляване на стойностите както на систолното, така и на диастолното АН. На първия месец спадът на систолното артериално налягане е  $-17.8$  mm Hg, като на 6-ия месец се задържа редукция от порядъка на  $-14.5$  mm Hg. По отношение на диастолното артериално налягане, средната редукция на първия месец е  $-8.9$  mm Hg, а на 6-ия месец  $-7.2$  mm Hg. По отношение на антихипертензивното лечение при проследяването се наблюдава лек спад на приема на всички класове антихипертензивни медикаменти. **Заключение:** Установено е, че съществена част от хората с хипертония са с неконтролирана такава (както резистентни на лечение, така и поради непридържане към лечението или допълнителни патофизиологични механизми, поддържащи високото АН) и това се превръща в значим медико-социален и фармако-икономически проблем. RDN е доказала своята ефективност при пациенти с резистентна хипертония, но ние смятаме, че процедурата може да има място и в при лечението на „трудно лечим пациент с хипертония“, както и при такива с висок сърдечно-съдов риск или за подпомагане на вторичната профилактика.

**Ключови думи:** ренална денервация, неконтролирана артериална хипертония, висок сърдечно-съдов риск, брахиален достъп

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## INTRODUCTION

Arterial hypertension (AH) is the most common correctable risk factor for death worldwide. It affects more than 75 million adult people in the USA and more than 1 billion people worldwide, so almost every 4th adult person has AH. Even though the widely available anti-hypertensive drugs, studies show that a very small part of the patients achieve the targeted blood pressure values. Achievement of therapeutic goal is hampered by multiple factors including non-adherence to drug therapy and individual physiological resistance. For that reason, new therapeutic options are becoming more and more used in the last years. In addition to lifestyle changes and advanced pharmacotherapy, renal denervation (RDN) has emerged as the most advanced and promising device-based technology for the treatment of resistant and uncontrolled hypertension. Renal denervation is an adjunctive, device-based method of treating uncontrolled hypertension for which a body of scientific evidence has accumulated regarding its effectiveness and safety [1, 2, 3].

### Literature

In Bulgaria, awareness of the problem – arterial hypertension, treatment and populational control of the blood pressure (BP) have improved significantly in recent decades, but there is still much to be achieved [1]. The prevalence of high BP in Bulgaria is about 55%, compared to Europe with average of 35-45% [2]. According to a cross-sectional survey data in 4 major Bulgarian cities in 2012, 791 people (50.9%) were found to have high blood pressure values  $> 140/90$  mm Hg [3]. Another significant problem concerning directly the control of hypertension is that adherence to long-term therapy for chronic diseases in developed countries is on average – 50%. It is undeniable, that many patients have difficulty adhering to treatment recommendations.

Insufficient adherence to long-term therapies (which, in the vast majority of cases, is the therapy for arterial hypertension) seriously compromises the effectiveness of widely used treatment approaches, making this a critical problem for the population health, both in terms of prognosis and quality of life and for the health economics. Arterial hypertension is the most common diagnosis establishing patient's non-adherence to treatment. [4] Strategies aimed at improving, would provide a significant positive return on investment beyond primary prevention (control of risk factors) and secondary prevention of adverse health outcomes. It has long been known, that increasing the effectiveness of adherence strategies to current therapy can have a much greater impact on the population's health than any other innovation or improvement in specific medical treatments [5]. However, no single strategy or plan will prove effective for all patients, conditions, and settings. Consequently, management must be tailored to the specific requirements associated with a particular disease [4]. Patient's non-cooperation has been identified as a major cause of failure in the control of hypertension [6].

According to the European Society of Hypertension clinical guidelines, resistant hypertension (RH) is defined as BP  $> 140/90$  mm Hg, despite adequate lifestyle and treatment with more than 3 full-dose antihypertensive medications, at least one of which is a diuretic [7]. The American Heart Association includes in this group patients with medically „controlled“ resistant hypertension with extremely high medication load (more than five medications), i.e. inadequate blood pressure control must be confirmed in therapy-adherent patients by ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) [9]. The prevalence of RH is 9-27%, showing an increasing trend. Clinical studies have shown a significantly higher risk of cardiovascular events, renal failure

and death in patients with RH. Medication-resistant hypertension (RH), especially that induced by increased sympathetic tone, is a significant public health problem because of its association with an early-onset target organ damage and increased risk of adverse clinical events. In order to have an idea of how important it is, we should highlight that in individuals aged 40-69 years, a 20 mm Hg increase in systolic blood pressure or a 10 mm Hg increase in diastolic blood pressure, irrespective of baseline values, is associated with more than twice the risk of stroke or death from coronary heart disease, whereas a 5 mm Hg reduction in systolic blood pressure can reduce stroke mortality by 14% and cardiovascular disease mortality by 9%. At older age ( $\geq 80$  years), the corresponding relative risk is somewhat lower, but the absolute risk is far greater [10].

Given the global burden of hypertension (average 20-25% prevalence in adult populations), the inadequate rate of hypertension control worldwide (typically  $< 50\%$ ), and the widespread nonadherence to long-term antihypertensive medication ( $> 50\%$  in treated patients, as seen in other chronic diseases), the cardiology medical community rightly expects the availability of a concomitant interventional procedure that can safely and effectively achieve long-term, clinically meaningful reductions in blood pressure [12, 13]. In addition to lifestyle changes and advanced pharmacotherapy, renal denervation (RDN) has emerged as the most advanced and promising device-based technology for the treatment of resistant and uncontrolled hypertension [14]. In Bulgaria, clinical experience with the use of catheter-based renal denervation dates back to 2008. The first renal denervation was performed in our country by our team and during these 13 years, a lot of data has been accumulated regarding the methodology of the procedure, patient selection, safety and outcomes, although the lack of reimbursement and validated indications in clinical guidelines have been an obstacle to its wider use [15, 16, 17]. The guidelines of the European Society of Hypertension and the European Society of Cardiology [ESC/ESH] state that „the clinical evidence supporting RDN as an effective technique for lowering blood pressure is conflicting“ and that „the use of device-based therapies, is not recommended for the routine treatment of hypertension, in the context of the expected results of clinical trials, including randomized sham-controlled RCTs, to demonstrate the safety and efficacy“ of this catheter-based therapeutic modality [18]. The main text of the 2018 ESC/ESH recommendations gives a Class IIb recommendation for procedures such as renal denervation and baroreceptor stimulation in the event of ineffectiveness of drug treatment [10].

## AIMS

The aim was to determine the effectiveness of renal denervation in lowering systolic blood pressure (SBP) and diastolic blood pressure (DBP) at months 1 and 6, in patients with uncontrolled hypertension and high cardiovascular risk, in whom lowering BP would also lead to risk reduction and lower incidence of possible future cardiovascular events.

## MATERIAL AND METHODS

The procedure was performed in 39 patients with resistant hypertension, admitted to the University Hospital „Acibadem City Clinic – Cardiovascular Center“ (Sofia) for the period January 2017–June 2020. Vascular access of choice was brachial, using the Simplicity Spiral catheter, at an average of 19.5 ablation points. The number of complications as well as mean systolic and diastolic BP values at 1<sup>st</sup> and 6<sup>th</sup> month were recorded. Baseline and follow-up medical treatment was monitored, as well as the risk profile of the study group.

In the study, we took into account the risk profile of the studied group, differentiated the classes of medications taken and the percentage of patients taking more than one diuretic or centrally acting medication. We studied the dynamics in renal function after the procedure, radiation dose and contrast load.

## RESULTS

### Clinical Characteristics of the study group

Patients included in the study were aged 34 to 76 years (median age – 61 years). Females predominated (61,5%), but the female/male distribution was almost equal. Of the risk factors, dyslipidemia, diabetes mellitus and previous intervention for significant atherosclerotic involvement were the most prevalent. We had 17 patients (43,6%) who were smokers or ex-smokers. Two patients had NYHA class III-IV heart failure and one woman underwent a repeat renal denervation (Table 1).

**Table 1. Patient characteristics**

Patient characteristics	Number (%)
Male	15 (38.46%)
Age	61.35 (34-76y)
Smoking	17 (43.6%)
Arterial hypertension	26 (66,67%)
Diabetes mellitus	21 (53,8%)
Sleep apnea	5 (12.8%)
Dyslipidemia	33 (84.61%)
Obesitas > III	4 (10%)
Heart failure III-IV NYHA	2 (5%)
Atherosclerosis	21 (53,84%)

### Medication therapy before the intervention

Among the subjects, the mean number of antihypertensive medications taken was 4.65 (range 2 to 9), and the only patient on 2-drug therapy was a woman with polyallergy and intolerance to most classes of antihypertensive drugs. A high percentage – more than 80% – were taking diuretics, calcium antagonists, centrally acting drugs and beta-blockers. In total, more than 90% are treated with either an ACEI or an ARB blocker. Seventeen patients or 43.58% were taking two or more diuretics and 10 (25.64%) were on therapy with more than one centrally acting drug. Spironolactone was present in the therapy of 23 patients (58.97%) (Figure 1).

### Procedure protocol

Under fluoroscopic control and local anesthesia, a 5 Fr Radifocus® Introducer (Terumo) 10 cm radial introducer is inserted into the right brachial artery. Using a 5 Fr Judkins right diagnostic catheter with a Cordis Storz (Cardinal Health) floppy wire protruding beyond the tip, the aortic arch was crossed toward the descending aorta. After reaching the subdiaphragmal aorta, over the Storz wire a 90 cm.

Shuttle sheath (Cook) was introduced up to the immediate suprarenal zone of the aorta. An initial subtraction angiogram of the abdominal aorta is performed with a pigtail catheter positioned at the level of the first lumbar vertebra to visualize both renal arteries – including number and size of the renal arteries. Using a „road map“ (a „road map“ created by imaging a digital mask of the contrasted underlying vessel), supraselective renal artery cannulation is performed using the same diagnostic JR catheter and over this catheter, the long sheath was gently introduced suspraselectively in the first targeted renal artery, using a „push-pull“ maneuver. A floppy .014' wire was introduced distally in one of the big branches. Once the supra-selective placement

is achieved, application of renal denervation energy is initiated from distal to proximal in a helicoidal pattern with at least 3 ablation sessions per renal artery with mandatory Rf energy delivery over the branch arteries bigger than 4 mm in diameter and main vessel as well. This strategy is providing at least 12 ablation points per kidney artery because the Spiral catheter carries 4 ablation electrodes. The Simplicity Spiral ablation catheter was used in the present study, and the mean number of ablation points per renal artery was 19.5. In case of failed brachial access for supraseductive renal artery cannulation, a femoral access was prepared. A final angiogram was performed before removal to assess the number of ablation scars („noches“) and potential renal artery injury. No one crossover from brachial to femoral access was not registered in this series of patients. After achieving the initial vascular access, an i.v. bolus of Heparin (70 IU per kg body weight) was administered. In addition to mild conscious sedation, further local anesthesia was performed with direct infusion of 10 ml of 1% lidocaine into the ablated renal artery. Only ablations that left a visible scar („notch“) in the vessel wall on fluoroscopic imaging with impedance reduction > 10% and temperature > 60° C were counted as „true ablation points“. The average amount of contrast used during the procedure was 61.5 ml with an average X-ray time of 14 min.

### Complications and Follow-up period

Three hematomas at the puncture site (only one requiring vascular surgical intervention) were recorded, and no other complications were observed. We did not register any renal artery dissection or perforation. Two patients were found to have renal artery stenosis at baseline angiography and were intervened with balloon angioplasty before the ablation and finalized by stent implantation.

Creatinine values were measured both before and after the procedure to assess the possible effect of

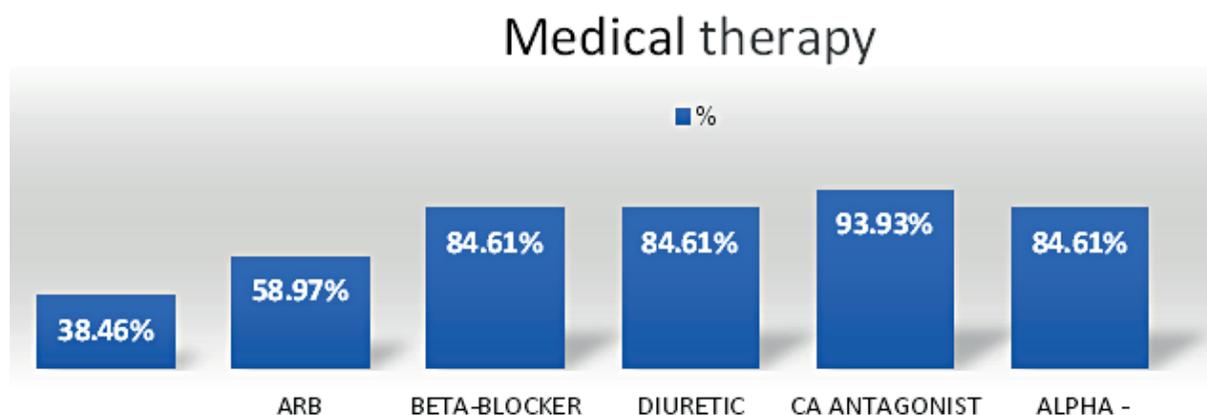
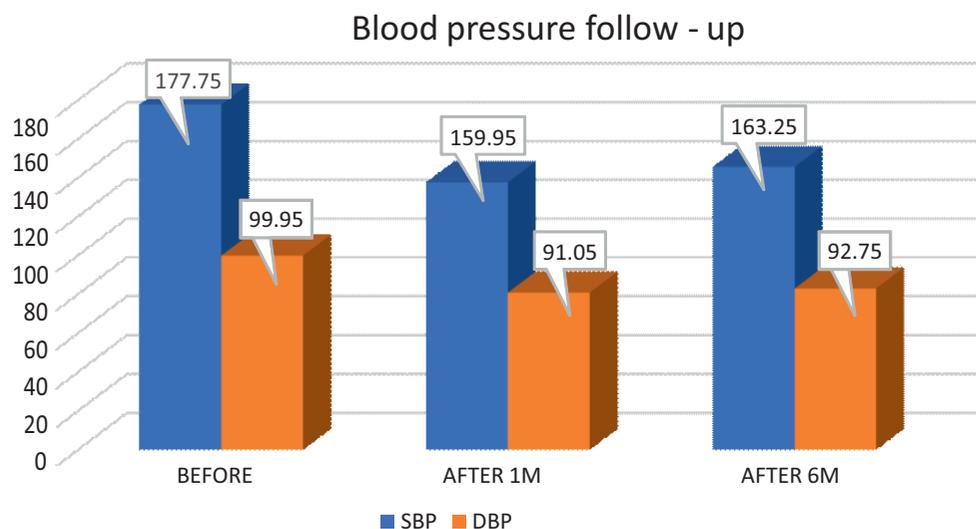


Fig. 1. Antihypertensive therapy before the procedure

the larger number of lesions on renal function. Limited dual antiplatelet prophylaxis (ASA 100 mg/day plus clopidogrel 75 mg/day) was administered for 1 month. Office blood pressure measurements were performed at baseline and at months 1<sup>st</sup> and 6<sup>th</sup> after the procedure (Figure 2). Routine duplex renal artery examination was performed during follow-up visits to evaluate the main vessels and branches patency. Ambulatory 24-hour blood pressure recordings were performed at baseline and at the 6<sup>th</sup> month after the procedure.

chronic renal and heart failure, RDN may become a new treatment option for such patient populations, like shown in several published trials and meta-analyses [20]. Given this and the reported additional positive effects of RDN, we suggest expanding the criteria for patients who would benefit from the procedure. The authors of this article, fully agree with the proposal of the Italian Society of Arterial Hypertension to extend the definition of „difficult-to-treat hypertensive patient“ to „patient with uncontrolled BP“ (daily ambulatory BP

at least 135/85 mm Hg) in a multidisciplinary assessment process, taking into account appropriateness, tolerability and adherence to medical treatment, comorbidities, patient preferences and screening for secondary hypertension [19]. In the international global Simplicity registry, 3-year follow-up of patients showed impressive consistency of the achieved anti-hypertensive effect, there was no difference in blood pressure values 6 months, 1, 2 and 3 years after the procedure, even a further



**Fig. 2.** Change in SAN and DAN values at months one and six after the procedure

At follow-up, a significant reduction in both systolic and diastolic BP values was observed. At the first month, the average reduction in SBP was  $-17.8$  mm, with a persistent reduction of  $-14.5$  mm at month 6. In terms of diastolic BP, the mean reduction at the first month was  $-8.9$  mm Hg and at the 6<sup>th</sup> month it was  $-7.2$  mm Hg. With regard to antihypertensive treatment, a non-significant percentage decline was observed at follow-up – minimal reduction of the antihypertensive medication with a mean 1.1 medication per patient. There was a consistent trend towards lower values for both SBP and DBP, as seen above. However, no objective testing of adherence to antihypertensive therapy has been performed.

## DISCUSSION

Initially, RDN was used only in patients diagnosed with resistant to treatment hypertension, but the procedure has also shown its effectiveness in patients nonadherent to their medical therapy and not fully meeting the definition for resistant hypertension [19]. Sympathetic renal nerves play a role in the pathogenesis not only of arterial hypertension, but also of cardiac arrhythmias, renal and heart failure. Since, increased sympathetic activity has a role in the progression of

slight decrease in values was observed [21]. This durability of effects is in full agreement with histological data recently published, which demonstrated that no reinnervation is observed after an effectively performed denervation procedure and renal transplantation in humans [22]. The global registry examined baseline risk for atherosclerotic cardiovascular disease (ASCVD), and this was calculated for patients with available office SBP measurements, antihypertensive medication, laboratory cholesterol values, and history of diabetes and smoking. Efficacy was assessed by serial office and ambulatory BP measurements (when available) during the 3 years of follow-up after RDN. Baseline risk estimates for ASCVD were calculated for 1485 patients (56% of the total) mainly because of missing cholesterol measurements. The mean ASCVD risk estimate was 19.8% (Q1, Q3: 9%, 37%). Blood pressure reductions in patients with measurements at 6, 12, 24, and 36 months showed similar reductions in office and 24-hour SBP for the different baseline ASCVD risk scores [21]. Elevated BP is the strongest, proven risk factor for nearly all cardiovascular events, but the inverse relationship is also valid, i.e. lowering BP by 5 mm Hg reduces the risk of stroke by up to 34% and the incidence of ischemic heart disease by 21% [23, 24]. In our study, we found a significant and sustained

reduction in BP values over time, averaged for a relatively high-risk patient population. We also report only a few minor complications (access site hematomas), which could be addressed to the brachial artery access that was used in all of the patients. Complications of brachial vascular access are gradually decreasing and our team has a growing experience not only obtaining the access, but also achieving adequate hemostasis. In the same time the brachial access is much more appropriate in terms of successful selective cannulation, compared to femoral, for any renal percutaneous interventions in hypertensive subjects because of the tortuosity of the infrarenal aorta and the down-slope trajectory of the renal arteries [25]. Despite the fact that there are no RCTs available that investigate the effect of RDN on the incidence of cardiovascular events, we can say that the procedure should be considered as an option that lowers blood pressure and contributes to an improved cardiovascular prognosis in hypertensive patients, since the protective effect of BP-lowering treatment is due to the BP lowering itself, regardless of the way this is achieved [26].

## CONCLUSION

It is well established that a substantial proportion of people with hypertension have uncontrolled hypertension (both resistant to treatment and due to non-adherence to treatment or additional pathophysiological mechanisms maintaining high BP). RDN is safe and has proven effective in patients with uncontrolled hypertension and high cardiovascular risk. That is why, we propose for the extension of the definition – „difficult-to-treat hypertensive patient“ to „patient with uncontrolled BP“ (daily ambulatory BP at least 135/85 mm Hg) in a multidisciplinary assessment process, taking into account appropriateness, tolerability and adherence to medical treatment, comorbidities, patient preferences and screening for secondary hypertension.

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*No conflict of interest was declared*

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