RENAI\textsc{N} DA\textsc{N} E\textsc{E} R\textsc{V}\textsc{A} TION 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\textsuperscript{st} and 6\textsuperscript{th} 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\textsuperscript{st} and 6\textsuperscript{th} 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\textsuperscript{th} month. In terms of DBP (diastolic BP), the mean reduction at the first month was –8.9 mm Hg and at the 6\textsuperscript{th} 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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**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 antihypertensive 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 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 (≥ 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 pharma- cotherapy, 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 1st and 6th 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

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15 (38.46%)</td>
</tr>
<tr>
<td>Age</td>
<td>61.35 (34-76y)</td>
</tr>
<tr>
<td>Smoking</td>
<td>17 (43.6%)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>26 (66.67%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21 (53.8%)</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>5 (12.8%)</td>
</tr>
<tr>
<td>Dysplidemia</td>
<td>33 (84.61%)</td>
</tr>
<tr>
<td>Obesitas &gt; III</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Heart failure III-IV NYHA</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>21 (53.84%)</td>
</tr>
</tbody>
</table>
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 Storq (Cardinal Health) floppy wire protruding beyond the tip, the aortic arch was crossed toward the descending aorta. After reaching the subdiafragmal aorta, over the Storq 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 supraselectively 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 supraselective 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
the larger number of lesions on renal function. Limit-
ed 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 1st and 6th after the proce-
dure (Figure 2). Routine duplex renal artery examina-
tion 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 6th month after the procedure.

At follow-up, a significant reduction in both systol-
ic 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 6th 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 objec-
tive 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 pro-
cedure 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 pathogene-
sis 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
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 assess-
ment process, taking into account appropriateness,
tolerability and adherence to medical treatment, co-
morbidities, patient preferences and screening for
secondary hypertension [19]. In the international
global Simplicity registry, 3-year follow-up of patients
showed impressive consistence 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

![Blood pressure follow - up](image)

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

No conflict of interest was declared.

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