



Role of renal denervation in the treatment of arterial hypertension: a review

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Regardless of the fact that arterial hypertension is the focus of modern cardiology, resistance to therapy is still an important public health problem with adverse medical, social, and economic consequences. Aim of study: systematizing the available results of studies of the effectiveness of renal denervation in the treatment of patients with resistant AH. Search within databases (PubMed, Cochrane Library) was performed for randomized controlled studies of second-generation catheter-assisted renal denervation and sham-controlled studies. We have used PRISMA protocol for preparing our paper. The neutral results of the SYMPLICITY HTN-3 study significantly weakened the interest of practical cardiology in this procedure, however recently published data from the EnligHTNed IDE, SPYRAL HTN OFF MED, and SPYRAL HTN-ON MED studies confirmed the effectiveness and safety of the technique. As the result the second-generation catheters (multielectrode catheters) used for renal denervation confirmed the effectiveness and safety of the procedure, and also expanded the technique usage beyond resistant hypertension. However, the question of the reliability of long-term effects of the procedure still remains, as well as establishing mechanisms to identify predictors of planned intervention responsiveness.

Keywords: renal denervation, device-based therapy, hypertension, sympathetic nervous system, resistant.

Relationships and Activities: none.

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AH — arterial hypertension, BP — blood pressure, CI — confidence interval, SBP — systolic blood pressure.

Received: 29.04.2021

Revision Received: 07.06.2021

Accepted: 07.06.2021



For citation: Orekhov A.Yu., Karazhanova L.K. Role of renal denervation in the treatment of arterial hypertension: a review. *Russian Journal of Cardiology*. 2021;26(9):4497. (In Russ.) doi:10.15829/1560-4071-2021-4497

Роль почечной денервации в лечении артериальной гипертензии

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Несмотря на то, что артериальной гипертензии (АГ) уделяется много внимания в современной кардиологии, резистентность к медикаментозной терапии по-прежнему остается важной проблемой общественного здравоохранения, сопряженной с неблагоприятными медицинскими, социальными и экономическими последствиями. Цель: систематизировать результаты исследований по эффективности денервации почечных артерий в лечении пациентов с резистентной АГ. В ходе работы осуществлялся поиск рандомизированных контролируемых испытаний (PubMed, Кокрановская библиотека) и плацебо-контролируемых исследований по ренальной денервации с помощью катетеров второго поколения. Мы использовали протокол PRISMA для подготовки статьи. Результаты исследования SYMPLICITY HTN-3, не показавшие преимуществ денервации почечных артерий, значительно ослабили интерес практической кардиологии к данной процедуре, однако недавно опубликованные данные исследований EnligHTNed IDE, SPYRAL HTN OFF MED и SPYRAL HTN-ON MED подтвердили эффективность и безопасность метода. В результате катетеры второго поколения, используемые для ренальной денервации, подтвердили эффективность и безопасность процедуры, а также показали возможность применения техники не только при резистентной АГ. Тем не менее, вопрос об эффективности процедуры в отдаленном периоде остается открытым. Кроме того, требуется дополнительное изучение и поиск предикторов ответа на лечение с помощью ренальной денервации.

Ключевые слова: денервация почечных артерий, терапия на основе устройств, артериальная гипертензия, симпатическая нервная система, резистентность.

Отношения и деятельность: нет.

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Рукопись получена 29.04.2021

Рецензия получена 07.06.2021

Принята к публикации 07.06.2021

Для цитирования: Орехов А. Ю., Каражанова Л. К. Роль почечной денервации в лечении артериальной гипертензии. *Российский кардиологический журнал*. 2021;26(9):4497. doi:10.15829/1560-4071-2021-4497

Arterial hypertension is one of the most pressing challenges of modern cardiovascular medicine, as well as the main modifiable cause of cardiovascular mortality worldwide. Currently, there is a large scientific base in understanding the pathophysiology and clinical significance of conditions associated with increased blood pressure (BP). Significant progress has also been

made in expanding the evidence showing that a decrease in BP is accompanied by a significant reduction in premature morbidity and mortality. A large number of available and highly effective methods of correcting arterial hypertension (AH) does exist, including non-pharmacological methods of treatment, an arsenal of drugs that reduce not only the level of BP, but also have

a wide range of pleiotropic effects. Nevertheless, the control of BP remains quite low in developed countries and even more so in developing countries [1].

A contributor to the lack of achieving the target BP is resistant AH, which means the inability to achieve the target values of systolic BP or diastolic BP, despite the recommended treatment strategy, i.e., lifestyle modification and the use of optimal or maximum tolerated doses of three or more drugs, including a diuretic [1]. The prevalence of truly resistant AH is about 12–15% [2], while taking into account the study's results (SPRINT) [3] and the revised target values of BP in the recently published American and European recommendations, an increase in the number of patients with uncontrolled AH is expected.

Numerous causes of the phenomenon of resistance are considered in the literature. Normally, risk factors for developing hypertension resistant to drug therapy include age, female gender, higher baseline systolic BP, obesity, type 2 diabetes, metabolic syndrome, left ventricular hypertrophy, as well as increased salt and alcohol consumption and low level of education [2]. As the research results show, the high activity of the sympathetic nervous system is of great importance in the pathophysiology of resistance. Increased activity of the sympathetic nerves plays a crucial role in the development of AH. It has been found that activation of efferent renal nerves can cause delayed sodium excretion, decreased renal blood flow, and activation of the renin-angiotensin-aldosterone system. Moreover, afferent sympathetic nerve fibers have been shown to increase the sympathetic tone of the entire body [4].

The technique of sympathetic denervation of the renal arteries, proposed in 2003 by H. Levin and M. Gelfand, nowadays can serve as an additional, and sometimes alternative, method of treating hypertension [5]. The absolute safety of the procedure is no longer in doubt; however, the effectiveness of the method has been the subject of discussion more than once.

Thus, the aim of this work was to systematize the available results of studies on the effectiveness of sympathetic denervation of the renal arteries in the treatment of patients with resistant hypertension.

A new chapter in sympathetic denervation of the renal arteries

The results of the first and certainly significant studies of Symplicity HTN-1 [6] and Symplicity HTN-2 [7] were of great importance in determining the role of sympathetic denervation of the renal arteries in the treatment of resistant hypertension; the data obtained facilitated the interest in studying the role of the sympathetic nervous system in the genesis of resistance, and also put catheter technologies as one of the most promising treatment methods. Open studies of Symplicity HTN-1 and Symplicity HTN-2 evaluated the effect of

monoelectrode radiofrequency denervation of the renal arteries, showed a significant influence in reducing office BP in patients with resistant AH, in addition, the procedure was absolutely safe, no significant adverse events were detected, including a decrease in kidney function. In view of this, the results of Symplicity HTN-3, a prospective, randomized, Charm — controlled study, were unexpected [8]. The results of this study did not show a significant advantage in reducing office BP in patients after renal denervation in comparison with a fictitious procedure. As a result, there was a significant decrease in interest, both in the scientific and practical environment, in this procedure. However, even in this study, the absolute safety of renal denervation was shown.

For a long time, the possible reasons for this result have been discussed in the literature. The analysis of confounding factors conducted by Kandzari DE is curious [9]. So, according to the analysis, three critical issues are important: during this series of studies, mono electrode radiofrequency catheters were used, procedures were performed mainly in the proximal parts of the renal arteries, the group included patients with severe resistant AH with severe vascular wall disorders, as well as low patient adherence in terms of pharmacotherapy. Thus, the authors propose to take into account the following factors in future planned studies and routine clinical practice (with changes):

1. Procedure: Distal intervention shows greater effect and possibly additional impact;
2. Population: respondents of renal denervation may be patients with pronounced BP variability;
3. Patients: Adherence to therapy is a key factor; the procedure should be considered not only in patients with resistant AH.

In support of this, the results of histological studies have shown that in some cases, the renal arteries do not have true sympathetic plexuses at the level of the proximal segments, in addition, it is shown that it is in the distal segment that a closer contact with the artery wall is revealed [10]. According to this, a greater number of ablation points and their localization in the distal segments is associated with a higher efficiency of the procedure.

Further understanding of the features of sympathetic regulation of renal hemodynamics led to the creation of a second generation of catheters — multielectrode catheters. As a result of studies using these modifications of catheters, reliable evidence of the effectiveness and safety of renal denervation was obtained.

One of these studies was EnligHTN™ Renal Denervation System [11], the first prospective multicenter non-randomized trial involving 39 patients with resistant hypertension, which examined the effectiveness of generation 2 catheters. It is important to note that the study evaluated the long-term effect of the procedure — the duration of follow-up was 24 months. As a result, it was

Table 1

Key features of some studies (revised, Lucas Lauder, 2019) [19]

FEATURE	SYMPPLICITY HTN-3	SPYRAL HTN-OFF MED	EnligHTNed IDE
Centers	The USA	The USA, Europe, Japan, Australia	The USA
Procedure technique	Radiofrequency monoelectrode catheter	Radiofrequency monoelectrode catheter, Medtronic Vascular, Santa Rosa, CA, USA	Radiofrequency monoelectrode catheter, St. Jude Medical, St. Paul, MN, USA
Ablation site	Proximal segment	Proximal and distal segment	Proximal segment
Inclusion criteria (by BP), mm Hg	Office SBP ≥ 160 mm Hg, SBP by ABPM data ≥ 135 mm Hg	Office SBP ≥ 150 -179 mm Hg, SBP by ABPM data ≥ 140 -169 mm Hg	Office SBP ≥ 160 mm Hg
Experimental group	Sham-control	Sham-control	None
Antihypertensive therapy	Standard therapy	No medication intake	Standard therapy
Primary endpoint	Office BP	ABPM	Office BP
Degree of BP reduction compared to control	-2/39 mm Hg (95% CI -6.89 to 2/12, p=0/26)	-3,9 mm Hg (95% CI -6,2 to -1,6, p=0.0005)	-

Note: ABPM — ambulatory blood pressure monitoring, BP — blood pressure, CI — confidence interval, SBP — systolic blood pressure.

possible to achieve a decrease in office BP in comparison with the initial one by 19/7, 26/9, 25/7, 23/7, 27/9 after 1, 3, 6, 12, 24 months, respectively ($p < 0.0001$).

The SPIRAL Pivotal series of studies used a spiral multielectrode catheter for renal denervation. The results of SPYRAL HTN-OFF MED are interesting [12], a randomized, sham-controlled trial that included patients who either had not previously received therapy, or patients after 4 weeks of discontinuation of antihypertensive drugs, to confirm the effectiveness of renal denervation in reducing blood pressure. The study included 2 groups of patients randomized in a 1:1 ratio — the renal denervation group ($n=166$) and the sham procedure group ($n=165$). As a result, a significant reduction in blood pressure was achieved; thus, the difference in treatment between the two groups for 24-hour systolic blood pressure (SBP) was -3.9 mm Hg (95% confidence interval (CI) from -6.2 to -1.6), for office SBP the difference was -6.5 mm Hg (from -9.6 to -3.5). At the same time, again, the safety of the procedure was shown, no serious complications associated with the device or procedure were identified.

Thus, this study raises a legitimate question — whether renal denervation is an alternative to antihypertensive therapy. The peculiarity of SPYRAL HTN-OFF MED is precisely in the absence of pharmacological treatment, respectively, we consider not only the population of patients with truly resistant AH. Pseudo-resistance to treatment, namely, the lack of an adequate level of adherence to treatment, may become a new indication for this procedure. The literature discusses possible future scenarios for the use of renal denervation as a procedure that not only reduces the number of drugs taken [13], but also as an alternative to pharmacological therapy in general.

Another study, SPYRAL HTN-ON MED [14], evaluated the effectiveness of renal denervation with spiral catheters against the background of ongoing antihypertensive therapy. According to the preliminary analysis

of 80 patients, there was a significant decrease in the average SBP and diastolic BP in the renal denervation group: the average daily SBP -7.0 mm Hg (95% CI -12.0-2.1; $p=0.0059$), the average diastolic BP -4.3 mm Hg (95% CI -7.8-0.8; $p=0.0174$).

Thus, the use of second-generation catheters shows a reliable effect according to sham studies; the proven absolute safety of the renal denervation procedure is important (Table 1).

Sympathetic denervation of the renal arteries: expanding the horizons

Nowadays, it is almost obvious that renal denervation is an effective and safe method of controlling blood pressure, however the literature is actively discussing 4 main issues of widespread use of the procedure, namely: 1) How does it work?; 2) Who to treat?; 3) How to treat?; 4) How long does effect last? [15].

It is crucial to determine the name of the “Perfect” patient for sympathetic denervation of the renal arteries; the search for predictors of the response to therapy remains open. According to one of the largest guidelines on renal denervation [5], most likely the procedure cannot have a class-effect, a positive result can be achieved in a certain number of patients. So, today, difficult-to-control (and not always resistant) AH is still a priority, especially given the rather low level of adherence to therapy, which, according to one of the meta-analyses, is 59% [16]. In addition, renal denervation may be recommended in high- and very high-risk patients with any severity of AH, especially in the presence of hypertension-mediated organ damage or severe concomitant diseases (Table 2).

Unfortunately, the data available today do not allow us to verify with high accuracy the respondent patients for the procedure of renal denervation. The available potential predictors have a rather low level of reproducibility of the results in real practice [5]. However, the

Table 2

Current and potential candidate hypertensive populations for renal denervation therapy (out of 5, revised)

Patient group	Pro	Con
Current candidates		
Difficult-to-control hypertensive patients (with office SBP between 140 and 170 mm Hg or diastolic BP between 90 and 109 mm Hg)	Current target population Solid evidence base	Narrow group
Potential candidates		
CAD patients, especially patients undergoing PCI	Very high-risk patients Low rates of BP control in daily care	Prolonged procedure (PCI + renal denervation)
White-coat hypertension on medications Masked	High-risk groups Large population	Untested therapy in this population Uncertain reproducibility of current data on risk Not well-recognized as candidates Need for renal denervation not proven
CHF with HTN	Pathogenetically justified Large number of patients Pilot studies exist	Not well-recognized as candidates
AF, in case of having indications for the radiofrequency ablation procedure	Very high-risk patients Low rates of BP control in daily care Pilot studies exist	Prolonged procedure Not proven for this patient's category

Note: AF — atrial fibrillation, BP — blood pressure, CAD — coronary artery disease, CHF — chronic heart failure, HTN — hypertension, PCI — percutaneous coronary intervention, SBP — systolic blood pressure.

heart rate (HR), which reflects the degree of hyper-sympathicotonia, is the most reasonable marker of the clinical effectiveness of renal denervation [17]. Thus, in the previously mentioned study of SPYRAL HTN-OFF MED [12], a heart rate exceeding the median (73.5 beats per minute) showed a significant predictive role in reducing the average daily Systolic BP, daily diastolic BP, and office sBP [18].

Conclusion

Despite the attitude towards renal denervation after the publication of the results of the SYMPPLICITY HTN-3 study, the procedure is currently experiencing a kind of renaissance. Positive data obtained in a series of studies (EnligHTNed IDE, SPYRAL HTN OFF MED, SPYRAL HTN-ON MED) using a new generation of catheters — multispiral catheters — proved the

effectiveness and confirmed the safety of the procedure. However, skepticism remains in the clinical sphere, in particular due to the presence of unresolved issues, including limited data on the long-term effectiveness of the procedure, the assessment of the impact of renal denervation on organ damage mediated by hypertension, and most importantly, the identification of patients with the highest probability of responding to the procedure of renal denervation based on a reliable and reproducible selection method. In this paper, the authors tried to summarize the available data on the effectiveness and safety of the procedure, as well as to show possible prospects for using the procedure of sympathetic denervation of the renal arteries outside the framework of resistant arterial hypertension.

Relationships and Activities: none.

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