Response and non-response to renal denervation: who is the ideal candidate?

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Abstract

Catheter-based renal denervation (RDN) leads to a considerable decrease of blood pressure in the vast majority of patients with resistant hypertension. However, only minor or no blood pressure change is achieved in some patients. This non-response is defined as a reduction of office systolic blood pressure of less than 10 mmHg following RDN. The rates of non-response vary between 8-37%. Here several causes are discussed such as inappropriate patient selection, an ineffective procedure, the subordinate contribution of sympathetic activation for the maintenance of hypertension, and patient conditions such as non-adherence to drug therapy. Based on current evidence, an ideal candidate for RDN has high baseline blood pressure, which is known to be the best predictor for blood pressure reduction after RDN. In order to ensure treatment success further criteria have to be fulfilled, such as exclusion of secondary hypertension and optimised medical therapy.

KEYWORDS

- non-response
- patient selection
- procedural parameters
- sympathetic activation

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Introduction

Catheter-based renal denervation (RDN) has been shown to reduce sympathetic nerve activity and blood pressure in patients with resistant hypertension. The published trials have reported a considerable decrease of blood pressure after RDN in patients with a mean baseline blood pressure of 180/110 mmHg despite an average intake of more than four antihypertensive drugs. However, blood pressure response after RDN varies and in 8-37% only minor or no blood pressure changes are achieved (non-response). In daily clinical practice, it is challenging for physicians to select appropriate patients for RDN in order to minimize treatment failure. This review highlights the prevalence and possible causes of non-response to RDN and current knowledge on the ideal candidate for RDN.

Non-responders

In immunology and oncology non-response is defined as the failure of a specific treatment. In cardiology, it is used for patients who fail to show clinical or echocardiographic improvement after receiving a cardiac resynchronization device. In hypertension, the definition of non-response was introduced for the first time in the Symplicity HTN-1 trial. Arbitrarily, it has been defined as a reduction of office systolic blood pressure (SBP) of less than 10 mmHg after six months following RDN. In previously published studies, the rates of non-response after RDN ranged between 8-17%. However, the rate of non-responders in the crossover group of Symplicity HTN-2 was 37.1%. The causes of non-response are not completely understood but here we will discuss several hypotheses (Figure 1).

INAPPROPRIATE PATIENT SELECTION

The selection of appropriate patients is key to ensuring successful treatment. At the present time, only patients with resistant hypertension after exclusion of pseudo-resistance and reversible or secondary cause are considered for RDN. The presence of secondary hypertension may be a cause for non-response. For instance, patients with primary aldosteronism, a common finding in patients with uncontrolled hypertension, will probably not perceive a significant change of blood pressure after RDN, but it is more likely to respond to an aldosterone antagonist. Additionally, it has become clear that the degree of blood pressure reduction depends on the baseline blood pressure. Recent data has suggested that the higher the blood pressure is at baseline, the greater the reduction of blood pressure after RDN will be (Figure 2). Consequently, baseline blood pressure was identified in several populations as a predictor of a greater blood pressure reduction after RDN. However, these observations may partly be explained by the statistical phenomenon of “regression to the mean”. A small study reported that in patients with a milder form of resistant hypertension (SBP 140-160 mmHg), the blood pressure lowering effect of RDN was less pronounced compared to the Symplicity trials. Advancing the indications for RDN to milder forms of hypertension, a smaller magnitude of blood pressure reduction will be associated with the procedure. The current definition of non-response may then not be appropriate and additional surrogate parameters, such as heart rate, might be needed. Indeed it is well documented, that even modest blood pressure reductions are accompanied by significant improvements of cardiovascular morbidity and mortality.

INEFFECTIVE RENAL DENERVATION PROCEDURE

Different renal denervation systems are already available or will soon be released. These devices differ amongst others concerning the delivered energy, the number of electrodes, and the duration of ablation. However, a major unresolved issue is how to monitor treatment success intraprocedurally and this issue has not been answered by any currently available device. Blood pressure changes rarely occur directly after the procedure but rather take weeks to months. The captured procedural parameters, such as numbers of ablations, temperature, power, and impedances, vary depending on the device used. Data showing an association between procedural parameters and the procedure, power, and impedances, vary depending on the device used.

Figure 1. Possible causes of non-response to renal denervation. RDN: renal denervation; SBP: systolic blood pressure

Figure 2. Systolic blood pressure (SBP) at baseline correlates with reduction of blood pressure after renal denervation. Patients with resistant hypertension (n=88) were grouped according to the tertiles of SBP at baseline (Group 1: SBP<160; Group 2: 160-175; Group 3 >175 mmHg) showing this association. SBP: systolic blood pressure.
have to accept a black box during the procedure, as no procedural parameters of treatment success are available. This fact underlines the importance of a close cooperation between the interventionalist and the referring hypertension expert in order to get feedback on the success of RDN during follow-up.

SUBORDINATE RELEVANCE OF SYMPATHETIC ACTIVATION

The exact mechanism of blood pressure reduction by RDN is not yet fully understood. A reduction of local and central sympathetic activity may exhibit beneficial effects as a reduction in total peripheral resistance, reduced renin release, and changes in water and sodium handling\textsuperscript{15,16}. Although sympathetic activation plays a pivotal role, the pathophysiology of hypertension is multifactorial\textsuperscript{14}. Therefore, it may be speculated that some cases of non-response are related to a non-significant contribution of the sympathetic nervous system to the expression of hypertension. In favour of this hypothesis, a substantial number of non-responding patients have a reduction of heart rate, another effect of RDN, which has recently been described\textsuperscript{14,15}. Based on these findings, it may be speculated that in some non-responding patients sympathetic activity is reduced by RDN, observed for instance by a reduction of heart rate indicating a sufficient procedure. Other pleiotropic effects of RDN, such as changes in glucose metabolism\textsuperscript{19}, reduction in the severity of obstructive sleep apnoea\textsuperscript{20}, and improvement of ventricular mass and diastolic function\textsuperscript{21}, need further investigation concerning their association with RDN-dependent blood pressure changes.

PATIENT CONDITION

Due to the high blood pressure values and the burden of antihypertensive medication, quality of life in patients with resistant hypertension is often impaired\textsuperscript{22}. Additionally, the media, such as newspapers and television, create expectations in patients referred for RDN treatment. Serious misinformation among patients and newspapers and television create expectations in patients referred to and the referring physician.

Characteristics of the ideal candidate for renal denervation

The ideal candidate for RDN may be summarised as a patient having severely elevated blood pressure in office and home measurement despite optimised medical therapy, with optimal renal anatomy, in whom RDN can be performed safely, and finally who shows a large drop in blood pressure and displays other pleiotropic effects.

In daily clinical practice, patient selection is based on the available evidence, summarised in Table 1\textsuperscript{14,15}. Eligible patients fulfil the criteria of treatment resistant hypertension, defined as office systolic blood pressure $\geq 160$ mmHg ($\geq 150$ mmHg in type II diabetics) despite treatment with at least three antihypertensive agents including one diuretic, all taken in maximum or maximum tolerated dosages. Elevated office blood pressure should be confirmed by ambulatory blood pressure measurement to exclude pseudo-resistance. A key step in the evaluation process should be exclusion of secondary causes of hypertension, in particular primary hyperaldosteronism, renal artery stenosis, OSA, pheochromocytoma, and hyperthyroidism. Although evidence on the safety and efficacy of RDN in a small number of patients with mild to moderate chronic kidney disease exists, kidney function should be preserved, defined as a glomerular filtration rate $\geq 45$ ml/min/1.73 m$^2$. Finally, the renal anatomy should meet the eligibility criteria to allow a safe and effective procedure: $\geq 4$ mm in diameter and $\geq 20$ mm in length with absence of significant renal artery stenosis ($\geq 50\%$) or prior intervention (balloon angioplasty or stenting).

Table 1. Criteria for the appropriate patient selection for renal denervation.

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<td>- Office-based systolic BP $\geq 160$ mmHg ($\geq 150$ mmHg in type II</td>
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<td>diabetes)</td>
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<td>- $\geq 3$ antihypertensive agents, including one diuretic, in maximum</td>
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<td>tolerated dosages</td>
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<td>- Confirmed adherence to medical treatment</td>
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<td>- Exclusion of white-coat hypertension with ABPM (average SBP $\geq 130$</td>
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<td>mmHg or daytime SBP $\geq 135$ mmHg)</td>
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<tr>
<td>- Preserved renal function (GFR $\geq 45$ ml/min/1.73 m$^2$)</td>
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<tr>
<td>- Eligible renal anatomy (excluded renal stenosis, no prior renal</td>
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<td>intervention, renal diameter $\geq 4$ mm, renal length $\geq 20$ mm)</td>
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ABPM: ambulatory blood pressure monitoring; BP: blood pressure; GFR: glomerular filtration rate; SBP: systolic blood pressure

Conclusion and perspective

The current knowledge indicates that RDN is an effective and safe treatment option if used in well-selected patients. Patients with a high treatment success are those with true resistant hypertension and a markedly elevated blood pressure. Treating physicians also have to face the problem of non-response. Several hypotheses on the causes of non-response exist and the truth is probably a composite of all of these. Substantial research is needed to enhance the understanding of non-response and to identify potential predictors of response.

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References