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Review

# Can we predict the blood pressure response to renal denervation?

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ABSTRACT

Renal denervation (RDN) is a new therapy used to treat drug-resistant hypertension in the clinical setting. Published human trials show substantial inter-individual variability in the blood pressure (BP) response to RDN, even when technical aspects of the treatment are standardized as much as possible between patients. Widespread acceptance of RDN for treating hypertension will require accurate identification of patients likely to respond to RDN with a fall in BP that is clinically significant in magnitude, well-maintained over time and does not cause adverse consequences. In this paper we review and evaluate clinical studies that address possible predictors of the BP response to RDN. We conclude that only one generally reliable predictor has been identified to date, namely pre-RDN BP level, although there is some evidence for a few other factors. Experimental interventions in laboratory animals provide the opportunity to explore potential predictors that are difficult to investigate in human patients. Therefore we also describe results (from our lab and others) with RDN in spontaneously hypertensive rats. Since virtually all patients receiving RDN are taking three or more antihypertensive drugs, a particular focus of our work was on how ongoing antihypertensive drug treatment might alter the BP response to RDN. We conclude that patient age (or duration of hypertension) and concomitant treatment with certain drugs can affect the blood pressure response to RDN and that this information could help predict a favorable clinical response.



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## 1. Introduction

Variability in the magnitude of BP response to catheter-based RDN reported by research centers around the world would not be surprising if there are important technical differences in the way the procedure is performed in different centers. In addition, however, responses are reported to be quite variable from patient-to-patient even within a given study population, ranging from very large falls to small increases in BP (Azizi et al., 2015; Brinkmann et al., 2012; Esler et al., 2010; Howard et al., 2013; Bhatt et al., 2014; Symplicity, 2011). This suggests that specific patient characteristics also can be a key determinant of variability in response magnitude. As with other antihypertensive treatment strategies, it is important to understand the source of this variability, since a very large fall in BP could cause serious adverse effects due to hypotension, whereas a very small or transient reduction in BP would not be expected to produce the long-term reduction in adverse cardiovascular events that is the main purpose of anti-hypertensive therapy. These concerns are magnified by the fact that the BP response to RDN appears to persist in at least some patients for many years (Esler et al., 2014). The clinical desirability of being able to accurately predict the quantitative response of BP to RDN in an individual patient has been noted repeatedly (Wang, 2014; Donazzan et al., 2014). Factors likely to be involved in the variability of responses include: 1) technical issues with the procedure itself or with the measurement of BP (e.g. operator experience, type of catheter, number and/or location of ablations, placebo effect, regression to the mean, altered drug adherence, etc.), 2) baseline patient characteristics (e.g. sex, age, race, body weight, and overall health status), and 3) concomitant anti-hypertensive therapies (since virtually all studies have been performed in patients already taking three or more antihypertensive medications). This review will not focus on technical issues because they have been well covered elsewhere (Esler, 2014; Kandzari et al., 2015). Instead we will mainly discuss how patient characteristics, and in particular concomitant anti-hypertensive drug therapy, might affect the BP response to RDN. There are important limitations in the ability to study potential drug effects in the clinical setting, so we also will present experimental animal data on this issue that we (and others) have recently obtained using the spontaneously hypertensive rat (SHR) as a model system.

### *1.1. How have response predictors been identified in clinical studies?*

Attempts to identify patient characteristics that predict the BP response to RDN have mostly relied on post-hoc analyses of data from studies evaluating the impact of RDN in a broad range of drug resistant hypertensive patients. This has been done either by comparing the magnitude of BP response in different groups of subjects (e.g. men versus women) or by classifying patients as “responders” or “non-responders” to RDN and then comparing the baseline characteristics of the patients in the two groups. However, a few studies have been designed, at least in part, to test prospectively the effect of RDN on BP in specific patient groups, e.g. elderly subjects (Ziegler et al., 2015).

### *1.2. What patient characteristics have been shown to affect BP response?*

A very common finding across RDN studies is that higher baseline SBP predicts a blood pressure lowering response (Symplicity, 2011; Kandzari et al., 2015; Ewen et al., 2015; Id et al., 2015; Prochnau et al., 2013; Rohla et al., 2016; Vogel et al., 2014; Persu et al., 2014). A study focusing more specifically on this question provides support: RDN did not significantly lower BP in patients with mild hypertension (Desch et al., 2015). On the whole then there is good agreement that BP can be expected to fall more after RDN in patients with higher pre-intervention BPs, although this finding may well be confounded by technical issues involved in BP measurement (Howard et al., 2013; Fadl Elmula et al., 2015; Howard et al., 2016).

One report indicates that renal artery anatomy can predict the response to RDN, i.e. a simple renal artery anatomy is favorable for a larger BP response (Hering et al., 2016). Cardiac baroreflex activity also was reported to predict the BP response to RDN (Zuern et al., 2013). Although interesting if confirmed, neither of these would likely be a practical approach to screening patients for RDN treatment. Several other variables, including sex, BMI, eGFR, and number of attempted ablations have demonstrated a positive predictive role in at least one study (Symplicity, 2011; Kandzari et al., 2015; Id et al., 2015; Rohla et al., 2016; Persu et al., 2014; Krum et al., 2011); however the importance of these factors remains disputed as other studies have not supported similar predictive power (Ewen et al., 2015; Prochnau et al., 2013; Vogel et al., 2014; Flack et al., 2015). Other baseline patient characteristics, such as age, comorbidities, isolated systolic HTN, baseline DBP, and race, have been consistently shown not to predict the magnitude of BP response to RDN (Symplicity, 2011; Kandzari et al., 2015; Ewen et al., 2015; Prochnau et al., 2013; Rohla et al., 2016; Krum et al., 2011; Flack et al., 2015). The impact of antihypertensive drug treatment will be considered in a later section of the review.

### *1.3. Limitations of efforts to identify response predictors in clinical studies*

The methodology of the studies examining the effect of RDN on BP has been criticized in several reviews. Key limitations include: open-label design, lack of statistical power, lack of a confirmatory test to ensure denervation, small effect size, and confounding due to inappropriate adjustment of anti-hypertensive regimen during the observation period after RDN (Howard et al., 2013; Esler, 2014; Fadl Elmula et al., 2015; Howard et al., 2016; Epstein and de Marchena, 2015; Bohm and Mahfoud, 2014). As noted above, critics have pointed to the regression to mean phenomenon observed in similarly designed, open label drug trials, where significant discrepancies between office BP and ambulatory BP reductions are reported, as evidence that RDN data from office BP measurements should be interpreted cautiously (Howard et al., 2013). Since the post-hoc analyses attempting to identify predictors of the BP response to RDN also were based on these data sets, the likelihood of some spurious associations is high. Thus, at this point in time there does not appear to be any reliable way to predict a clinically desirable BP response to RDN based on any specific characteristics of individual patients, with the exception of higher pre-RDN BP.

### *1.4. Effects of antihypertensive drug treatment on BP response to RDN*

Virtually all clinical trials investigating RDN have been performed in patients with treatment resistant hypertension, defined by a hypertensive BP despite treatment with at least 3 anti-hypertensive medications. In many trials, patients were taking 5 or more medications (Esler et al., 2010; Brandt et al., 2012; Ezzahti et al., 2013; Goliasch et al., 2010; Krum et al., 2009; Persu et al., 2013; Rosa et al., 2015; Voskuil et al., 2011), and modification of drug therapy after RDN was generally allowed if deemed clinically necessary or desirable. In many studies, the number of antihypertensive drugs taken was modestly reduced after RDN. Therefore, it is unavoidable that anti-hypertensive drug therapy may have been an important factor influencing the BP response to RDN. This issue was first explored in the 24 month follow-up analysis of Symplicity HTN 1 patients. Somewhat surprisingly, since reduced sympathetic activity to the whole cardiovascular system (not just the kidney) has been proposed to be a major cause of the BP fall after RDN (Vink and Blankestijn, 2013), the BP reduction following RDN was actually greater in patients that presumably already had low sympathetic activity due to treatment with central sympatholytics (Symplicity, 2011; Krum et al., 2011). Later analysis of Symplicity HTN 3 data revealed that patients receiving aldosterone antagonists responded to RDN with a greater BP reduction (Kandzari et al., 2015). These findings are counterintuitive as both classes of medications are known sympatholytics; if the mechanism responsible for the BP reduction to RDN is