Nonresponders to Renal Denervation for Resistant Hypertension

What do we know at this time, and what questions remain to be answered?

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"There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know."

— Donald Rumsfeld

Resistant hypertension has been defined as a failure to reach blood pressure targets despite a combination of three to four antihypertensive drugs from different drug classes (including a diuretic) at optimal dosages.[1] The goal blood pressure is defined as < 140/90 mm Hg for the general population and < 130/80 mm Hg for those with diabetes mellitus or chronic kidney disease. Resistant hypertension is not the same as uncontrolled hypertension (ie, hypertension due to inadequate treatment regimen or poor adherence, or secondary hypertension).

Resistant hypertension is a problem with a reported prevalence of 12% to 15%.[2] Fewer than 50% of treated hypertensive patients are reported to reach blood pressure targets.[3] A study from the United Kingdom estimates the prevalence to be 500,000 to 1 million patients.[4] Clinical trials such as ASCOT, ALLHAT, and ACCOMPLISH had even higher rates of up to 35%, which is thought to be due to the high component of elderly hypertensive patients with high cardiovascular risk.[5] The percentage of uncontrolled hypertension patients in special populations, such as those with chronic kidney disease, may be higher than 60%.[6]

A new therapy, renal denervation, has been developed in response to this problem. Based on the knowledge learned from surgical thoracolumbar splanchnicectomy,[7] the development of a percutaneous endovascular approach to renal sympathetic nerve ablation has led to significant reported decreases in blood pressure. In the Symplicity HTN-1 cohort, we were able to show a mean reduction in office-based blood pressure (OBP) of -32/-14 mm Hg[8] at 2 years and -33/-19 mm Hg at 3 years (n = 24).[9]

However, the results of these studies also describe patients who have not had the same reported decrease in blood pressure. The prevalence of these nonresponders was 10% to 13% in Symplicity HTN-1[10] and Symplicity HTN-2.[11] To date, no review has focused on these nonresponders, etiology, risk factors, or possible treatment strategies.

DEFINING NONRESPONDERS

Prevalence

A nonresponder to renal denervation has been described as a patient who has a < 10 mm Hg decline in the systolic blood pressure, as in the Symplicity HTN-1 trial. At 6 months, the prevalence of nonresponders in

this trial was 13% (six of 45 patients), followed by 10% of patients in the Symplicity HTN-2 trial (five of 49 patients). In control patients, the nonresponse rate was 47%. According to this definition, other studies report a renal denervation nonresponse rate of 11% at 3 months[12] or 3% at 3 months.[13]

Another way nonresponder status could potentially be described would be an increase in blood pressure medications before 6-month follow-up; in the Symplicity HTN-2 trial, this was reported in 8% of renal denervation patients (four of 49 patients in an intention-to-treat analysis) and 12% of control patients (six of 51 patients in an intention-to-treat analysis). However, this may be difficult to measure. Blood pressure medications may be decreased due to an ability to reach target blood pressure, kept the same, increased due to nonresponder status, or increased due to enthusiasm to reach target blood pressure. Another possible definition of nonresponders would be patients who did not achieve optimal blood pressure, which depends on the original starting blood pressure.

Timing of Response

There is evidence to support a greater increase in the responder rate with time.[11] This is attributed to the absence of nerve fiber recovery, nerve fiber regrowth, or development of counterregulatory blood pressure mechanisms.[14] There may be also a resetting of the baroreflex response or reversed vascular remodeling that overrides any functional reinnervation after the procedure.[8] According to the available preclinical and clinical data, the mechanism of sustained response is not clear.

This leads to the question of whether nonresponders show a late improvement in blood pressure. Are there patients who may be termed "late responders" or "delayed responders?" The Symplicity HTN-1 data show that among 45 patients who were initially deemed nonresponders, 58% responded at 3 months, 64% at 1 year, 82% by 2 years, and 100% at 3 years. At 6 months, the Symplicity HTN-2 trial had eight of 52 patients allocated to the denervation group who were deemed nonresponders, leading to a reported 6-month nonresponder rate of 10%; if the three patients lost to follow-up are excluded, the rate is 16%.[11] At 12 months, the reported rate of nonresponders was 21% (10 of 47 patients).[15] It is unknown whether nonresponders become responders or vice versa during the follow-up period.

Sobotka et al also showed that eight patients who were not responders initially became responders after 3 years.[16] While this is helpful, this is a small number of patients. Studies from the year presented at ESC 2013, namely Symplicity HTN-1 results at 3 years by Krum et al[17] and results from the Global SYMPLICITY registry presented by Boehm et al,[18] do not explicitly state the nonresponder rate at each time frame or the change from responder to nonresponder or vice versa. Although these are abstracts, this is the type of information that should be included in the upcoming accepted peer-reviewed publication. At this time, there is insufficient evidence to answer the question as to whether nonresponder status is a static or dynamic condition.

Type of Blood Pressure Measurement

The type of blood pressure measurement may also be an important factor in this discussion. Studies have mainly reported two types of blood pressure measurement, namely OBP and 24-hour ambulatory blood pressure (ABP). In the Symplicity HTN-2 trial, a special office-based automatic blood pressure monitor was used with a printer for documentation. The averages of triplicate measurements were used in the analysis.[15] The 24-hour ABP method consists of noninvasive measurement at regular intervals. Although trials of renal denervation have included both OBP and 24-hour ABP monitoring, most of the data have been reported in the form of OBP monitoring.

Multiple, separate pieces of information are gained by 24-hour ABP measurement. First, it allows an assessment of daytime and nocturnal hypertension. These changes can be used to evaluate whether the patient has a nocturnal dip in blood pressure, does not have a nocturnal dip in blood pressure, or has a nocturnal increase in blood pressure. Absence of a nocturnal dip can be associated with increased mortality,[19] and the presence of nocturnal hypertension is associated with end-organ damage.[20] Second, the use of 24-hour ABP monitoring provides a blood pressure profile independent of the medical environment (which may lead to "white-coat hypertension"). Third, this technique monitors blood pressure behavior during the patient's regular activities. Finally, the use of ABP monitoring can demonstrate efficacy of medication (or in this case, renal intervention) during a 24-hour period. However, the ABP technique requires special training for use, may cause discomfort to the patient, and is more expensive than conventional measurement.[21]

One study examining OBP and ABP for the Dietary Approaches to Stop Hypertension trial showed comparable standard deviations of change in systolic blood pressure and change in diastolic blood pressure. ABP was also more efficient (smaller sample size for a given blood pressure change) and required fewer clinic visits.[22] A meta-analysis measuring blood pressure monitoring in regard to predicting target organ damage due to hypertension found that

TABLE 1. SAMPLING OF DATA FOR RENAL DENERVATION NONRESPONSE BY TIME[a]

Time	Number of Nonresponders	Catheter Device Used	Study
1 month	44/143 (31%)	Symplicity	Symplicity HTN-1 (2009)[16]
	0/10 (0%)	ThermoCool	Ahmed et al, 2012[24]
	10/46 (22%)	EnligHTN	ARSENAL (EuroPCR 2012)[25]
3 months	4/37 (11%)	Symplicity	Ukena et al, 2011[12]
	0/10 (0%)	ThermoCool	Ahmed et al, 2012[24]
6 months	21/82 (26%) including both catheter and crossover patients	Symplicity	Symplicity HTN-2 (2010)[15]
	15/88 (17%)	Symplicity	Mahfoud et al, 2012[26]
	0/10 (0%)	ThermoCool	Ahmed et al, 2012[24]
	11/46 (24%)	EnligHTN	Papademetriou, 2012[27]
12 months	27/130 (21%)	Symplicity	Symplicity HTN-1[16]
	10/47 (21%)	Symplicity	Symplicity HTN-2[15]
24 months	6/59 (10%)	Symplicity	Symplicity HTN-1[16]
36 months	0/24 (0%)	Symplicity	Symplicity HTN-1[16]

[a]These data were selected based on representative status and reporting of nonresponse rates. Of note, some articles included patients who were part of the SYMPLICITY-HTN trials. Therefore, a group value was not calculated.

ABP was superior to OBP in measuring preclinical organ damage as assessed by echocardiographic left ventricular mass index.[23]

The potential discrepancies between OBP and ABP monitoring have led some to identify various hypertensive patient populations. These include sustained normotensive patients (both OBP and ABP are high), white-coat hypertensive patients (OBP is high, ABP is normal), masked hypertensive patients (OBP is normal, ABP is high), and sustained hypertensive patients (both OBP and ABP are high).[28] The white-coat effect for patients with resistant hypertension has been reported to be as high as 40%, with a concurrent masked hypertension effect in controlled patients as high as 31%.[29]

As previously mentioned, most of the data reported in trials of renal denervation have been in terms of OBP rather than 24-hour ABP. As Nainggolan reported on theheart.org, Axel Bauer found only borderline significant effect of renal denervation on ABP, Michael Voskuil did not find a decrease in ABP in 28 patients, and Mylotte et al found that effects on ABP were "less dramatic" than office-based blood pressure.[30] In the Symplicity HTN-2 trial, data were available for ABP for only 72% of patients.[11] At the 1-year mark, an attempt was made to collect data, but because of patient nonadherence and incomplete records, the data were unavailable.[15] For a brief overview of the articles published on nonresponders, please see Table 1.

PREDICTORS OF NONRESPONSE

In the Symplicity HTN-1 trial, univariate analysis showed no clear association between a systolic OBP reduction of 10 mm Hg or more and age, sex, ethnic origin, history of coronary heart disease, type 2 diabetes, hyperlipidemia, baseline systolic or diastolic blood pressure, baseline glomerular filtration rate, baseline heart rate, baseline number of antihypertensive medications, baseline antihypertensive drug types, or number of ablations.[10] At 2 years, higher baseline systolic blood pressure and use of central sympatholytic agents were found to be positive markers.[8] However, it may be that a higher starting point in systolic blood pressure may be associated with a higher likelihood of decline in systolic blood pressure. Taking this forward, one may argue that central sympatholytic agents are correlated with a higher initial systolic blood pressure, as one may use them for resistant hypertension as a third- or fourth-line agent. At this point, there is insufficient evidence to point to a systematic, patient-based predictor for nonresponder status to renal denervation for resistant hypertension.

POTENTIAL CAUSES OF NONRESPONSE

There are many reasons for treatment-resistant hypertension. These include factors related to measurement, patient lifestyle, coincident medications, and secondary hypertension. We describe these in further detail in the following paragraphs.

Pseudoresistance may be due to inaccurate blood pressure measurement (due to an inadequate cuff, too short a resting period before blood pressure measurement, or an inadequate sphygmomanometer), or inadequate medication compliance or adherence (often with an inverse relationship between the number of tablets and accuracy of their intake). The patient should also be on an optimized therapeutic regimen with avoidance of therapeutic inertia (failure to uptitrate medications despite high blood pressure readings). There may be unfavorable lifestyle factors, such as obesity, high salt intake, or high alcohol consumption.[31]

Some medications may increase blood pressure or interact with blood pressure medications to reduce efficacy. These include NSAIDs, corticosteroids, sympathomimetics (decongestants), illicit drugs (cocaine, amphetamines), migraine medications (triptans, ergot derivatives), oral contraceptive pills, immunosuppresants (cyclosporine, tacrolimus), erythropoietin, excess licorice ingestion, and herbal remedies (ephedra).[31]

The prevalence of secondary hypertension is 5% to 10% of essential hypertension patients,[32,33] but the prevalence of secondary hypertension in resistant hypertension is not well known. One study of patients with resistant hypertension found that 113 of 200 patients had a secondary form of hypertension.[34] Ideally, this should have been known before the procedure; however, the patient may have developed a new illness or had worsening of a mild condition during the follow-up period. Common causes include obstructive sleep apnea, renal parenchymal hypertension, primary hyperaldosteronism, and renal artery stenosis, as well as rare causes such as pheochromocytoma, hyperparathyroidism, aortic coarctation, and intracranial tumor.[31] Multiple approaches exist for outpatient evaluation of secondary causes of hypertension.[1,35,36]

There are reports of renovascular stenosis after renal denervation therapy.[35] This may be ostial at the site of focal ablation or separate at a site with preexistent mild renal artery stenosis,[8,11,15] which may be due to ablation-related injury or progression of previously mild disease. It is possible that there may still be some benefit of renal denervation in cases of secondary hypertension, but whenever possible, every attempt should be made to find and treat a secondary cause of hypertension.

There are also other sources of sympathetic innervation that are involved in hypertension. Arterial baroreceptors, such as those in the carotid sinus and aortic arch, modulate blood pressure by increasing the firing of baroreceptor afferents in response to increasing blood pressure. Over time, these baroreceptors become less sensitive due to peripheral and central contributions. Resetting this baroreceptor reflex and restoring carotid sinus nerve activity may lead to persistent resistant hypertension after renal denervation. Sympathetic activity has been involved in essential hypertension, obesity-related hypertension, renal hypertension, obstructive sleep apnea, and preeclampsia.[37] Other sources of sympathetic stimulation may be cardiac, hepatomesenteric, adrenal medullary, skeletal muscular, and/or related to the central nervous system.[38]

PROCEDURAL CAUSES OF NONRESPONSE

Anatomical Issues

There are various anatomical considerations that must be taken into account before a renal denervation procedure. The Symplicity trials did not include patients who had hemodynamically significant renal artery stenosis, previous renal artery intervention, or renal artery anatomy that precluded treatment (defined as < 4 in mm diameter, < 20 mm in length, or more than one main renal artery).[11]

An accessory renal artery left unablated can be a cause of persistent hypertension after renal denervation. Accessory renal arteries are found in 2.3% of human cadavers,[39] and most trials have excluded patients in whom a second renal artery has been found. Lack of recognition of a second renal artery (either directly by angiographic visualization, or indirectly by recognition of a signal void in the kidney silhouette) may lead to a lack of effective treatment.[40] As far as stenosis in the accessory renal artery, an MRI study found no statistically significant difference in the prevalence of renal artery stenosis between patients with accessory renal arteries and those without, which led them to conclude that this was not a direct cause of hypertension.[41] What role accessory renal artery nerves play in resistant hypertension, if any, is unknown.

In addition, patients who have previously undergone stent treatment have undergone renal denervation.[42] Individual devices, including balloon-based therapy, also have specific anatomic criteria, such as vessel diameter and length, that may preclude therapy. The Symplicity HTN-1 study excluded five of 50 patients for anatomical reasons (primarily dual renal systems)[10]; in Symplicity HTN-2, 30 of 90 patients were excluded.[11] One study in a real-world setting that identified 24 patients eligible for renal denervation found unsuitable renal anatomy in nine patients.[34]

Therapeutic Issues

Patients may have inadequate ablation or complications that hinder therapeutic efficacy. It is believed that thor-

ough ablation of the renal nerves in multiple quadrants of the cross-sectional artery is necessary for an appropriate response. The depth and prevalence of the renal arteries has been studied by various techniques, showing that either 50% of renal nerves were at a depth of 0.5 to 1 mm,[43] or 30% of renal nerves were at a depth of 2 to 4 mm.[44]

Although the number of ablations with the Symplicity catheter (Medtronic, Inc., Minneapolis, MN) was not found to be a predictor of response/nonresponse,[10] it is our practice to attempt at least six to seven ablations per side, whenever possible.

Device Issues

At this point, there exist various radiofrequency ablation devices. These include single-electrode catheters (Symplicity), multielectrode catheters (EnligHTN, St. Jude Medical, Inc., St. Paul, MN), balloon-mounted catheters (V2, Boston Scientific Corporation, Natick, MA), irrigated balloon-mounted catheters (OneShot catheter, Covidien, Mansfield, MA), and irrigated catheters (ThermoCool, Biosense Webster, Inc., Diamond Bar, CA). There are also devices that use ultrasonic ablation (eg, Paradise ultrasonic balloon catheter [ReCor Medical, Menlo Park, CA], TIVUS [Therapeutic IntraVascular UltraSound] autoregulating balloon catheter [CardioSonic, Tel Aviv, Israel], and Kona low-intensity external ultrasonic ablation system [Kona Medical, Campbell CA]). Devices that utilize local-tissue drug delivery, such as the Bullfrog microneedle-equipped balloon microinfusion catheter (Mercator MedSystems, Inc., San Leandro, CA), are also being developed.[45] Each device has advantages and disadvantages to its use. At this point, there are insufficient data to prove the efficacy of one device over another in terms of responder rate, response durability, decrease in medication rate, or reaching the goal blood pressure.

Measuring a Decrease in Sympathetic Tone

Given the differences in devices and the prevalence of nonresponders to therapy, there may be benefit in invasive measurement of denervation effectiveness. In Symplicity HTN-1, procedural success was measured with the release of noradrenaline from the renal sympathetic nerves bilaterally with the isotope dilution renal noradrenaline spillover method.[38] It has been postulated that the decrease in renal norepinephrine spillover suggests a reduction of renal efferent activity, whereas a decrease in total body norepinephrine spillover suggests a reduction in central sympathetic drive through the renal afferent pathway.[46]

Another option is to look at multiunit postganglionic sympathetic nerve activity, which is often recorded through the use of microneurography in the peroneal nerve.[47] Single-nerve muscle sympathetic nerve activity is measured and plotted as bursts per minute, with a decrease noted in patients in the Symplicity HTN-1 trial.[10] However, this is prone to error due to medications that are known or likely to affect multiunit postganglionic sympathetic nerve activity.[48] Another option for measuring a decrease in sympathetic tone is observing a decrease in plasma renin activity.

TREATMENT OPTIONS FOR NONRESPONDERS

First, it is important to isolate the cause of nonresponder status based on what is known so far. Blood pressure measurements should be repeated, and 24-hour ABP monitoring should be used when available. Pseudoresistance, unfavorable lifestyle factors, unfavorable co-medications, and secondary hypertension should be carefully ruled out. The procedure dictation and film should be carefully reviewed to evaluate for anatomical or procedural factors that can be associated with persistent hypertension. When this has all been considered, there is still a possibility that the patient is a delayed responder, when there is an insufficient time period between renal denervation and assessment.

There are a few different options for treating patients who are nonresponders. First is medical therapy, which involves continuation of appropriate antihypertensive medications with uptitration when available. Second is a repeat procedure using the same device, which has been done at our center. We would suggest a higher number of ablations in the second intervention. A patient who relapses after early procedural success can be treated similarly.[49] Third would be a repeat renal denervation procedure using a different device, as was performed in three patients by Prochnau et al.[50] One patient with end-stage renal disease was successfully treated with initial radiofrequency ablation and then relapsed after 12 months; the other two were deemed primary nonresponders to renal denervation therapy with radiofrequency ablation (after a period of 4 months each). All three were then treated with cryoenergy ablation. There was improvement in the first two patients, but a relapse in the one of the primary nonresponders to radiofrequency therapy.

Other options involve the use of devices that affect other areas of the sympathetic nervous system. The Rheos baroreflex hypertension therapy system (CVRx, Inc., Minneapolis, MN) is an implantable device that activates the carotid baroreflex system. The DEBUT-HT study of 45 patients showed a mean blood pressure reduction of 21/12 mm Hg, which was sustained in 17 patients who completed 2 years of follow-up.[50] This was followed by the prospective, randomized, double-blind Rheos Pivotal trial, which evaluated 264 patients who successfully completed a mean duration of 21 months of chronic therapy. At 1-year follow-up, the

REMAINING QUESTIONS TO BE STUDIED

- What is the best definition of nonresponder? In what way should blood pressure be measured? What are the cutoffs?
- How much time is necessary before a patient is deemed a nonresponder? What percent of patients are "delayed responders?" (This will require reporting of nonresponder rates at interval time periods for all trials.)
- What are the risk factors that can predict nonresponder status?
- What is the prevalence of nonresponder therapy based on patient population and type of device used?
- What is the best method to treat a nonresponder: medical therapy, repeat renal denervation with the same device, repeat renal denervation with a different device, or implantation of a carotid baroreflex modulator? At what time point should this be done?
- How do we define patients that are relapsers, as in those who were originally responsive to renal denervation and then again experienced resistant hypertension? What is the prevalence of this by time point and device used? Are there any risk factors that can predict relapse? How should these patients be treated?

nonresponder rate was 19%.[51] However, the device needs to be surgically implanted, and a few patients in the trial had significant complications (ie, infection requiring explantation, stroke, and intraoperative hypoglossal nerve injury).[52] Another device, the MobiusHD (Vascular Dynamics, Inc., Mountain View, CA), is a stent-like nitinol device that is placed in the carotid sinus to modulate the baroreceptor reflex. This is currently being tested in animal trials, but a first-in-man trial is planned for late 2013.[53]

There are also surgical options that have existed since before the development of percutaneous renal denervation. Bilateral nephrectomy of native kidneys in patients with end-stage renal disease and kidney transplant can improve or normalize blood pressure.[54,55]

Thoracolumbar splanchnicectomy was performed in 1,266 patients and showed a significant lowering of blood pressure in 45% of patients in the first 5 years.[7] Although there was a 5-year mortality risk of 19% with an absolute risk reduction of 34%, there was an increased risk of postural hypotension, erectile dysfunction, and syncope. Due to the excessive morbidity, this approach has been largely abandoned.

FURTHER RESEARCH

In the new and exciting field of renal denervation, it is important to understand the definition, prevalence, and treatment of patients with resistant hypertension who are nonresponders to renal denervation. Multiple significant questions still need to be asked. These center on how we know what we know, what we know we don't know, and other issues that have yet to arise (see the *Remaining Questions to Be Studied* sidebar). This will require further large randomized controlled trials and real-world registries. ■

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