Drug-resistant hypertension is a clinically relevant problem that has attracted increasing attention over the past few years. This is certainly attributable to a growing awareness of the importance of blood pressure (BP) control in reducing hypertension-related cardiovascular risk. It is also due, however, to a recent major breakthrough in the management of resistant hypertension, because of the introduction of 2 novel invasive therapeutic approaches: carotid baroreceptor stimulation and catheter-based renal sympathetic denervation (RDN). For a number of reasons, the latter method seems to be taking the upper hand and is used with growing enthusiasm all over the world, even if the strength of the evidence in its support is not currently overwhelming.

The concept of RDN derives from a known pressor effect of sympathetic stimuli, arriving to the kidney via efferent fibers located in the adventitia of renal arteries, in the frame of a complex regulation of sympathetic activity also including reflex modulation by renal afferent neural influences. Hence, the hypothesis was made that destruction of these fibers, by bilaterally applying radiofrequency electric current through an ablation catheter positioned inside renal artery, might reduce sympathetic activity in general. It was also hypothesized that, in particular, renal sympathetic fiber ablation might interfere with sympathetic renal modulation, leading to increased sodium and water excretion and to vasodilation, thereby effectively lowering elevated BP levels. This hypothesis was first tested in animal studies and subsequently explored in 2 major studies in humans: Renal sympathetic denervation in patients with Refractory Hypertension (The Symplicity HTN-1 Trial) and Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial), followed by a growing number of reports from registries.

Although the results of Symplicity studies clearly supported the efficacy of RDN in lowering office BP, their design left several major questions unanswered. One of the key issues was related to the fact that, strangely enough, resistant hypertension status was only defined based on conventional BP measurements, and pseudoresistance resulting from a white-coat effect had not been excluded by means of out-of-office measurements. Focus on conventional office BP only was a common approach in most available RDN studies, an approach that is somehow surprising, on the background of the growing awareness of the limitations of office BP measurements and of the acknowledged need to combine them with out-of-office BP monitoring through home self-BP measurements or, even better, through 24-hour ambulatory BP monitoring (ABPM).

Basing available RDN studies on office BP measurements only, and thus failing to exclude patients whose office BP elevation was largely attributable to a white-coat effect, also raises some ethical concerns, because the contribution of the white-coat effect to cardiovascular risk is modest, and the prognostic benefits (if any) derived from improving office BP control in subjects with controlled out-of-office BP may not outweigh the risks of an invasive procedure such as RDN. Indeed, ABPM was only performed in a small subset of Symplicity participants, and the principal assessment of efficacy was based on office BP. Apart from the issue of a white-coat phenomenon, an office BP–based approach to assessing the efficacy of antihypertensive intervention has been extensively criticized in the past for several reasons: (1) The selection of patients only based on elevated office BP in a clinical study frequently leads to a bias owing to the imperfect standardization of the procedure (usually with overestimation of true BP) and to an observer bias. Although the investigators of the Symplicity HTN-2 trial tried to overcome this problem, at least in part, by using automated BP-measuring devices with data printout, this approach might have prevented only the observer bias, but not the alarm reaction induced by the medical visit. Moreover, not all studies have properly reported the type of device used for office BP measurement as in the case of Symplicity HTN-1. (2) Office BP is highly variable and thus affected by a regression to the mean phenomenon (a patient may be recruited based on a high BP value even if his or her usual BP levels may be lower, thus leading to an artificial BP lowering during subsequent follow-up measurements). In fact, these problems led European Medicines Agency to recommend that BP-lowering efficacy by treatment should be assessed by means of ABPM in registration studies of antihypertensive drugs. These issues might be largely resolved when Symplicity HTN-3 trial results are available. This trial is in fact designed as a randomized study with a control group undergoing a sham procedure, a blinded outcome assessment, and 24-hour BP as a secondary outcome,
and it will exclude patients with controlled or mildly elevated 24-hour BP. At present, however, only nonrandomized observations on the 24-hour ambulatory BP (ABP) effects of RDN are available. Several such reports have already been published, but the number of subjects included has been invariably small. The article by Mahfoud et al published in this issue of Circulation, offers for the first time data on ABP changes after RDN in a relatively large sample (n=346) of subjects who underwent RDN following the Symplicity protocol and were followed for up to 12 months. The principal result of the analysis conducted on such a data set is the demonstration that in true resistant hypertensive patients (ie, patients with office SBP ≥160 mm Hg, or ≥150 mm Hg for diabetic patients, combined with 24-hour SBP >130 mm Hg in subjects treated with a diuretic) clinically and statistically significant reductions occurred in ambulatory systolic BP (SBP) and diastolic BP (8–10 mm Hg and 4–7 mm Hg, respectively, at different follow-up times). Much larger reductions in office SBP and diastolic BP also occurred (21–27 mm Hg and 9–12 mm Hg, respectively), which were however slightly less pronounced than in the Symplicity studies. ABP reductions were similar during daytime and nighttime. Among possible predictors of response to RDN, only baseline BP resulted in being significantly related to BP reduction.

These results need to be placed in the context of previous studies comparing the effect of various antihypertensive therapies on office BP and ABP. In a vast majority of these articles, the reductions in office BP with treatment exceeded those in ABP. As shown in a meta-analysis of a large number of such drug studies, the reductions in ABP on average corresponded to 70% of the reductions in office BP. In the article by Mahfoud et al, the corresponding figures are much lower: at 3 months, 24-hour ABP reduction corresponded to 39% (systolic) and 47% (diastolic) reduction in office systolic or diastolic BP, respectively; these figures are higher than those reported in some of the previous studies. These data are shown in the Figure, which compares reductions in office BP and in 24-hour ABP reported in drug studies with the corresponding reductions described in the available RDN studies in which both methods of BP measurements were implemented (Figure).

This greater discrepancy between office BP and ABP reduction might be attributable to a less controlled office BP measurement setting in the study by Mahfoud et al (ie, to a larger bias in office BP assessment), in comparison with clinical trials on antihypertensive drugs, and to true attenuation of a white-coat effect by RDN, as suggested by the authors. Whichever the case, these results, although confirming the antihypertensive efficacy of RDN, indicate that the degree of ABP reduction is not as impressive as that of office BP.

Another interesting finding of the study by Mahfoud et al is that the reduction in nighttime BP was similar to that in daytime BP and, consequently, no improvement occurred in altered (nondipper or reverse dipper) circadian BP profiles. Although an additional benefit in this regard would be welcome, the finding that nighttime BP is effectively reduced by RDN is nevertheless reassuring, on the background of the results of several studies and of a large meta-analysis that indicated that nocturnal BP may be more closely related to outcome than daytime BP levels.

Importantly, 43 of the subjects included in the study by Mahfoud et al had pseudoresistant hypertension (ie, 24-hour SBP <130 mm Hg at recruitment). Although performing RDN in these subjects may be questioned on ethical grounds, it provides some answers (but probably also raises more questions) on the effects of RDN in these particular cases. In these patients, significant reduction occurred in office BP, whereas ABP, already within normal range, remained unaffected. This is an important finding in terms of subjects’ safety, because, apparently, no clinically relevant hypotension occurred in these subjects, despite their having normal 24-hour ABP at the time of RDN. Given the uncontrolled design of the study, however, it is impossible to conclude to what extent the intrinsic limitations of office BP measurement contributed to such an effect. We cannot exclude, however, that RDN, by attenuating sympathetic activity, reduced excessive BP responsiveness to external stimuli (related to white-coat effect) in otherwise controlled subjects. This hypothesis is supported by previous findings of reduction in BP variability after RDN, findings that need to be confirmed by additional evidence, however. The question remains open whether office BP lowering provides any benefit in these patients and, consequently, whether pseudoresistant hypertensive patients should be considered eligible for this interventional approach.

This issue needs to be considered in the context of an even more important problem related to RDN efficacy: not only are no hard-outcome studies available to support the value of

![Figure. Discrepant effects of antihypertensive pharmacological treatment (○) and renal sympathetic denervation (■) on office and ambulatory BP levels.](http://circ.ahajournals.org/)

Regression line with 95% confidence intervals refers to the relationship between office and ambulatory BP reductions in pharmacological studies. BP indicates blood pressure; EnLighHTN-1, safety and efficacy of the EnLighHTN Multi-Electrode Renal Denervation System for patients with drug-resistant hypertension; SBP, systolic blood pressure; Symplicity HTN-1, Renal Denervation in Patients With Refractory Hypertension; and Symplicity HTN-2, Renal Denervation in Patients With Uncontrolled Hypertension. Adapted from Mancia and Parati with permission of the publisher. Copyright © 2004, Wolters Kluwer Health.)
this approach, but also, only 2 studies have reported on its effects in terms of organ damage markers, one on left ventricular mass and one on pulse wave velocity. This is surprising, because these markers are routinely obtained in resistant hypertensive patients and have proved useful in assessing the efficacy of pharmacological therapies in hypertension, even over relatively short follow-up periods.

Apart from a nonrandomized and uncontrolled design, the study by Mahfoud et al has another important limitation, that is, a high rate of subjects lost to follow-up. In fact, follow-up ABPM data at 3 months are available only in 245 of 346 patients who entered the study. The figure is similar at 6 months (236), and data at 12 months are available in only 90 subjects. This inevitably raises questions on possible biases owing to the exclusion of a large subgroup of patients from the analyses. There may also be some doubts regarding the quality of ABPM recordings, because as many as 47 patients did not record nighttime BP at baseline.

Despite these limitations, while waiting for the Symplicity-3 results, the study by Mahfoud et al provides interesting novel insights into the efficacy of RDN, supporting the use of this approach in patients with true resistant hypertension. At the same time, the results of this study emphasize the importance of combining office BP with out-of-office BP measurements, in particular 24-hour ABPM, to properly assess the effects of RDN on hypertension control in daily life.

Disclosures

None.

References


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Renal Sympathetic Denervation and Daily Life Blood Pressure in Resistant Hypertension: Simplicity or Complexity?
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