Diagnosis and Treatment of Resistant Hypertension: The Critical Role of Ambulatory Blood Pressure Monitoring

J. Rick Turner, BSc, PhD;[1] Eoin O'Brien, DSc, MD, FRCP[2]

From Clinical Communications, Quintiles, Durham, NC;[1] and The Conway Institute, University College Dublin, Dublin, Ireland[2]

Hypertension is an illness that generally requires lifelong treatment with blood pressure (BP)–lowering drugs. It is, therefore, understandable that increasing attention is being paid to interventional procedures that might provide a "cure" for hypertension and obviate the need for costly therapy that is not always without unwanted effects. Such interventional techniques are confined, for the moment, to patients with drug-resistant hypertension, ie, BP levels above a specified target despite adherence to at least 3 optimally dosed antihypertensive medications of different classes, including a diuretic,[1,2] to which we would add for a minimum of 3 months on such maximal treatment.

In clinical research involving these procedures (as for research involving pharmaceutical therapies), two key aspects of a given trial's design merit particular attention: verification that individuals enrolled in the trial truly have drug-resistant hypertension and that there is no underlying cause for hypertension (ie, secondary hypertension); and the choice of BP endpoints to be assessed at specified timepoints following surgical interventions. There are now various measurement methodologies available to us with which to obtain BP data in both contexts, ie, as inclusion/exclusion criteria for entry into the trial and as measures of the intervention's efficacy. A question we must ask in both settings is: What is the most informative way we can assess BP? We believe the answers are uniform and clear: ambulatory BP monitoring (ABPM) is the most appropriate and informative methodology and should be mandatory in all studies to investigate interventional efficacy.

TWO BP MEASUREMENT METHODOLOGIES

Conventional clinical BP measurement (CBPM) in a physician's office or at an investigational site during pharmacologic trials traditionally utilized the auscultatory technique that is more than 100 years old, although, recently, trials have used automated devices to measure BP.[3] While we believe that the auscultatory technique is inherently accurate, "it is dependent on observer attention to detail, which is often lacking, and it provides only a momentary measurement of BP, usually under circumstances that can influence the level of BP being measured."[4] Moreover, even though automated techniques may improve accuracy,[5] the BP-measuring process is seriously flawed by providing only a snapshot of BP under circumstances that may elevate BP. For example, the phenomenon of white-coat hypertension,[6] in which an individual demonstrates higher BP levels in a physician's office or clinic than in other settings, is problematic when using CBPM (as is masked hypertension, the phenomenon of appearing normotensive in the office but having hypertension in other settings).[7]

Two arguments can reasonably be postulated. First, if participants in a clinical trial of a procedural intervention have been enrolled based on CBPM values that were indeed influenced by the white-coat phenomenon and then undergo the intervention, their true (lower) BP values are less likely to be reduced by that intervention, thereby lessening the likelihood of finding compelling evidence that the intervention is truly effective. Second, if familiarization (with or without regression to the mean) occurs during the trial, the beneficial reduction in BP may be erroneously attributed to the intervention. In addition, while some trials that employ CBPM may be very well conducted and may indeed show an effect on BP at the snapshot in time at which a measurement is taken (which may only be at one point in a 24-hour cycle, typically during daytime hours), they cannot provide information on the duration of an effect on BP throughout a 24-hour period or its effect during the nocturnal period.

In contrast, ABPM offers important advantages in clinical research of antihypertensive interventions.[8–10] First, it provides a profile of BP behavior over a 24-hour period. This profile facilitates assessment of the effects of an intervention not only aggregated during the entire 24-hour period but also during specific windows of this time cycle, most simply daytime hours and nighttime hours. Second, mean ABPM measurements during daytime and nighttime periods are largely devoid of the white-coat and placebo effects.[4] In the guideline on ABPM published recently by the European Society of Hypertension,[4] the following recommendation is made: "We do not yet know whether treatment strategies based on BP assessment by ABPM are significantly better than office BP in reducing the rate of cardiovascular events. Notwithstanding this limitation, the above-mentioned advantages of ABPM strongly support the inclusion of ABPM in all future pharmacologic trials of antihypertensive drug therapy." We would add that the same considerations apply to trials of interventional techniques.

Address for correspondence: J. Rick Turner, Clinical Communications, Quintiles, 4820 Emperor Boulevard, Durham, NC 27703
E-mail: rick.turner@quintiles.com

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THREE INTERVENTIONAL TECHNIQUES OF CURRENT INTEREST

BP-lowering drugs have been the mainstay of managing hypertension except in relatively rare instances when an intervention can be curative (eg, the removal of suprarenal secreting adenomata in Conn's syndrome or pheochromocytoma). However, interventions with curative potential have recently started to dominate the literature. If their popularity were assessed in terms of published data and reviews, these procedures may be ranked as, firstly, renal sympathetic denervation (RDN)[11–19]; secondly, carotid baroreflex activation therapy (BAT)[20–23]; and thirdly renal arteriovenous fistula (RAVF).[24,25]

Renal Sympathetic Denervation

In RDN, a catheter is passed via the femoral artery into both renal arteries and radiofrequency energy is then used to ablate the sympathetic nerve fibers. Several clinical trials have been reported and other trials are currently underway. In 2012, Doumas and colleagues[26] published a review including discussion of 4 completed trials, 3 RDN trials, and 1 BAT trial (the latter is discussed below) in which postprocedure BP reductions were evaluated by both CBPM and ABPM, each from their respectively assessed baseline values: the RDN trial reports were published by Krum and colleagues,[27] Esler and colleagues,[28] and Witkowski and colleagues.[29] For each trial and the BP parameters within them, ratios expressed in percentage terms were calculated for systolic BP (SBP) and diastolic BP (DBP) as change in ABPM value divided by change in CBPM value. Values ranged from 18% to 58% (mean = 38%), thereby indicating that reductions expressed in ABPM terms were considerably less than those expressed in CBPM terms. The Table presents analogous data for 3 additional RDN studies reported by Zuern and colleagues,[30] Kiuchi and colleagues,[31] and Worthley and colleagues,[32] where values calculated in the same manner ranged from 23% to 60% (mean = 39%). Overall, using this analysis strategy, these 6 studies yielded very similar results.

As Doumas and colleagues[26] noted, it is true that reductions expressed in ABPM values are also typically less than when expressed in CBPM terms in trials of antihypertensive drugs, but the respective ratios are typically in the 60% to 80% range,[33–36] leading them to comment that reductions in BP evaluated by CBPM in the studies they discussed were "disproportionately greater" than those evaluated in the same respective studies by ABPM. The 3 studies addressing RDN reported in the Table of our present paper support that observation. We therefore echo the sentiments of Doumas and colleagues, who expressed their belief that "meticulous exclusion of patients with white-coat hypertension" in future clinical trials of BAT and RDN interventions represents "a *sine qua non* prerequisite" for the accurate evaluation of their efficacy.[26] (See Schmieder and colleagues[37] and Mancia and colleagues[38] for additional discussion of the relationship between CBPM and ABPM.)

Baroreflex Activation Therapy

BAT has evolved through a number of technologic phases. The current Rheos system (CVRx, Maple Grove, MN) consists of an implanted pulse generator, 2 carotid leads, and a programmer system. The two leads are tunneled subcutaneously and are attached bilaterally around the carotid sinuses, avoiding the carotid sinus nerves and their blood supply. The device is programmable after surgical implantation. Under normal circumstances the baroreceptors protect against

TABLE. CBPM and ABPM Reductions Following Interventional Procedures[a]

Study Authors (N)	Baseline CBPM SBP/DBP, mm Hg	Baseline ABPM SBP/DBP, mm Hg	Reduction in CBPM SBP/DBP (Time After Intervention)	Reduction in ABPM SBP/DBP, mm Hg	Comparison (ABPM Over CBPM) for SBP/DBP, %
Renal sympathetic denervation					
Zuern et al[30] (11)	189/92	149/NP[b]	30.4/2.9 (6 mo)	7.0/NP[b]	23/NA
Kiuchi et al[31] (24)	186/108	151/92	51/20 (180 d)	19/7	37/35
Worthley et al[32] (46)	176/96	150/83	28/10 (1 mo)	10/5	36/50
			27/10 (3 mo)	10/5	37/50
			26/10 (6 mo)	10/6	38/60[c]
Renal arteriovenous fistula technique					
Brouwers et al[25] (8)	175.3/87.3	151.8/82.0	12.5/11.8 (3 mo)	5.6/10.0	45/85
			17.8/13.6 (6 mo)	9.4/13.0	53/96

Abbreviations: CBPM, clinical blood pressure measurement; DBP, diastolic blood pressure; NA, not applicable; NP, not presented; SBP, systolic blood pressure.

[a]Mode of presentation based on that employed by Doumas and colleagues.[26]

[b]Information not presented numerically in the paper (the focus was on blood pressure variability).

[c]Single reading from the study by Worthley and colleagues used in the calculation of mean percentages for the 3 renal sympathetic denervation studies as cited in the text (this is the value least supportive of our arguments).

surges in BP elicited by psychological or physical stress.[20] Increased baroreceptor firing induces an increase in parasympathetic (vagal) stimulation, which leads to lower BP via a cascade of physiological adaptations.[39] The premise of BAT is that triggered stimulation of the carotid nerves will function as a constant influence to lower BP.

The BAT trial included in the Doumas and colleagues[26] editorial discussed earlier, a multicenter feasibility study, was reported by Scheffers and colleagues.[40] Using the same methodology comparing reductions assessed by CBPM and ABPM, Doumas and colleagues[26] noted that the values for SBP and DBP were 29% and 33%, respectively, again indicating that reductions expressed in ABPM values were considerably less than those expressed in CBPM values.

Renal Arteriovenous Fistula Technique

The technique of RAVF in the present context is not yet as well discussed in the literature, but clinical trials are underway and the technique deserves inclusion in our discussions. In this procedure an iliofemoral arteriovenous fistula is created using the ROX Anastomotic Coupler System (ROX Medical, Inc, San Clemente, CA). The procedure has been used in patients with severe chronic obstructive airways disease in whom it was noticed there was a fall in systemic BP, suggesting that the technique may provide another interventional technique for treating pharmacotherapy-resistant hypertensive patients.

The results of a small prospective open-label multicenter pilot study by Brouwers and colleagues[25] are summarized as the last entry in the Table. Using the same methodology to calculate relative reductions in CBPM and ABPM levels, the percentage values for SBP reduction at 3 and 6 months postintervention were 45% and 53%, respectively, figures not dissimilar to those for both SBP and DPB in the first 3 studies reported in our Table and those reported by Doumas and colleagues.[26] However, the respective percentage values for DBP were 85% and 96%. Looking at the difference between baseline DBP values obtained from CBPM and ABPM in the studies listed in the Table may be instructive here. That difference was 5.3 mm Hg, a relatively small difference compared with the equivalent values for the 2 studies immediately above it, ie, 16 mm Hg for the Kiuchi and colleagues study and 13 mm Hg for the Worthley and colleagues study. Those mean differences were associated with considerably lower percentage values of 35% and 60%.

Interpretation of the Data

While we are the first to acknowledge that making generalizations from 4 studies with very small sample sizes might give readers pause for thought, we would like to make the following interpretation: the more discrepant the baseline CBPM and ABPM levels (ie, the greater the degree to which the CBPM level is higher than the ABPM level), the more dramatic the post-treatment reductions in BP as measured by CBPM tend to appear.

This is not really an ingenious insight since various other observations would support it, including the phenomenon of regression to the mean, whereby any extreme measurement tends to become closer to the mean value when remeasured. Indeed, just as we were finishing our work on this commentary, we became aware of an excellent paper from the European Network for Coordinating Research on Renal Denervation,[41] a paper we highly recommend to readers for many reasons, including formal examination of regression to the mean. It presents "the first subject-level meta-analysis of the 6-month responses of both office and ambulatory blood pressure to RDN in carefully selected patients in whom secondary hypertension was excluded and who had resistant hypertension confirmed by ambulatory monitoring." For SBP, the mean CBPM and 24-hour ABPM reductions at 6 months were 17.6 mm Hg and 7.1 mm Hg, respectively. For DBP, the respective values were 5.9 mm Hg and 3.5 mm Hg. Again using the methodology of Doumas and colleagues, these values generate comparative reduction percentages of 40% and 59%, respectively. Considered along with the magnitude of the respective percentages, these add considerable weight to our arguments. Their results further compel us to advocate for rigorous experimental methodology in all future prospective trials of interventional procedures for resistant hypertension: ABPM should be used when recruiting participants for the studies and for evaluating the interventions' therapeutic benefits.

ADDITIONAL THOUGHTS ON SCREENING POTENTIAL TRIAL PARTICIPANTS

As a brief extension of the previous comment, consider the following two points. First, Verloop and colleagues[42] recently provided "the first report reviewing the results of a clinical screening programme of patients" referred for RDN. This is a comprehensive and systematic screening program conducted in a multidisciplinary setting, emphasizing the care needed when considering the clinical use of this intervention. Along with the use of ABPM, the program contains items including examination and consideration of white-coat hypertension, estimated glomerular filtration rate, known secondary hypertension (eg, hypercortisolism, hyperparathyroidism, hyperaldosteronism, thyroid dysfunctions, and pheochromocytoma), history of renal artery stenting, severe comorbidities, noninvasive imaging of the renal arteries, and hypokalemia. Only when the multidisciplinary team has examined all evidence in a step-wise fashion do patients become eligible for RDN. As pragmatists, we realize that the implementation of such a protocol would require considerable additional effort in determining participants. As clinical scientists and trialists, we would note that the greater degree to which researchers do everything to ensure the

veracity of their results, the more compelling those results become.

Second, as we have noted previously,[43] "While it is essential that appropriate hardware is employed in clinical trials employing ABPM, it is equally (and arguably more) important that appropriately informative software is employed. ABPM monitoring fulfills its full promise when sophisticated software is employed to collate, interpret, analyze, and electronically transmit data for central hosting and analysis." This allows maximum use of ABPM data for both screening potential trial participants and evaluating the intervention's therapeutic benefit at the end of the trial.

ISSUES OF ADHERENCE

We mentioned adherence in the first paragraph of this paper when defining drug-resistant hypertension, and it deserves more discussion here. As Howrans[44] observed, the term adherence is used "to describe the extent to which an individual's behavior coincides with health-related instructions or recommendations given by a health care provider in the context of a specific disease or disorder." As is the case for other chronic diseases, adherence to antihypertensive regimens leaves much to be desired,[45–49] which forces us to ask: Are patients who enter interventional trials truly drug-resistant? Fadl Elmula and colleagues[50] recently reported a study in which they endeavored to investigate the BP-lowering effect of RDN by excluding patients with poor drug adherence. BP declines were less dramatic than in other reports. These authors also raised the question of whether BP declines following RDN are due to "denervation itself or concomitantly improved drug adherence" following the intervention, an observation that leads one to wonder whether considerably improved adherence in individuals with particularly poor adherence before the intervention could be a major factor in post-treatment BP declines. Fadl Elmula and colleagues[50] noted their belief that RDN is indicated for some patients, but also that "much more research is needed to assess the precise responder rate and, at least importantly, identify clinically relevant predictors of who will respond."

Jung and colleagues[51] recently reported "the first study assessing adherence in patients with apparent resistant hypertension systematically via toxicological urine screening." Liquid chromatography-mass spectrometry analysis was used for antihypertensive drugs or their corresponding metabolites. Low adherence was the most common cause of poor BP control in patients with apparent resistant hypertension. Perhaps not surprisingly, incomplete adherence was far more common than complete nonadherence, but as the authors observed, assessment of adherence in patients on a multidrug regimen is only reliable when all of their drugs are included in the assessment. They concluded that "assessing adherence by toxicological urine screening is a useful tool in detecting low adherence, especially in the setting of multidrug regimen as a cause of apparently resistant hypertension."[51]

DURATION OF MAXIMAL TRIPLE-DRUG THERAPY BEFORE RDN INTERVENTION

Following up from our comment in the first paragraph, an issue that is generally passed over in defining resistant hypertension is the duration of therapy on a maximal triple-drug regimen. Indeed, in many of the interventional studies we have reviewed, this important aspect is not alluded to. It may therefore be reasonably assumed that, in at least some (if not many) instances, interventional procedures may have been initiated within weeks of the patients being started on maximal doses of 3 drugs. As Elliott[52] observed, some authorities recommend a minimum duration of 3 months of such pharmacologic treatment, a figure with which we agree, whereas others insist that the medications "must be appropriately chosen, the patient adherent, and/or the patient referred by a physician to a hypertension center." The definition at the start of the scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research on resistant hypertension[1] does not make reference to the duration of treatment. Likewise, a comprehensive review by Moser and Setaro[53] did not address duration of therapy.

This omission is understandable in the clinical setting where the objective is to maximize the therapeutic effect as rapidly as possible so as to achieve BP control in patients who are at high risk. In a trial of an interventional procedure, however, while it may be desirable to do likewise for all participants, it is essential to stipulate in the trial's protocol and published report a minimum period for which patients must have been on maximal pharmacologic treatment to become a potential trial participant. Failure to do so will result in patients being adjudged to benefit from the interventional procedure as distinct from pharmacologic therapy that has simply not been given adequate time to be effective. Given the absence of data on this issue and allowing for the necessity to err in favor of having sound scientific data, we therefore believe that 3 months of treatment with maximal tolerable doses of 3 drugs is not unreasonable.

MODERATE RESISTANT HYPERTENSION AND MILD TO MODERATE NONRESISTANT HYPERTENSION

Finally, we would like to note a study recently reported by Ott and colleagues[54] that investigated the effect of RDN in individuals with treatment resistant hypertension defined as CBPM ≥140/90 mm Hg (with at least 3 antihypertensive drugs, including a diuretic, in adequate doses) and confirmed by 24-hour ABPM. The study is of interest to us for two reasons. First, it utilized ABPM both in the recruitment of participants for the study and in the evaluation of the intervention's therapeutic benefit, which

we applaud. Second, to our knowledge, it is the first study reported that tested the intervention in individuals with moderate treatment-resistant hypertension, defined as CBPM ≥140/90 mm Hg and <160/100 mm Hg with the diagnosis being confirmed by 24-hour ABPM ≥130/80 mm Hg. For 36 participants, ABPM values were lower by 14/7 mm Hg 6 months post-intervention. The authors concluded that RDN may reduce both CBPM and ABPM substantially in patients with moderate treatment-resistant hypertension.

If this study is indicative of a move toward recommending that RDN (and potentially other interventional procedures) may be a suitable widespread clinical practice for patients with moderate resistant hypertension, as well as those with severe treatment-resistant hypertension, the importance of rigorous evaluation of the intervention in future studies becomes even more important. While the risks of the procedure seem to be relatively low from the short-term data available, long-term data are certainly needed for a more comprehensive risk evaluation. In addition, the intervention's benefit-risk-cost balance at the public health level may be quite different for patients with moderate and those with severe resistant hypertension. There are also many more patients with moderate than severe resistant hypertension: the latter accounts for only 15% to 20% of all hypertensive patients. Hence, implementation in widespread clinical practice would be commensurately more challenging.

Moreover, Bohm and colleagues[55] recently wrote as follows: "Controlled studies in patients with mild-to-moderate, nonresistant hypertension and comorbid conditions such as heart failure, diabetes mellitus, sleep apnea, and arrhythmias are needed to investigate the capability of renal sympathetic denervation to improve cardiovascular outcomes." This could be interpreted as a prophetic aspiration or intention for increasingly wide use of RDN in multiple patient populations. In our opinion, one cannot countenance a move towards using these techniques in 'mild-to-moderate, nonresistant hypertension' until they have been shown unequivocally to be effective in resistant hypertension. Should that time come, our comments in the previous paragraph about varying benefit-risk profiles are also pertinent here, as would be the economics of such widespread utilization of the intervention. And going a step or two more, imagine the ramifications should the use of RDN be championed in "regular" hypertension.

CONCLUDING COMMENT

It will be of great interest to many of us, both clinical trialists and practicing physicians, to follow developments in this therapeutic domain. For now, we must wait to see if and when compelling evidence of these interventions' efficacy and long-term safety is forthcoming. With regard to the intervention receiving most attention, RDN, at the present time we must concur with the conclusion of the largest published meta-analysis on RDN by Pescu and colleagues,[41] who commented as follows: "From a clinical point of view, only a small minority of treatment resistant patients qualifies for RDN. RDN is an invasive procedure that is not devoid of risk and comes at a high cost. The widespread deployment of RDN in routine clinical practice, in particular on referral to interventionists without involvement of a multidisciplinary team including a hypertension specialist, does not meet the ethical precept in medicine: "*primum non nocere*." RDN should remain the last resort in patients in whom all other means to control blood pressure failed."

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