Exploring Issues in Difficult-to-Treat Hypertension

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The past few years have seen a major increase in clinician interest in difficult-to-treat hypertension, sometimes referred to as treatment-resistant hypertension. This interest has been stimulated largely by new opportunities to treat refractory or severe hypertension with more effective strategies. For instance, new drug combinations, including up to three powerful and well-tolerated agents all within a single tablet, have provided a simple solution for many patients who require multiple drugs to control their hypertension.

Perhaps the biggest stimulus to discussions of treatment-resistant hypertension, however, has been the recent development of the technique of renal denervation. This method of treating hypertension depends on ablation of the renal nerves produced by applying energy—most usually by radiofrequency—through catheters placed in the renal arteries. But even as this new technology has become available, experts in hypertension are starting to question whether, in fact, we could do an equally effective job in managing difficult hypertension with improved regimens based on pharmacologic agents already available.

This question goes beyond simply being a matter of therapeutics, because the diagnosis of treatment-resistant hypertension is also now being scrutinized. The standard definition of this condition is that it describes patients whose blood pressures (BPs) remain uncontrolled despite receiving at least three effective and well-dosed drugs, typically including a diuretic. However, all these aspects in a given patient are open to challenge. Is the pressure truly uncontrolled, or is the patient's high BP simply a reflection of a white-coat effect? And, just as importantly, how can we be certain that the patient is actually taking the three or more drugs that have been prescribed? It may even be appropriate to ask whether a patient with treatment-resistant hypertension might unknowingly be taking other types of treatment, such as nonsteroidal anti-inflammatory agents, that could be interfering with the BP medications and preventing an adequate reduction in BP. And if all these questions have been adequately addressed, the possibility of an unsuspected form of secondary hypertension must be considered.

Several articles providing information and opinions on this interesting and difficult area have recently been published in this and other journals and provide us an opportunity to review interesting information that can bring further clarity to this evolving area.

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BACKGROUND TO TREATMENT-RESISTANT HYPERTENSION AND ITS CAUSES

The epidemiology of resistant hypertension has been efficiently described by Pantelis Sarafidis.[1] Using the definition of resistant hypertension provided by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[2]—failure to control BP despite at least three well-dosed drugs—Sarafidis has speculated on the prevalence of this condition. He makes the interesting observation that there is likely to be far less resistant hypertension in primary care practices than in specialty centers that typically deal with patients who have difficult hypertension problems. So whereas about 5% of patients seen in primary care settings have treatment-resistant hypertension, as many as 50% of patients seen in nephrology clinics may have this issue.[3]

Sarafidis also pointed out that patients with treatment-resistant hypertension have a poor cardiovascular prognosis.[4] There are two obvious explanations for this. The first is the cardiovascular risk associated with high BP itself, such that a failure to control it leads to an excess of strokes, coronary events, and other major outcomes. The second explanation is related to the fact that high BP, particularly when it is unresponsive to therapy, serves as a biomarker of advanced arterial disease and is a powerful risk predictor. So, even if their BPs can ultimately be controlled, these patients may still have a compromised prognosis.[5]

Among the influences on contemporary treatment of hypertension has been JNC 7[2] and some of the recent major clinical outcomes trials in hypertension, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[6] A group of investigators affiliated with ALLHAT and with the JNC explored whether the publication of these articles in 2002 and 2003 have influenced hypertension control rates.[7] They argue that there has been an increased awareness of hypertension, and based on a study of a database provided by a large health plan, they have shown that control rates in hypertension improved from 38% to 50% of treated patients when comparing data from 2001–2002 with 2003–2004. In an interesting discovery, this article pointed out that the main reason for improved control rates is that an increased awareness of the importance of hypertension has prompted clinicians to initiate hypertension therapy at lower levels of BP than previously had been the case. This is an

interesting perspective that does not cast light on treatment-resistant hypertension but at least indicates a growing belief among clinicians that hypertension at all levels requires a more urgent and thorough approach.

PRACTICAL REASONS FOR RESISTANT HYPERTENSION

Because of the possibility that apparent treatment-resistant hypertension might reflect a white-coat effect, investigators have studied whether ambulatory BP monitoring (ABPM) might be a useful tool for evaluating these patients. Shafi and colleagues investigated patients with chronic kidney disease, an obvious source of treatment-resistant hypertension, with ABPM.[8] Somewhat surprisingly, they found that even in patients with advanced kidney disease there was a 36% incidence of white-coat hypertension. In support of this finding, a meta-analysis by other researchers of studies in patients with chronic kidney disease showed that 18% had white-coat hypertension,[9] again a meaningful proportion of patients considered strong candidates to have refractory hypertension. Likewise, studies in patients from primary care practices have also shown a high prevalence of white-coat hypertension; perhaps best known is the large experience reported from Spain in which ABPM demonstrated that more than 30% of patients with treatment-resistant hypertension did not to have this condition.[10]

Many experts believe that a failure to follow standard treatment protocols for BP control can explain unsatisfactory results in hypertension. Clearly, many patients treated for hypertension do not have their BPs adequately controlled.[11] This can be at least partly explained by what has been termed "clinical inertia" in which intensification of hypertension therapy, which should be undertaken in patients with uncontrolled hypertension, is not, in fact, prescribed. It has been shown that the failure to appropriately upgrade hypertension therapy occurs in as many as two thirds of cases of uncontrolled hypertension.[12] Huebschmann and colleagues[13] conducted a study in primary care patients who were randomized to usual care or to an intervention that provided awareness and instruction to patients and physicians regarding the need for taking action when BPs were not controlled. The good news from this study was that clinical inertia was reduced from 29% of cases down to 11%. Unfortunately, despite this positive result, average BPs between the intervention and usual care groups were not significantly different. These authors suggested that it may be important to provide more detailed guidance to clinicians on optimal drug choices and strategies when adjusting therapy.

In considering clinical inertia, it is relevant to ask what characterizes those physicians least likely to effectively control BP. According to a report by Nelson and associates,[14] the chief problem among primary care physicians is a reluctance to get engaged in appropriate polypharmacy. In fact, these investigators found that in patients with uncontrolled hypertension only 25% of them received three or more drugs. It can also be noted that this reluctance to upgrade therapy is not unique to hypertension and has been reported in patients with other cardiovascular conditions as well.[15]

Not all the blame can be targeted at physicians. Irvin and associates[16] reported that only 66% of patients taking three or more drugs for hypertension were adherent to their treatment regimens. Several factors could explain the problem, although the investigators point out that it was somewhat more common in women, in patients with depressive symptoms, and in patients with evidence of coronary heart disease. Similar findings have been reported by others.[17] In a further perspective on this problem, Trogdon and coworkers[18] evaluated a hypertension education program conducted by the Utah Department of Health. This trial used voice response technology to provide direct support for patients and, just as important, provided BP monitors to the patients so they could be aware of their own progress. Remarkably, in a large cohort of patients being monitored by the Department of Health, the investigators observed a decrease in event rates for myocardial infarction, stroke, heart failure, and renal failure and there was an increase in patient life years. This innovative program, according to the investigators, was shown to be cost-effective and could serve as a model for other major health organizations to follow.

Joel Handler has written a very thoughtful essay on psychological and psychiatric factors that can influence patient noncompliance with hypertension (and other) treatments.[19] He makes the point that patients generally are aware of the risks associated with not controlling their BPs, yet there remains a high rate of poor adherence to treatment. This can reach true pathologic extremes; for example, Handler reported a particular patient who went to the extreme of hiding swallowed pills in his cheek after being admitted to the hospital and having professional observers confirm that he was actually taking medications. This somewhat extreme case emphasizes that there are powerful mechanisms at work in hypertensive patients that can sabotage even the best of treatment plans, and it is a reflection on our contemporary state of medical knowledge that we are not better equipped to understand the counterproductive emotional factors that put patients at such serious risk.

The causes of true treatment resistance include factors such as obesity, comorbid cardiovascular conditions, sleep disturbances, aldosterone excess, and poor economic circumstances. The National Health and Nutrition Examination Survey (NHANES) conducted during 2005–2008 evaluated some of these factors in patients with uncontrolled hypertension.[20] In a review of the NHANES data, Bansil and colleagues[21] came to the conclusion that sleep disturbances were a major factor in treatment-resistant hypertension. It is not entirely clear what aspects of sleep disturbances are the predominant factors, although short sleep and poor sleep

quality are related to poor BP outcomes. In a further evaluation of the NHANES database, Walia and associates[22] examined other factors that could be relevant. They also found that patients with sleep apnea were prone to resistant hypertension, but that poorly controlled diabetes had an even stronger association with poor hypertension results. In fact, these investigators questioned some of the relationships between sleep disorders and hypertension; for instance, such complaints as snoring and snorting during sleep, although popularly thought to be associated with sleep-related hypertension treatment resistance, were found not to be significantly predictive. Clearly, further prospective work is required to better characterize the relationships between sleep abnormalities and hypertension.

Because it has been shown that spironolactone or other aldosterone antagonists can be effective in reducing BP in patients with resistant hypertension, primary aldosteronism might be an important and relatively common cause of this condition. Using a computerized database, Garcia and coworkers searched for patients with treatment-resistant hypertension who had low or normal potassium levels and who were not taking aldosterone antagonists. Their screening test defined hyperaldosteronism as an aldosterone/renin ratio (ARR) of 30 or greater. In patients who had an ARR measured, more than 20% had values greater than 30, suggesting that aldosterone excess may be a relatively common finding in patients with resistant hypertension and should be considered on a routine basis.[23]

Indeed, guidelines on the management of refractory hypertension have recommended that aldosterone antagonists such as spironolactone should be regularly considered in such patients.[24] Even so, this strategy does not always work. Acelajado and colleagues[25] reported that despite all appropriate strategies in dealing with treatment-resistant hypertension, a substantial number of patients still have unacceptably high BPs. Interestingly, they found that spironolactone was far more effective in reducing BPs in patients whose BPs were ultimately brought under control than in those who remained refractory, even though the responders and nonresponders to spironolactone had similar renin and aldosterone measurements. Clearly, aldosteronism is not always the explanation in treatment resistance, and it is also possible that spironolactone, even when effective in reducing BP, may simply be acting as an additional natriuretic agent rather than as a specific treatment for aldosterone excess.

ISSUES IN MANAGEMENT

In his review of resistant hypertension, Samuel Mann provided a mechanism-based algorithm for selecting drugs in patients with this condition.[26] The review points at three basic mechanisms underlying refractory hypertension: volume, renin angiotensin system, and sympathetic nervous system. Dr Mann has assumed that a blocker of the renin angiotensin system and a thiazide will be the usual first two drugs used in difficult-to-treat patients, so then the choice for further therapy becomes either to augment the diuretic (best done by adding spironolactone) or by introducing a sympathetic blocker (a β-blocker, or α-blocker or combined β-/α-blocker). Finally, if needed, a calcium channel blocker can be added and, beyond that, agents such as hydralazine or central α-agonists. For those of us who believe that calcium channel blockers should be part of initial therapy,[27] Dr Mann acknowledges that agents from this class can be used as alternatives to diuretics as core therapy. In a follow-up to his article, Dr Mann reported a retrospective chart review in which it was possible to examine the effectiveness of his proposed strategy.[28] His method worked well in 24 of 27 patients. Depending on clinical circumstances, patients who received add-ons of spironolactone, or an α-/β-blocker, or both, accounted for virtually all of the successful outcomes.

MORE ON COMBINATION THERAPIES

It is well accepted that combinations of two drugs with complementary mechanisms of action can be far more powerful than even full-dose monotherapies in reducing BP. One of the favored approaches comprises an angiotensin receptor blocker (ARB) combined with the calcium channel blocker amlodipine. A trial utilizing telmisartan combined with amlodipine in patients with very severe hypertension (systolic BPs >180 mm Hg) demonstrated remarkable reductions averaging >45 mm Hg).[29] Beyond the powerful efficacy, one of the attractions for using amlodipine rather than a thiazide in combination with a renin angiotensin system blocker is the evidence that the amlodipine-based combination is significantly more effective in preventing major cardiovascular endpoints.[27]

On the other hand, there are good arguments that can be made in favor of thiazide or thiazide-like agents. Most notably, the effects of chlorthalidone in the Systolic Hypertension in the Elderly Program (SHEP) in reducing stroke and coronary events has established this agent as an important consideration in antihypertensive therapy.[30] A recently available combination of the ARB azilsartan medoximil with chlorthalidone has been shown to be highly effective in reducing BP. In fact, Sica and colleagues[31] reported that in patients with stage 2 hypertension this combination reduced systolic BPs by 40 mm Hg in clinic measurements and by about 30 mm Hg when measured by ABPM. This powerful result confirms that chlorthalidone, beyond its clinical outcomes benefits, is a powerful antihypertensive agent.[32]

Given these findings, it has been inevitable that investigators would turn their attention to the obvious triple therapy of a blocker of the renin angiotensin system, amlodipine, and a thiazide diuretic. Eguchi and his colleagues used such a triple combination in patients with uncontrolled hypertension and diabetes, with a target of <125/75 mm Hg.[33] These authors explained that their consideration of this target was prompted to some extent by awareness of other trials that have tested

relatively aggressive BP goals.[34] They observed a highly significant reduction in BP, both in the clinic and by ABPM. Of particular interest, they also reported that flow-mediated vasodilation (an index of endothelial function) was increased and that central measures of the aortic augmentation index and pulse wave velocity were significantly reduced. Similarly, there was a reduction in the urinary albumin/creatinine ratio.[33] These findings represent strong mechanistic encouragement for this therapeutic approach.

Several papers have further documented the usefulness of combinations of an ARB amlodipine and a thiazide. For instance, a triple combination based on olmesartan was shown to be significantly more effective than any of the two drug combinations that could be created from the three agents involved.[35] This superiority was not just a short-term finding but was shown to be fully maintained, with reductions in systolic BP exceeding 40 mm Hg, during a 40-week extension period.[36] Indeed, the strength of this type of combination was further emphasized by the fact that in a trial using only intermediate doses of three agents, the triple combination remained significantly more effective in reducing BP than a fully dosed two-drug combination.[37]Not surprisingly, in a similar three-drug combination, but where the renin inhibitor aliskiren was used rather than an ARB, powerful antihypertensive effects were also reported.[38]

There has been interest in using combination therapies as single-pill formulations. Sherrill and coworkers[39] reported a meta-analysis of single-pill combinations with their individual components. Using 12 databases, they demonstrated that single-pill combinations—compared with prescribing the individual components separately—significantly reduced the annual costs of hypertension therapy (by about $1000 per patient) and also produced better adherence by patients to their therapy and increased long-term persistence with treatment.[24] It is well-known that noncompliance with hypertension treatment is costly because of the adverse consequences caused by uncontrolled hypertension,[40] further adding to the impact of these findings.

REPORTS ON RENAL DENERVATION

In a focused discussion of renal denervation, Drs Cohen and Townsend reviewed the historical approaches to severe hypertension, including the radical but effective strategy of surgical sympathectomy.[41] Because of its severe side effects, that kind of intervention has long since been abandoned, but, unfortunately, most of the drugs that effectively block the sympathetic nervous system have also not been free of symptomatic side effects. These authors concisely describe the emerging technique of employing a catheter to apply radiofrequency energy through the lumen of the renal arteries to destroy the renal sympathetic nerves. There is no question that the strategy of bilateral renal denervation produces substantial BP reductions in patients with severe treatment-resistant hypertension.[42] However, as Drs Cohen and Townsend point out, we are still awaiting further data on the long-term safety of this therapeutic approach.

It is inevitable that using a technique to interrupt the renal nerves will raise questions about renal function. Very little is known about the role of the sympathetic nerves in patients with end-stage renal disease. However, in a very interesting article, Ott and associates[43] reported the case of a woman on chronic hemodialysis who had treatment-resistant hypertension and was treated with renal denervation even though her renal arteries were of a lesser diameter than would normally be considered appropriate for radiofrequency ablation. Six months after the procedure, this patient had a dramatic reduction in her systolic BP from >170 mm Hg to <140 mm Hg. In the past, the approach of bilateral nephrectomy has also been used in patients with end-stage kidney disease who have refractory hypertension and has been shown to not only reduce BP but also reduce sympathetic activity, thus supporting these new findings with renal denervation.[44]

In another report, Himmel and researchers reported the case of an elderly woman who underwent renal denervation, but during the procedure, after successful radiofrequency ablation of her left renal nerves, she was found to have renal artery anatomy on the right side that was not consistent with safely completing the procedure on that side.[45] Even so, this patient experienced a substantial reduction in BP. If replicated, this finding could be important since there are likely reasonable numbers of patients for whom renal denervation may be considered but where the renal artery anatomy on one side may not be suitable for this technique. In another brief report, Ho and coworkers[46] described a morbidly obese man in need of bariatric surgery whose procedure could not be conducted because of an unacceptably high BP despite rigorous attempts at drug therapy. Therefore, it was decided to undertake renal denervation before proceeding to bariatric surgery. These authors reported a substantial fall in BP that allowed the surgeons to safely proceed with the operation.

Although it is useful to report that renal denervation produces significant reductions in BP, it is still important to demonstrate that these reductions in BP are associated with improvements in cardiovascular outcomes. Truly major endpoints such as fatal and nonfatal cardiovascular events will probably need to await analysis of registries that are being created for the long-term follow-up of patients undergoing this procedure. In the meanwhile, however, measures such as central BPs and other vascular properties can be considered, particularly as these intermediate outcomes appear to be predictive of major events.[47] Mortensen and coworkers[48] performed such measurements in patients who had undergone renal denervation. After 6 months, they reported that central BP was significantly reduced and that the aortic augmentation index and pulse wave velocity, both measures of arterial stiffness,

were significantly improved. They also noted a general tendency for greater improvements in these measurements in patients whose BPs were most effectively reduced by the renal denervation. This appears to be a promising start to the evaluation of potential benefits of renal denervation.

FINAL COMMENT

It is interesting that this array of articles published during the past 2 years have looked at a variety of issues relating to the management of severe hypertension and, in particular, the difficult clinical problem of treatment resistance. It is clear that we have much to learn about this issue. Many patients with apparent treatment resistance can actually be shown to have simple explanations, ranging from poor compliance to treatment, white-coat hypertension, or inadequate use of effective antihypertensive agents. It is encouraging, however, that the development of better pharmacologic strategies has allowed much improvement in how these high-risk patients can be effectively managed. The new technique of renal denervation promises to be a useful additional modality for patients whose treatment-resistant hypertension cannot be effectively resolved by more traditional approaches. We anticipate that a great deal more information on this important area of hypertension will become available during the next year or two.

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