Refractory Hypertension
An Important Clinical Phenotype

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Calhoun et al1 in this edition of the journal report on an important clinical phenotype: refractory hypertension. They provide important information on the prevalence, risk factors, and comorbidities for refractory hypertension in a large observational study, including adults from across the United States.2 They note that 0.5% of the patients receiving antihypertensive treatment and 3.6% of the individuals with resistant hypertension had refractory hypertension. These observations are of great importance and provide key evidence that true antihypertensive treatment failure is uncommon. Moreover, the observations also help us appreciate the paradox that with an increasing number of medications needed to treat hypertension, there is an association with greater proclivity for refractory hypertension.

In their study, they note that patients of African descent, and those with albuminuria and diabetes mellitus, were more likely to have refractory hypertension, even after multivariable adjustment. Moreover, individuals with refractory hypertension had a much higher 10-year Framingham coronary heart disease and stroke risk score than those without. This observation underscores the importance of hypertension as a major risk factor for promoting cardiovascular disease.

So what is the cause of refractory hypertension? Is it simply noncompliance, or are there biological factors? Are African descent and chronic kidney disease important underlying factors? Is this related to insufficient use or dose of diuretics or abnormal hormonal pathways? The investigators monitored the blood pressure in the patient’s home and assessed medication adherence using the 4-item Morisky Medication Adherence Scale that is a validated measure of medication adherence. On the basis of their data, we conclude that noncompliance was not a factor. Other studies have suggested that patients with resistant hypertension exhibit high medication compliance. In a large study using data from Kaiser Permanente Southern California Health System, 93% of patients with resistant hypertensive had ≥80% of days covered with medication use based on prescription refill rates.3 The fact that blood pressure was measured in the patient’s home is of some interest. This might eliminate some of the white-coat effect and could provide a more valid measure of blood pressure load. More studies now indicate that home readings or ambulatory blood pressure readings are of value in predicting kidney disease progression, especially in patients with kidney disease.4 However, no 24-hour ambulatory measures were taken to distinguish between white-coat and masked hypertension.

What about biological factors? In a prior study, Acelajado et al5 noted that individuals with refractory hypertension had higher heart rates when compared with those with controlled resistant hypertension. In the current study, there was a lack of difference in heart rates between refractory and resistant hypertensives, which may be related to the greater use of β-blockers in participants with refractory hypertension. It is possible that more β-blocker use masked a potential difference between the 2 groups. If higher heart rate is a common phenotype, this would argue that excessive sympathetic output may be an important target for treatment in refractory hypertensives. Given the recent advances in device therapy for renal sympathetic nerve ablation, this population group could potentially be ideal for this type of procedure although it remains to be seen how well the heart rate predicts the blood pressure response to renal denervation.6

Another important observation in the current study reported by Calhoun et al1 is the low use of mineralocorticoid receptor antagonist (MRAs): only 18% of participants with refractory hypertension were receiving these drugs. Their observations are in concert with results of other large population-based studies that indicate significant underuse of MRAs in the treatment of resistant hypertension.7 What is of significant interest is how low the refractory hypertension rates are given the low use of MRAs. Moreover, in the current study, there was no opportunity to gauge the dosage of medications being used. This may be particularly important with MRAs where higher doses may be required in individuals with excess aldosterone production. Given the lack of information on dosage of medications, and the low usage of MRAs, it is likely that the current analysis of the reasons for geographic and racial differences in stroke (REGARDS) data set overestimates the cases of resistant and refractory hypertension.

This report serves as an important reminder that our currently available antihypertensive medications are effective in the majority of patients if used in the correct doses with adequate diuretic support and careful assessment of blood pressure, side effects, and compliance. However, this report...
also highlights the fact that there are clearly patients in our
practice that may need 4, 5, or possibly even 6 antihyperten-
sive medications for adequate control of their blood pressure.
It is in these individuals that a careful assessment for revers-
ible causes of resistant or refractory hypertension is essential.
Avoidance of medications, such as nonsteroidal anti-inflam-
matory drugs, correction of obstructive sleep apnea, appropri-
ate use, and dosage of MRAs are necessary considerations to
reduce the likelihood of refractory hypertension.

These observations from a large contemporary cohort make
an important contribution in the management of hypertension,
particularly as device-based interventions undergo clinical
research testing in the United States. In particular, they dem-
strate the need for careful out-of-office assessment of blood
pressure, which has not been a prominent feature in completed
renal denervation trials, but is a part of the ongoing, fully
enrolled SYMPLICITY Hypertension 3 trial. In addition, more
critical work is needed to assess why patients of African heri-
tage are at greater risk for refractory hypertension. Also impor-
tant are the issues surrounding those with diabetes mellitus or
albuminuria and those with greater sympathetic tone. A better
understanding of the biology leading to refractory hypertension
may lead to more effective forms of clinical management.

Disclosures

None.

References

1. Calhoun DA, Booth JN 3rd, Oparil S, Irvin MR, Shimbo D, Lackland DT,
Howard G, Stafford MM, Muntner P. Refractory hypertension: determina-
tion of prevalence, risk factors, and comorbidities in a large, population-
differences in stroke study: objectives and design. Neuroepidemiology.
3. Sim JJ, Bhandari SK, Shi J, Liu IL, Calhoun DA, McGlynn EA, Kalantar-
Zadeh K, Jacobsen SJ. Characteristics of resistant hypertension in a large,
ethnically diverse hypertension population of an integrated health system.
4. Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood
2006;69:1175–1180.
B, Foley SS, Oparil S, Calhoun DA. Refractory hypertension: definition,
prevalence, and patient characteristics. J Clin Hypertens (Greenwich).
2012;14:7–12.
6. Esler MD, Krum H, Sobotka PA, Schaich MP, Schmieder RE, Bohm M.
Renal sympathetic denervation in patients with treatment-resistant hyper-
tension (The Symplicity HTN-2 Trial): a randomised controlled trial.
7. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled
and apparent treatment resistant hypertension in the United States, 1988 to
8. Kandzari DE, Bhatt DL, Sobotka PA, O’Neill WW, Esler M, Flack JM,
Katzen BT, Leon MB, Massaro JM, Negoita M, Oparil S, Rocha-Singh K,
Straley C, Townsend RR, Bakris G. Catheter-based renal denervation for
resistant hypertension: rationale and design of the SYMPLICITY HTN-3
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