Refractory Hypertension
A Novel Phenotype of Antihypertensive Treatment Failure

Tanja Dudenbostel, Mohammed Siddiqui, Suzanne Oparil, David A. Calhoun

The term resistant hypertension has been used since the early 1960s to identify patients with difficult-to-treat hypertension, meaning mostly, resistance to pharmacological therapy. In the 5 decades since the term was seemingly first applied, resistant hypertension has been consistently defined as failure to control high blood pressure despite of use of ≥3 antihypertensive agents of different classes, including a diuretic. The 2008 American Heart Association Scientific Statement on resistant hypertension included in its definition patients whose blood pressure had been uncontrolled with 3 medications, but controlled with ≥4 medications. Although the number of medications required to satisfy the definition is arbitrary, the purpose of creating a category of resistant hypertension is to identify patients who, because of the difficulty in controlling their blood pressure, may benefit from special diagnostic and therapeutic considerations, including referral to a hypertension specialist. Having an agreed on definition that can be reliably applied to different cohorts has also facilitated research for this subgroup of patients, including identification of risk factors and underlying mechanisms, assessing outcomes and developing targeted treatments.

The term refractory hypertension has often been used interchangeably with resistant hypertension to also refer to patients with difficult-to-treat hypertension. However, based on the number of respective PubMed citations resistant hypertension has been used much more often than refractory hypertension to indicate patients with hypertension resistant to pharmacological treatment.

Recently, the term refractory hypertension has been applied to a small group of patients who are truly refractory to treatment, that is, patients who fail to achieve target blood pressure on maximal antihypertensive therapy. Determining whether such patients simply represent extreme cases of resistant hypertension or a novel phenotype in terms of risk and cause has been the focus of initial attempts to define and characterize the phenotype and potentially identify mechanisms of antihypertensive treatment failure. In this brief review, we discuss the emerging data pertaining to this novel phenotype of antihypertensive treatment failure and how it compares and contrasts with resistant hypertension in terms of definition, prevalence, patient characteristics, risk factors, and possible underlying causes. We hope that an early discussion of the 2 phenotypes will serve to distinguish refractory from resistant hypertension and engender further research testing the clinical significance of that distinction.
Campinas, Brazil, Modolo et al\textsuperscript{6} compared 36 patients with refractory hypertension with 80 patients with resistant hypertension. Refractory hypertension was defined as uncontrolled hypertension in spite of the use of at least 5 different classes of antihypertensive agents. Diuretic usage was not specified, but all of the refractory patients were receiving a diuretic and slightly >70% were receiving spironolactone.

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is a large population-based cohort study of >30,000 participants, of whom, 14,854 are being treated for hypertension.\textsuperscript{9} In a cross-sectional analysis of this cohort, Calhoun et al\textsuperscript{10} identified 78 participants as having refractory hypertension based on having uncontrolled hypertension in spite of being prescribed ≥5 antihypertensive agents. All participants identified as having refractory hypertension were receiving a diuretic, but <20% were prescribed a mineralocorticoid receptor antagonist such as spironolactone.

Among the 4 published studies of refractory hypertension, the phenotype was defined variably as either failing treatment after at least 3 months of care by a hypertension specialist; failing to control blood pressure with use of ≥5 different classes of antihypertensive agents; or, most rigorously, failing treatment comprised ≥2 different classes of antihypertensive agents, including chlorthalidone and spironolactone. The latter more rigorous definition is what we think the most appropriate. Given the well-established superiority of the thiazide-type diuretic chlorthalidone over hydrochlorothiazide to reduce blood pressure and the preferential benefit of chlorthalidone over hydrochlorothiazide in failing treatment based on having uncontrolled hypertension, any treatment regimen should not be considered truly maximal unless it incorporates intensive diuretic therapy based on the combined use of both of these agents.\textsuperscript{1,11–14} A schematic of different hypertensive categories, including refractory hypertension, based on blood control and the number of prescribed antihypertensive medications is shown in Figure 1.

Prevalence

Resistant Hypertension

The prevalence of resistant hypertension has been consistently reported as 10% to 20% of all persons with hypertension.\textsuperscript{4,15–17} These estimates have generally been based on the number of medications prescribed according to the American Heart Association definition (uncontrolled blood pressure on ≥3 antihypertensive agents or controlled blood pressure on ≥4 agents).\textsuperscript{4} In one of the largest assessments, Sim et al\textsuperscript{17} analyzed data from individuals enrolled in the Kaiser Permanente Southern California healthcare system. The analysis included >470,000 individuals with hypertension, of whom >60,000 met the criteria for resistant hypertension. Overall, 12.8% of all hypertensive individuals and 15.3% of those taking antihypertensive medications had resistant hypertension in this analysis. The majority of these individuals had uncontrolled blood pressure while taking ≥3 antihypertensive agents; the remainder had controlled resistant hypertension, ie, blood pressure <140/90 mmHg with the use of ≥4 medications.

European studies have reported similar prevalence rates of resistant hypertension in large cohorts. For example, de la Sierra et al\textsuperscript{15} evaluated the prevalence of resistant hypertension in >60,000 hypertensive individuals participating in the Spanish Ambulatory Blood Pressure Monitoring Registry. More than 10,000 or 14.8% of participants were identified as having resistant hypertension based on an elevated office blood pressure (>140/90 mmHg) despite the use of 3 antihypertensive agents or treatment with ≥4 agents regardless of the level of office blood pressure. Most (12.2%) of the participants with resistant hypertension had uncontrolled blood pressure levels; only a small proportion (2.6%) had controlled resistant hypertension.

The prevalence of resistant hypertension is higher in patients of African origin, who are overweight or obese, who are older, and especially, in those with chronic kidney disease (CKD). In a recent cross-sectional analysis of the 3,367 hypertensive participants in the Chronic Renal Insufficiency Cohort, 40.4% were identified as having resistant hypertension according to the American Heart Association definition (including both controlled and uncontrolled resistant hypertension).\textsuperscript{18} In contrast to the Kaiser Permanente and Spanish Ambulatory Blood Pressure Monitoring Registry cohorts, in which blood pressure was uncontrolled in most participants with resistant hypertension, resistant hypertension in the Chronic Renal Insufficiency Cohort (CRIC) cohort was almost evenly divided between individuals with uncontrolled and controlled resistant hypertension (52.5% versus 47.5%, respectively). As in many other studies, black race, higher body mass index, and older age were all independent predictors of having resistant hypertension.\textsuperscript{18}

Refractory Hypertension

Estimates of prevalence of the phenotype of refractory hypertension are limited to 4 published studies.\textsuperscript{6–8,10} The studies are consistent in indicating that refractory hypertension is uncommon, especially if the more rigorous definition that requires patients to fail intensive antihypertensive diuretic treatment that includes chlorthalidone and spironolactone is applied. In the retrospective analysis by Acelajado et al,\textsuperscript{6} of the 304 consecutive patients with resistant hypertension included in the analysis, only 29 or 9.5% never achieved blood pressure control when being treated in a hypertension specialty clinic. In the follow-up prospective analysis from the same clinic, only
3% of the 559 patients originally referred for uncontrolled resistant hypertension were diagnosed with refractory hypertension. An important distinction between these 2 studies that likely explain the lower prevalence of refractory hypertension in the prospective analysis is that the latter study specifically required the use of chlorthalidone 25 mg and spironolactone 25 mg daily before defining a patient as being refractory to treatment, whereas in the earlier study, retrospective analysis had no such requirement. Many of the patients in the earlier retrospective study received hydrochlorothiazide, rather than chlorthalidone, and only 80% received spironolactone. In contrast, by definition, all of the participants in the prospective study received both agents. As suggested by the authors, underutilization of chlorthalidone and spironolactone likely contributed importantly to lower control rates, and thereby, the higher prevalence of refractory hypertension in the earlier study.

In contrast to the above studies of patients referred to a hypertension specialty clinic specifically for resistant hypertension, the REGARDS cohort includes a large, general hypertensive population. In the cross-sectional analysis of this cohort, the prevalence of refractory hypertension (uncontrolled blood pressure on ≥5 agents) was only 0.5% of all hypertensive participants and 3.6% of participants with resistant hypertension. This is likely an underestimate, as there was a large proportion of patients who were uncontrolled on 2 and 3 medications, such that after appropriate titration, a percentage would have remained uncontrolled on 5 agents and thus identified as having refractory hypertension. This is likely an underestimate, as there was a large proportion of patients who were uncontrolled on 2 and 3 medications, such that after appropriate titration, a percentage would have remained uncontrolled on 5 agents and thus identified as having refractory hypertension. The contrary, chlorthalidone and spironolactone were rarely used in this cohort, and with broader use, control rates would no doubt have been better. Overall, the findings of these studies indicate that in the general hypertensive population and with the intensive care provided by hypertension specialists, including the use of chlorthalidone and spironolactone, true antihypertensive treatment failure is rare (Figure 2).

**Apparent Versus True**

**Resistant Hypertension**

The term apparent as opposed to true resistant hypertension has been used by investigators to refer to patients with resistant hypertension based on the number of prescribed medications, without accounting for common causes of pseudoresistance, ie, inaccurate blood pressure measurements, nonadherence, undertreatment, or white-coat effects. Such causes of pseudoresistance are common such that ≤50% of patients with apparent resistant hypertension may not be truly resistant to treatment.

Estimates of the prevalence of the different causes of pseudoresistance have been largely done considering 1 factor at a time in different cohorts. Analysis of the Spanish Ambulatory Blood Pressure Monitoring Registry estimated that the prevalence of white-coat resistant hypertension, that is, uncontrolled office but controlled ambulatory blood pressure levels, to be 37.5% of participants otherwise fulfilling the criteria for having resistant hypertension. In a cross-sectional evaluation of ≈500 patients with resistant hypertension who had undergone ambulatory blood pressure monitoring, Muxfeldt et al reported similar results, with 37.0% of patients having white-coat resistant hypertension.

Poor adherence to antihypertensive drug treatment is a common cause of pseudoresistance among patients with apparent resistant hypertension. Jung et al evaluated patients referred to a university-based nephrology clinic for resistant hypertension. After exclusion of secondary causes of hypertension and white-coat resistant hypertension, adherence was quantified by testing for prescribed antihypertensive medications or their metabolites by liquid chromatography-mass spectrometry.

![Figure 2. Prevalence of resistant and refractory hypertension. Reprinted from Siddiqui et al with permission of the publisher. Copyright © 2015, Elsevier, Inc.](http://hyper.ahajournals.org/)

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**U.S. adults with Hypertension**

- **Resistant Hypertension**
  - Uncontrolled Resistant Hypertension: 32%
  - Controlled Resistant Hypertension: 65%
  - Refractory Hypertension: 3%

**Controlled Hypertension**

- Total: 65%

**Uncontrolled Hypertension**

- Total: 35%

**Resistant Hypertension**

- Total: 21%
The prevalence of contributors to pseudoresistance, ie, poor medication adherence, white-coat effects, and undertreatment, has not yet been quantified in patients with refractory hypertension. In the comparison of patients with refractory versus resistant hypertension by Modolo et al, a significant white-coat effect was reported as being much more common in the refractory group, but the actual prevalence of white-coat refractory hypertension was not indicated.

Dudenhoeft et al reported that ambulatory blood pressure levels were significantly higher in patients with refractory hypertension than in those with controlled resistant hypertension, but did not quantify the prevalence of white-coat refractory hypertension. None of the studies of refractory hypertension has reported adherence based on measurement of drug or drug metabolite levels in serum or urine. Application of the strictest definition of refractory hypertension, ie, use of 5 or medications including chlorthalidone and spironolactone (or pharmacological equivalents), excludes undertreatment as a cause of antihypertensive treatment failure. Furthermore, the contribution of inaccurate blood pressure measurement to apparent lack of blood pressure control has not been specifically quantified for either resistant or refractory hypertension.

Risk Factors and Comorbidities

Resistant Hypertension

Large, cross-sectional analyses consistently identify older age, increased body mass index, black race, and male sex as strong, independent risk factors for having resistant hypertension, with black race being the patient characteristic most commonly associated with treatment resistance. These studies also show that CKD, diabetes mellitus, heart disease, and left ventricular hypertrophy are common comorbidities associated with resistant hypertension, with CKD being especially common.

Refractory Hypertension

Important similarities and differences in risk factors have been identified in patients with refractory hypertension when compared with the larger population of patients with resistant hypertension. Both refractory and resistant hypertension are more common among patients of African ancestry than among those of European descent. In contrast, patients with refractory hypertension tend to be younger but of similar weight than the larger cohort of patients with resistant hypertension, indicating that increasing age and higher body mass index are not risk factors for having refractory hypertension when compared with resistant hypertension. There is evidence of sex differences between refractory and resistant hypertension cohorts. Although not observed in the retrospective or cross-sectional analyses, the prospective study of refractory hypertension that utilized the most rigorous definition of the phenotype, ie, requiring failure of ≥5 drug regimens including chlorthalidone and spironolactone, refractory hypertension was more common in women, such that black women were the race-sex subgroup most affected.

Although it seems intuitive that patients with refractory hypertension, given their history of severe blood pressure elevation, should have more comorbidities, particularly cardiovascular disease, than patients with resistant hypertension, the published literature has not consistently supported this conclusion. In the cross-sectional analysis of the REGARDS cohort, refractory hypertension was more commonly associated with CKD (ie, albuminuria) and diabetes mellitus than was resistant hypertension, and patients with refractory patients were more likely to have a history of stroke or heart disease than all hypertensive individuals.

In the retrospective analysis of patients referred to the University of Alabama at Birmingham Hypertension Clinic, patients with refractory, when compared with patients controlled resistant hypertension, were more likely to have a history of previous stroke or congestive heart failure (CHF), but not diabetes mellitus or CKD. Similarly, in the prospective assessment done by the same investigators, diabetes mellitus, CKD, and prior stroke were not more common in refractory patients when compared with those with controlled resistant hypertension, but refractory patients were more likely to have been hospitalized for CHF. The retrospective analysis by Modolo et al did not find differences
in comorbidities between patients with refractory versus resistant hypertension except that refractory patients were more likely to have left ventricular hypertrophy based on echocardiography.

The lack of consistency in the reported associations between refractory hypertension and various comorbidities is likely attributable, at least in part, to differences in study design, especially in how refractory hypertension was defined. For example, both the retrospective and prospective studies performed in the University of Alabama at Birmingham Hypertension Clinic and the cross-sectional analysis done at the Resistant Hypertension Clinic at the University of Campinas specifically excluded patients with stage 4 and 5 CKD, thereby precluding identification of any association between refractory hypertension and advanced CKD.24

**Mechanisms: Role of Excess Fluid Retention Versus Heightened Sympathetic Tone**

**Resistant Hypertension**

Although resistant hypertension is multifactorial in cause, a large body of literature implicates excess fluid retention as an important cause. A pathogenic role of fluid retention is suggested by studies demonstrating that successful control of resistant hypertension often requires intensification of diuretic therapy.14,26–31 Such a role is further supported by studies linking indices of increased volume expansion to resistant hypertension and reduction in fluid retention to overcoming treatment resistance. For example, Taler et al2 reported that resistant hypertension was characterized by increased thoracic fluid content as measured by thoracic impedance. Awareness of this increased fluid retention on an individual patient basis allowed treating clinicians to tailor prescribed antihypertensive regimens to achieve better blood pressure control rates, primarily through broader use of diuretic therapy. Gaddam et al33,34 also reported that patients with resistant hypertension have persistent fluid retention in spite of use of a standard thiazide diuretic (hydrochlorothiazide) that could be overcome by intensifying diuretic therapy by combining chlorthalidone with spironolactone. Well-recognized causes of the excess volume that characterizes resistant hypertension include increased salt sensitivity attributable to black race, CKD, older age, and obesity; high rates of hyperaldosteronism; and high dietary sodium intake.35,36

**Refractory Hypertension**

No study assessing the prognosis of patients with refractory hypertension has yet been reported. Although it seems intuitive that patients whose blood pressure cannot be controlled will fare more poorly than those whose blood pressure is controlled, even if it requires the use of multiple medications, evidence of such increased risk is currently unavailable.

**Prognosis**

**Resistant Hypertension**

Longitudinal studies indicate that patients with resistant hypertension, especially if uncontrolled, have a worse prognosis than general hypertensive cohorts, both in terms of cardiovascular events and total mortality.16,24–28 For example, in a secondary analysis of data from >14,000 hypertensive participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the incidence of coronary heart disease, stroke, CHF, peripheral arterial disease, and end-stage renal disease were all increased among those with controlled or uncontrolled resistant hypertension compared with those without resistant hypertension.16

In an analysis of the ongoing REGARDS study, Irvin et al24 found that the incidence of stroke, coronary heart disease, and all-cause mortality was increased in participants with controlled or uncontrolled resistant hypertension compared with those without resistant hypertension during a median follow-up of 5.9, 4.4, and 6.0 years for stroke, coronary heart disease, and total mortality, respectively. After full multivariable adjustment, the increased hazard ratio for coronary heart disease and all-cause mortality remained statistically significant, whereas the association of stroke and resistant hypertension did not. After initial adjustment, individuals with controlled resistant hypertension had an increased risk of all-cause mortality compared with participants without resistant hypertension; however, the risk was attenuated after full multivariable analysis. The hazard ratios for stroke and heart disease were not increased among individuals with controlled resistant hypertension compared with participants without resistant hypertension.24

Prognosis is particularly unfavorable in patients with resistant hypertension and CKD. In a recent analysis of hypertensive individuals with CKD participating the CRIC study, the incidence of stroke, CHF, renal events, and all-cause mortality, as well as the combined outcomes of stroke, myocardial infarction, and peripheral arterial disease, were increased in individuals with resistant hypertension (controlled or uncontrolled) compared with those without resistant hypertension. The higher risk for each event, except for stroke, remained statistically significant after full multivariable adjustment.
antihypertensive treatment failure than that seen in the general population of patients with resistant hypertension.

Stimulated by the observation of higher clinic heart rates in the earlier retrospective analysis of patients with refractory hypertension, the study of Dudenbostel et al. was designed to prospectively explore other indices of sympathetic tone. Patients with refractory hypertension were found to have higher resting heart rates than patients with controlled resistant hypertension both in the clinic and by ambulatory monitoring. The difference was most pronounced at night, with nighttime ambulatory heart rates of 72.7±9.0 versus 65.6±9.0 bpm in patients with refractory versus controlled resistant hypertension, respectively. Further evidence of increased sympathetic tone included increased 24-hour urinary excretion of normetanephrines, increased vascular resistance as indexed by pulse wave analysis and velocity, and reduced heart rate variability. If heightened sympathetic tone is confirmed by prospective assessments of these parameters in larger cohorts or by direct measurement of sympathetic outflow, the finding would suggest an important mechanistic distinction between refractory hypertension and controlled resistant hypertension that is, refractory hypertension may be more neurogenic in cause, whereas resistant hypertension tends to be more volume dependent. Furthermore, this observation may have important therapeutic implications in that control of refractory hypertension may require application of effective sympatholytic strategies either with pharmacological agents or with device-based approaches as opposed to continued intensification of diuretic therapy.

The finding of heightened sympathetic tone in patients with refractory hypertension is potentially critical in identifying an important mechanistic cause of antihypertensive treatment failure. However, the findings to date are not definitive and have not been consistently observed across studies. For example, higher heart rates were not observed in the cross-sectional analyses of participants in the REGARDS study or in the cross-sectional analysis of by Modolo et al. of patients with refractory hypertension in their university-based clinic. Furthermore, increases in sympathetic tone may represent a secondary phenomenon, rather than an underlying cause of refractory hypertension. Possible secondary causes of increased heart rates and sympathetic tone in patients with refractory hypertension include more severe CKD, underlying CHF, over diuresis, obstructive sleep apnea, and greater use of vasodilators, all of which are known to promote increased sympathetic output. Design of future studies to further explore this proposed phenotype should take these competing possibilities into consideration.

### Conclusions

A novel phenotype of antihypertensive treatment failure is proposed based on the inability to control high blood pressure with use of ≥5 different classes of antihypertensive agents, including a long-acting thiazide-type diuretic, such as chlorthalidone, and a mineralocorticoid receptor antagonist, such as spironolactone. Findings from a small number of recent studies suggest the phenotype is rare, with a prevalence of <5% of patients referred to hypertension centers for uncontrolled resistant hypertension. The degree to which pseudocauses of treatment failure, such as poor adherence and white-coat effects, contribute to the apparent prevalence the phenotype is unknown.

Studies characterizing patients with refractory hypertension indicate that, similar to resistant hypertension in general, being of African ancestry and having CKD increases risk of never achieving blood pressure control. However, patients with refractory hypertension tend to be younger and more likely women than their counterparts with controlled resistant hypertension (Table). Not surprisingly, patients with refractory hypertension are at greatly increased cardiovascular risk, especially related to left ventricular hypertrophy and CHF. Underlying mechanisms of refractory hypertension clearly lack full elucidation, but available findings do not support greater degrees of fluid retention and aldosterone excess as contributing causes. Findings of increased heart rate and

### Table. Characteristics of Patients With Refractory and Controlled Resistant Hypertension

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Refractory Hypertension</th>
<th>Controlled Resistant Hypertension</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
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<tr>
<td>Age, y</td>
<td>Younger</td>
<td>Older</td>
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<tr>
<td>Gender</td>
<td>More women</td>
<td>Both</td>
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<tr>
<td>African descent</td>
<td>Higher</td>
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</tr>
<tr>
<td>BMI</td>
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<tr>
<td><strong>Comorbidities</strong></td>
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<tr>
<td>Type 2 diabetes mellitus</td>
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<tr>
<td>Chronic kidney disease</td>
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<tr>
<td>Heart disease</td>
<td>No difference</td>
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<tr>
<td>Stroke</td>
<td>No difference</td>
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<tr>
<td>Heart failure</td>
<td>Higher</td>
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<tr>
<td><strong>Biochemical parameters</strong></td>
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<tr>
<td>eGFR</td>
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<tr>
<td>Plasma aldosterone</td>
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<tr>
<td>Plasma renin activity</td>
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<tr>
<td>24-h urinary aldosterone</td>
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<tr>
<td>24-h urinary sodium</td>
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<tr>
<td>24-h urinary normetanephrines</td>
<td>Higher</td>
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<tr>
<td><strong>Hemodynamic parameters</strong></td>
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<tr>
<td>Clinic heart rate</td>
<td>Higher</td>
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<td>Clinic systolic BP</td>
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<td>Clinic diastolic BP</td>
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<tr>
<td>Aortic stiffness</td>
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<td>Heart rate variability</td>
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<tr>
<td>Central aortic BP</td>
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<tr>
<td>24-h heart rate</td>
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<tr>
<td>24-h mean BP</td>
<td>Higher</td>
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</tbody>
</table>

BMI indicates body mass index; BP, blood pressure; and eGFR, estimated glomerular filtration rate.
catecholamine excretion suggest a possible role of increased sympathetic tone as an important mediator.

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**References**


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