Pathogenesis of Drug-Resistant Hypertension

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Summary: More is known about the epidemiology of drug-resistant hypertension than particular pathogenic factors and pathways. Several recurring themes, however, seem evident on using insight from epidemiology and general knowledge of the pathophysiology of hypertension. Specifically, 4 main pathways converge on drug resistance including sodium handling, sympathetic nervous system activation, endothelial dysfunction, and arterial stiffness. These factors, and the various pathways and elements contributing to them, are reviewed. In addition to describing how these factors exert their individual influences on resistant hypertension, several examples of how interactions between these factors, particularly in the case of chronic kidney disease, are included. At the conclusion of this review some thoughts are offered on additional mechanisms and areas for potential research.

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What pathogenic processes lead to drug resistant hypertension? After accepting this writing assignment, and turning to a common source of information (PubMed), it was sobering to find no articles returned when searching for "pathogenesis" and "drug resistant hypertension" in the title of publications indexed in the Library of Medicine. Therefore, in addressing this topic, I began with the following question: who are these people, and what characteristics do they have that separate them from controlled hypertensive patients? This was followed by a reverse reasoning process that asked: what is known about the relationship of blood pressure mechanisms to those characteristics that appear more commonly in those who did not, as compared with those who did, achieve blood pressure control while on drug therapy for hypertension?

WHAT CHARACTERIZES THE TRULY DRUG-RESISTANT HYPERTENSIVE PATIENT?

There is an article in this issue of *Seminars in Nephrology* by Burnier on Pathobiology of Resistant Hypertension that addresses the definitions and epidemiology of drug-resistant hypertension, therefore the focus from this point forward will assume that the literature supporting the discussion points chosen in identifying pathogenic factors already have been identified. In this section, the focus is on resistant (not refractory) hypertension. This is an increasingly important distinction because the focus in this area of blood pressure care could undergo substantial intensification if device-based interventions for true drug resistance are successful in the pivotal US trial Symplicity Hypertension-3.[1] The commentary from this point forward relates largely to hypertensive human beings with a systolic blood pressure greater than 140 mm Hg on at least 3 drugs at reasonable doses with at least one drug class in use being a diuretic. It is acknowledged that these patients have more target organ damage than those with more easily controlled blood pressure, but that does not help much in understanding the pathogenesis unless the target organ is an important contributor to pathogenesis (similar to the kidney). Consequently, the discussion in this section does not focus on mechanisms of stroke, left ventricular hypertrophy, peripheral arterial disease, and so forth, in drug-resistant hypertension. This discussion does not address the concerns raised by some on the remarkable prevalence of the white-coat effect in this population.[2]

A major finding is that it is principally the systolic pressure that identifies drug resistance. This is important not only in the definition of drug-resistant blood pressure, but to date it has been the only office-based independent determinant of the blood pressure response to renal denervation in resistant hypertension.[3]

The factors that are shared commonly between systolic pressure and true drug resistance are listed in Table 1. Table 1 was generated by consideration of the data presented in several references[4–6] as well as my own experience in this area. The sections that follow are in alphabetic order and are not listed according to their importance.

Age

The role of age as a determinant of systolic pressure is well appreciated from several sources.[7,8] The specifics

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Table 1. Considerations for Mechanisms of Antihypertensive Drug Resistance

Age
Arterial stiffness
Diabetes
Chronic kidney disease
Salt and interfering substances
Sympathetic nervous system
Systolic pressure
Vascular calcification

of how aging affects blood pressure over time have been subjected to a great deal of scrutiny. From a simplistic standpoint, aging is a vehicle by which persistent blood pressure increase has the opportunity to prolong detrimental effects on the vascular wall by continued defiance of efforts to lower it by any method. Lakatta et al[9] at the National Institutes of Health have been studying the association of aging with blood pressure effects for decades. Summarizing many years of research from this group at the National Institutes of Health, and in conjunction with this effort (and the efforts of others) and the data from the Baltimore Longitudinal Study of Aging, the contributions to resistant hypertension from aging include the following: a decrease in bioavailable nitric oxide,[9] activation of matrix metalloproteinase activity,[10] arterial stiffness,[11,12] an increase in a number of proinflammatory factors,[13] and angiotensin II.[14]

Within this list, the role of arterial stiffness may be of particular importance for the systolic component of uncontrolled blood pressure. It is clear that arterial stiffness, because it is clinically assessed by aortic pulse-wave velocity, typically increases with age, and increases more so when high blood pressure is present.[15] All the factors mentioned earlier have a greater chance of a cumulative effect promoting arterial stiffness the longer the circulation is exposed to them. Although it typically is stated that pulse pressure (ie, the systolic minus the diastolic blood pressure) best reflects the stiffness of the circulation, pulse pressure is driven largely by the systolic pressure, particularly after age 50.[16] Moreover, the decrease in diastolic pressure beginning in the mid-50s, which contributes even more to the widening of pulse pressure with age, is also a reflection of arterial stiffness.[17]

Age also may participate in arterial stiffness by virtue of the number, and amplitude, of blood pressure excursions experienced by the aorta. This was examined in the Caerphilly study, which enrolled Welsh men aged 45 to 59, and performed an aortic pulse-wave velocity measurement about 20 years after enrollment in 1,225 of the men.[18] Looking back, among the independent factors predicting increased aortic stiffness (higher aortic pulse-wave velocity) 20 years later, were the pulse pressure and heart rate at enrollment. The interaction of pulsatile load (the pulse pressure) and the frequency of load bearing (heart rate) work together to promote a degradation of elastin fragments, with repair of such damage by the better load bearing (but stiffer) collagen.[19,20]

Thus, although age is a factor in the pathogenesis of drug-resistant hypertension, it does seem a little odd to label it as a pathogenic factor per se when it is likely that age is simply a surrogate for the duration of exposure to noxious events that directly contribute to drug resistance.

Aldosterone

A repeated finding in the literature on the pharmacologic approaches to manage drug-resistant hypertension is that approximately 20% of people with drug resistance have an element of aldosterone excess.[21]

One clear mechanism by which aldosterone produces drug resistance, identified shortly after the discovery of the hormone itself, is through promoting distal nephron sodium reabsorption.[22] The means by which greater sodium exposure is associated with drug resistance is covered in more detail later. However, there are other aspects of aldosterone that could participate in resistant hypertension.

Nongenomic aspects of aldosterone have been observed in an isolated glomerulus preparation with direct visualization of afferent and efferent arteriolar caliber, in which aldosterone infusion reduces the caliber of the afferent and efferent arterioles.[23] It does this through activation of phospholipase C, and these actions are not blocked by spironolactone. These direct vascular actions of aldosterone are modulated by nitric oxide, as shown by the ability of N^G-nitro-L-arginine methyl ester, which inhibits nitric oxide production, to potentiate aldosterone-induced vasoconstriction,[24] emphasizing the role of the endothelial function.

An interesting aspect of aldosterone pathophysiology is the finding that sleep apnea often accompanies it, leading investigators to postulate a role for aldosterone action in patients with drug resistance and sleep apnea.[25] In a study of this phenomenon, Friedman et al[25] measured calf volumes during the day and at night in drug-resistant and controlled hypertensive patients with sleep apnea, noting that sleep apnea measures (apnea-hypopnea indices) were worse in the drug-resistant hypertensive patients. What they found is that calf volumes increased during the day, serving as a reservoir for fluid whose rostral shift during night time repose was thought to add swelling to an already compromised oropharyngeal anatomy, which contributed to the sleep apnea severity. Importantly, this same group observed an improvement in both morning blood