Reflections in Hypertension
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Arterial Stiffness as a Cause of Resistant Hypertension?

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A recent supplement of this journal reviewed the topic of resistant hypertension and described what is known about its underlying causes and appropriate diagnostic evaluation.[1,2] In one article, there was extensive discussion of poor compliance, but it focused exclusively on patient compliance (or adherence) with prescribed treatment.[2] What was not discussed was poor compliance of the arteries, or arterial stiffness. This is surprising since there has been an upsurge of interest in arterial stiffness in the past few years, both as a marker of target organ damage and as an independent predictor of cardiovascular risk. A list of common clinical conditions associated with resistant hypertension published in one of the reviews included obesity, diabetes, chronic kidney disease, black race, female sex, and the presence of left ventricular hypertrophy (LVH)[1]; one might also add older age to this list. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[3] provides some of the best data for examining predictors of resistance to treatment. In an analysis of the degree of blood pressure (BP) control (<140/90 mm Hg) at 3 years after the start of the trial in 33,357 participants, the independent predictors of poor control were older age, female sex, black race, diabetes, obesity, and LVH. (Renal function was not included in this analysis.)

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While at first sight this list may seem like a hodgepodge, a common thread is that they are all conditions characterized by increased arterial stiffness, and this may be the reason why it is so difficult to control BP.

PATHOPHYSIOLOGY OF ARTERIAL STIFFNESS

The first consideration is what is meant by arterial stiffness. The structure of the arteries changes greatly between the aorta and the arterioles, and most of the literature on stiffness refers to the large conduit arteries. These include the aorta, carotids, and femoral arteries, which contain little smooth muscle in their walls and have 2 main functions: as conduits for blood flow, and dampening of the pressure wave. The more distal resistance vessels and arterioles contain more smooth muscle and are the principal determinants of the peripheral resistance. The vast majority of the research on arterial stiffness has been concerned with the conduit arteries, wherein the best understood change is the increased stiffness that occurs with aging, the main effect of which is to increase the stiffness of the elastic conduit arteries (such as the carotid), but not the muscular arteries (such as the radial).[4] These changes lead to an increase in systolic pressure and a decrease in diastolic pressure. Systolic pressure is influenced by 3 main factors: (1) left ventricular ejection (stroke volume and duration); (2) dampening (compliance) of the large arteries; and (3) wave reflection.

Another major determinant of arterial stiffness is BP, but there are numerous other factors involved, which include endothelial dysfunction, vascular remodeling, and metabolic factors.[5] In the elastic arteries, the orderly arrangement of elastin fibers is

Table. Characteristics Associated With Resistant Hypertension and Corresponding Changes in Arterial Stiffness

Characteristic	Resistant Hypertension	Increased Arterial Stiffness
Old age	Yes	Yes
Female sex	Yes (older, not younger)	Yes (older, not younger)
Black race	Yes	Yes
Obesity/sleep apnea	Yes	Yes
Diabetes	Yes	Yes
Chronic kidney disease	Yes	Yes
Left ventricular hypertrophy	Yes	Yes

Adapted from Epstein.[1]

lost with increasing age and disease, and they may become fragmented and frayed. These degenerative changes are associated with an increase in collagen and ground substance.[6] One of the metabolic changes that leads to increased stiffness is the formation of cross-links between proteins by advanced glycation products (AGE) that accumulate on proteins such as elastin and collagen.

The 2 most commonly used methods for assessing arterial stiffness are the measurement of pulse wave velocity (PWV) and the augmentation index,[7] both of which measure stiffness of the conduit arteries but not of the resistance vessels.

ARE CONDITIONS RESISTANT TO TREATMENT ALSO CHARACTERIZED BY INCREASED ARTERIAL STIFFNESS?

The Table shows the characteristics identified by Epstein[1] as being related to resistant hypertension, with the addition of old age. It also shows whether the individual characteristics have been found to be associated with increased arterial stiffness. The justification for these statements is briefly summarized below.

Old Age

BP is harder to control in older patients, and this applies particularly to systolic pressure. In an analysis of the National Health and Nutrition Examination Survey (NHANES) data, Hyman and Pavlik[8] concluded that being older than 65 was the strongest predictor of poor control. Others have found similar results.[9] Increasing age is also the most important factor leading to increased arterial stiffness.[10]

Female Sex

The published data comparing BP control rates in men vs women is controversial. Women in the ALLHAT study showed poorer BP control than men.[3] An analysis of 15,768 patient visits in family practices concluded the same thing,[11] but a study of a working population found much better control rates in women.[12] A possible explanation for this is that the difference is age-dependent: in the NHANES data,[13] the control rates of treated subjects were much higher in women in the youngest age group (18–49 years, 68% controlled vs 42% of men), while in the oldest group (older than 70 years), control was slightly better in men (35% vs 33%).

One of the features of hypertension in women is that in early adulthood they have lower BP than men, at about the time of menopause they have similar rates, and in old age they have higher systolic pressures.[13] These changes are paralleled by changes in arterial stiffness. Younger women have less stiff arteries than men but, after menopause, women's arteries are stiffer.[14] In an analysis of data from the Atherosclerosis Risk in Communities (ARIC) study[15] (in which the average age of participants was 57) women had stiffer carotid arteries than men. One of the most extensive examinations of this issue was done by Berry and colleagues[16] as part of the Australian National Blood Pressure Study, in which several measures of arterial stiffness were made in 374 elderly women and 296 men whose antihypertensive treatment had been withdrawn for at least 2 weeks. Arterial stiffness (including the augmentation index) was higher in the women. Interestingly, the systolic pressures were the same in men and women, but pulse pressure was a little higher in women due to a lower diastolic pressure. The increased stiffness seen in women was not simply the result of being shorter than men.

Black Race

Lower rates of BP control in blacks compared with whites have been reported in several studies, including NHANES,[17] ALLHAT,[3] and the Multi-Ethnic Study of Atherosclerosis (MESA) study.[18]

In a study of the ARIC population, Din-Dzietham and colleagues[15] found that healthy middle-aged blacks had higher carotid artery stiffness than whites, even after controlling for differences in BP and body mass index. In another population

study, aortic stiffness was also increased (as measured by carotid-femoral PWV) compared with whites, again independent of any BP differences.[19] Endothelium-dependent vasodilatation is also impaired in healthy young blacks.[20]

Obesity

Obesity was one of the factors identified in ALLHAT that was related to poor BP control,[3] and the same was found in the Framingham Heart Study.[9] Obesity is closely related to sleep apnea, which is one of the most important determinants of resistant hypertension.[21] In a study of 41 patients with refractory hypertension, obstructive sleep apnea was present in 83%.[22]

It is well-established that obesity is associated with increased arterial stiffness, independent of BP,[23] and that it is more closely related to visceral adiposity than to increased body mass index.[24] Aortic PWV has been reported to be increased in patients with hypertension and sleep apnea when compared with hypertensives without sleep apnea, independent of obesity and BP.[25] Continuous Positive Airway Pressure (CPAP), which is the optimal treatment for sleep apnea, has been reported to lower PWV even if there is no change of BP.[26] The augmentation index increases during apneic episodes.[27] Sutton-Tyrrell and colleagues[24] compared PWV and several measures of obesity in 2488 elderly subjects; PWV was positively correlated with several markers of obesity, including abdominal visceral fat. It was also correlated with glucose, insulin, and hemoglobin A_{1c}.

Diabetes

In the Implementing New Strategies With Insulin Glargine for Hyperglycemia Therapy (INSIGHT) study, the strongest predictor of poor response to antihypertensive treatment was diabetes.[28] Diabetes was one of the factors identified in ALLHAT that was related to poor BP control.[3]

A study that compared hypertensive patients with and without diabetes found that PWV was higher in those with diabetes, even though the BPs were the same.[29] Fasting blood glucose was an independent predictor of PWV. Tomiyama and coworkers[30] studied 2080 healthy Japanese men who had PWV measured twice over a 3-year period. There was an interactive effect of BP and blood glucose that resulted in an accelerated increase of PWV during the period of observation.

Chronic Kidney Disease

A survey of the NHANES data[31] found that only 37% of subjects with chronic kidney disease had their BP controlled to <130/80 mm Hg and 56% had control to <140/90 mm Hg. As in other studies, it was the systolic pressure that was difficult to control: of those who were uncontrolled, 59% had only systolic elevation, while only 7% had isolated diastolic hypertension. Other factors that were related to poor control were older age, black race, and diabetes. A Spanish survey[32] found that 17% of patients with chronic kidney disease had their BP controlled below 130/80 mm Hg and 45% below 140/90 mm Hg. Lack of control was related to older age, proteinuria, and high low-density lipoprotein cholesterol.

Increased arterial stiffness is a well-recognized aspect of chronic kidney disease. One of the first demonstrations of the augmentation index predicting cardiovascular outcomes was made in patients with end-stage renal disease.[33] Even in patients without clinically manifested kidney disease, there is a correlation between plasma creatinine and arterial stiffness that is independent of BP and age.[34] The mechanism of the increased stiffness is not well understood but appears to be related to metabolic factors such as calcium-phosphate homeostasis and arterial calcification.[35]

Left Ventricular Hypertrophy

In an analysis of 286 patients with apparently resistant hypertension evaluated with ambulatory BP monitoring, predictors of true resistance (high ambulatory BP) were impaired renal function and LVH.[36] LVH was one of the factors related to poor BP control in ALLHAT[3] and the Framingham population.[9]

It has been known for many years that LVH is correlated with increased aortic stiffness in hypertensive patients,[37] and there is evidence to suggest that exposing the heart to an aorta that has been experimentally stiffened induces LVH.[38]

IMPLICATIONS FOR THE TREATMENT OF RESISTANT HYPERTENSION

The above considerations suggest that the conditions that are associated with resistant hypertension are also characterized by increased arterial stiffness. That does not necessarily indicate that the increased stiffness is the cause of the drug resistance, but it is certainly consistent with such a finding. Thus, a common aspect of resistant hypertension referred to in many of the studies above is that systolic pressure is much harder to control than diastolic and can be explained by the fact that increased stiffness elevates only the systolic pressure. The comparison between the sexes is also consistent with a relationship between treatment resistance and stiffness.

Reduction of the stiffness of the conduit arteries seems to be a desirable therapeutic goal that, so far, has not been achieved. Moreover, whether it can be achieved remains to be seen. In reviewing the long-term pathologic changes associated with aging and disease, Nichols and O'Rourke wrote, "There seems no real prospect for direct drug-induced improvement of aortic stiffness in adult humans."[39] We should, however, remember that arterial stiffness is pressure-dependent, and that any reduction of BP will reduce stiffness. The central problem is that the major effects of increased arterial stiffness are on the conduit or elastic arteries, while the effect of antihypertensive drugs is mostly on the muscular arterioles. Nevertheless, there are some encouraging possibilities, as outlined below, which include both lifestyle and drug-induced changes.

Lifestyle Changes

Several lifestyle and dietary changes have been shown to improve arterial stiffness independently of their effect on BP. People who exercise regularly have reduced artery stiffness, and it has been shown that an aerobic exercise training program can improve carotid artery stiffness in sedentary men to the same level that is seen in fit men of the same age.[40] Disappointingly, a small study of older patients (mean age, 64 years) with isolated systolic hypertension did not find any improvement in BP or arterial stiffness after 8 weeks of exercise training, even though maximal oxygen consumption was increased.[41] The explanation may be that the structural changes in the large arteries that occur with age may not be easily reversible. Drinking moderate amounts of alcohol has also been reported to improve stiffness independently of its effect on BP, which could be partly mediated by the effects of alcohol on high-density lipoprotein.[42] Older patients tend to be more salt-sensitive than younger ones, and sodium restriction has also been shown to reduce arterial stiffness. A study by Avolio and colleagues[43] studied 57 young and middle-aged normotensive subjects who ate a low-salt diet for an average of 2 years. Aortic PWV was reduced with the low-salt diet independently of BP.

Drug Treatment

While most of the currently used antihypertensive drugs cause vasodilation, they do not all affect the same parts of the arterial system. Nichols and O'Rourke[39] have emphasized the differences between drugs that predominantly work on the arterioles (such as hydralazine) and reduce peripheral resistance and drugs (such as nitrates) that have effects on larger arteries (although not on the main conduit vessels) and thus increase compliance and reduce wave reflection. There seem to be no major differences between the currently used major classes of antihypertensive drugs in terms of their effects on stiffness, with the exception of β-blockers, which are less effective,[6] presumably because they work at least in part by reducing cardiac output and slowing heart rate. β-Blockers that have vasodilator effects are better at reducing stiffness.[6]

The problem with conventional antihypertensive drugs is that they principally work on the muscular arteries and have little if any effect on the structural changes occurring in the conduit vessels, which are responsible for the treatment-resistant increase of systolic pressure. There are, however, some promising developments. In a study of moderately hypertensive patients with diabetes, pioglitazone reduced PWV after an 8-week course of treatment without any effect on systolic or diastolic pressure.[44] Another example is a drug called ALT-711, which breaks the AGE cross-links between proteins. In a study of 93 elderly patients with systolic hypertension (average BP, 159/84 mm Hg),[45] most of whom were taking antihypertensive agents, this drug selectively reduced pulse pressure due to an increase of diastolic pressure without any change of systolic pressure. Arterial stiffness was improved independently of BP. The drug has also been tested in aging monkeys, wherein it was found to reduce stiffness without affecting BP.[46] It was suggested that this was due to an increase in cardiac output.

CONCLUSIONS

Although there have been several recent reviews of resistant hypertension,[1,2,47,48] none (including the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7])[49] have given serious consideration to the possibility that arterial stiffness could be a major contributor, even though it seems intuitively obvious. The focus has been on 3 areas: blame the patient (for not taking the drugs); blame the doctor (for not prescribing the right drugs); and blame the system (for not facilitating contacts between patients and doctors or making the drugs more available). An aspect that has not been seriously considered is to blame the drugs (for not working adequately). Even in the best of hands, such as clinical trials where both patients and doctors are highly motivated, and patients at high risk

for resistance are generally few, the BP control rates have not exceeded about 70%.[50] The considerations discussed above suggest that reducing arterial stiffness *should* improve BP control in many resistant patients, but not that it actually *does*. The finding that ALT-711 raises diastolic pressure without lowering systolic pressure in patients with systolic hypertension is of great interest scientifically, but is not of much help therapeutically. Several other examples were quoted above where an intervention lowered arterial stiffness without affecting BP. It is possible that some compensatory mechanism such as improved baroreflex sensitivity or cardiac output is opposing the decrease in systolic pressure. Whatever the explanation, this area seems ripe for further research, both with pharmacologic and lifestyle interventions.

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