Epidemiological Findings Imply That Goals for Drug Treatment of Hypertension Need to Be Revised

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In the early trials exploring the benefit of antihypertensive drug treatment, diastolic blood pressure (DBP) was chosen as the only criterion for patient inclusion. This choice had, by definition, influenced the baseline characteristics of the hypertensive population. The subjects with both high systolic blood pressure (SBP) and low DBP and, hence, with a selectively increased pulse pressure (PP) were excluded from the trials and, therefore, not analyzed in the primary results. This bias was introduced not only in selecting the subjects at inclusion, but also at the end of follow-up. Those with an elevated SBP were considered adequately treated, although only DBP had been normalized (≥90 mm Hg). Perhaps for these reasons, antihypertensive drug therapy was consistently shown to prevent stroke more than it prevented ischemic heart disease. Such findings suggested that more attention should be given to SBP and PP, both of which are better independent predictors of cardiovascular (CV) risk than DBP alone.

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In recent years, numerous therapeutic trials using SBP as the principal inclusion criterion were performed in elderly populations. Cardiac events were reduced by ~24% to 27%, which is somewhat higher than that obtained in DBP-based trials. This diminution of cardiac events in SBP-based trials could reflect the choice of SBP as the specific enrolled criterion or the fact that these trials included only elderly subjects. Nevertheless, in the Hypertension Optimal Treatment (HOT) study, which was performed in middle-aged hypertensive subjects with systolic-diastolic hypertension, the failure to prove a benefit in terms of CV risk with a rigorously controlled DBP may be attributed to the fact that, although a decrease of SBP was indeed obtained, this decrease was less than that with DBP, and thus PP remained elevated.

The concept that PP plays an independent role in CV risk is difficult to demonstrate, because PP is no more than the arithmetic difference between SBP and DBP. Nevertheless, from the different studies reported in the literature and cited in Reference 6, it has been clearly demonstrated that, in hypertensive patients >55 years, brachial PP is a stronger CV risk factor than SBP alone, particularly for predicting myocardial infarction. The best predictor function among the possible linear combinations of SBP and DBP was similar to that of PP, suggesting that their association was real and not merely a statistical artifact caused by the correlation between SBP and PP. In particular, age >50 years, CV mortality and, most importantly, myocardial infarction are indeed positively correlated to the SBP level; however, for any given SBP value, CV risk is higher when DBP is lower. Other confirmations of the predictive value of PP were obtained in subjects with recurrent myocardial infarction, congestive heart failure, and myocardial dysfunction.

It is within this context that the article by Franklin et al should be evaluated. With increasing age, there is a gradual shift from DBP to SBP and PP as predictors of coronary heart disease risk. Below age 50, DBP is the strongest predictor. The decade from 50 to 59 is a transition period when all 3 BP indices are comparable predictors and, from 60 years onward, DBP is negatively related to coronary risk so that PP surpasses SBP. These findings should now be considered a consensus opinion. In fact, they mean that a DBP reduction in a patient >50 years of age might be due, in the long term, to the drug treatment of hypertension but also potentially to aging alone. The latter generates several problems associated with the definition of hypertension, the meaning of increased PP, and the drug treatment of hypertension that are addressed below.

In fact, PP is a very complex parameter to analyze. After ventricular ejection, the BP wave propagates at a given speed (~6 to 10 m/s), according to a well-established hemodynamic pattern: although mean BP remains relatively stable along the arterial tree, PP rises markedly from the central to the peripheral arteries. This PP amplification results in a significant increase of SBP, together with a slight decrease of DBP. The radial-aortic pressure differences measured invasively in normotensive subjects are ~12 mm Hg for SBP, ~0.8 mm Hg for mean BP, and ~1 mm Hg for DBP. These alterations, which in the case of SBP are higher than those introduced by the simple variability of BP measurements, result from 2 specific mechanisms. First, the pressure wave propagates from central to peripheral vessels restrained by the increasing rigidity of the arterial wall in association with a progressive reduction of vessel diameter. Second, the BP curve may be considered the summation of an incident pressure wave, which propagates from the heart to the peripheral vessels, and a reflected wave, which returns toward the heart from specific vascular sites, mainly located at the origin of resistance vessels and/or (in disease states) arterial bifurcation and calcified plaques.

With increasing age, PP amplification tends to be reduced due to the rapid elevation of aortic stiffness with age in conjunction with an earlier return of the backward pressure wave from reflection sites. Accordingly, by >50 years of age,
SBP, DBP, and PP become identical in all parts of the arterial tree. This finding concords with the epidemiological result of Franklin et al\(^7\) for individuals >50 years, but it raises the problem of identifying the best predictive values of aortic versus brachial DBP, SBP, or PP for those ≤50 years. SBP and PP are markedly lower in the aorta than in the brachial artery, suggesting that epidemiological findings could differ depending on whether aortic SBP and PP were considered rather than brachial SBP and PP to establish a predictive value. In addition, because PP amplification is known to rise markedly in the presence of increased heart rate (at all ages),\(^8\) it remains unknown whether the large number of subjects with tachycardia and classified as “hypertensive” on the basis of brachial artery measurements may, in fact, have no BP elevation at the aortic level.

Physiologically, PP is influenced by 3 hemodynamic factors: ventricular ejection, arterial stiffness, and wave reflections. Theoretically, in those >50 years, each of these factors might play a role in CV risk. However, ventricular ejection, which decreases with age, is not involved in increased PP. In an original approach, London et al\(^10\) showed that an increased PP is the hemodynamic hallmark of patients with end-stage renal disease. In these patients, aortic pulse wave velocity, independent of BP (and particularly PP), was a significant predictor of CV and overall mortality.\(^11\) A similar finding has been observed in subjects with essential hypertension and preserved renal function.\(^12\) Today, it remains to be determined whether an early return of aortic wave reflections might also be an independent predictor of CV risk. Indeed, such an earlier return may alter the heart-vessel coupling and be detrimental to cardiac function. At the same time, as mean DBP tends to decrease as a consequence of increased arterial stiffness, coronary perfusion is reduced, favoring myocardial ischemia.

The recent guidelines on the drug treatment of hypertension\(^13\) emphasized the need to control adequately DBP and SBP and, consequently, even PP. However, they did not indicate which regimen might most effectively obtain this result. Even if the goal of treatment trials is to reduce both DBP and SBP through multidrug therapy, the normalization of SBP (≈140 mm Hg) and, hence, PP is difficult or even impossible to obtain in ≈30% of the patients.\(^1,14\) Even in normotensive subjects, an increased PP remains a powerful independent predictor of CV risk.\(^6\) Alderman et al\(^15\) demonstrated that elevated PP is the only mechanical factor predicting CV risk in the presence of successful antihypertensive drug therapy. Concerning the dose-response curves for conventional antihypertensive drugs, few data in the literature indicate that DBP, SBP, and PP decrease in parallel under drug treatment, and some show that reductions of SBP and PP do not parallel that in DBP.\(^16\) Finally, the present study by Franklin et al\(^17\) leads to wonder whether the time has come to revise goals of antihypertensive drug therapy.

The first goal could be to reduce SBP and PP by modifying the timing of wave reflections, thereby delaying the return of the backward pressure wave. This alteration may be obtained easily with nitrates.\(^8,17\) This regimen has been shown to be effective in the long-term treatment of elderly subjects with isolated systolic hypertension. Normalization of SBP and PP can be obtained without any significant change in DBP, an aspect of treatment that may avoid the possible deleterious effects of a marked reduction of DBP in elderly populations. However, reductions of CV morbidity and mortality have never been tested using nitric oxide (NO) donors. From a pharmacological viewpoint, the potential use of NO donors and/or stimulators is of major interest, making the NO and cyclic GMP pathways the subject for drug research on the treatment of hypertension in the elderly.

The second goal could be to prevent the age-related increases of SBP and PP and the decrease in DBP that occur in the elderly independent of antihypertensive drug treatment. These aims might be obtained by reducing the increased arterial stiffness associated with aging and, hence, by limiting structural modifications of the arterial wall. Using this approach, drug treatment of hypertension should not only shift the BP toward lower levels but also prevent, in those >50 years, the age-dependent increase of SBP and decrease of DBP. In hypertensive rats, spironolactone, angiotensin-converting enzyme inhibitors, and angiotensin II type 1 receptor blockade prevented the aortic accumulation of collagen fibers\(^18\) and, hence, the age-related increase of arterial stiffness, independent of BP. In such trials, reduced sodium intake or diuretics might further improve the arterial mechanical properties.\(^18\) In aged rats, aminoguanidine can increase arterial stiffness independent of BP, without modifying collagen and elastin contents. This improvement is obtained through the action on glycosyl end-products, thereby suggesting that arterial mechanical properties can be modified through the use of interstitial molecules acting on cell-cell and cell-matrix attachments and in relationship with integrins and/or proteoglycans.\(^18\)

Finally, in an earlier study, Franklin et al\(^19\) showed that, after age 50, the increase of SBP and PP and decrease of DBP varied widely from one individual to another, suggesting that many environmental (sodium?) and genetic factors may modulate the age-related change of BP.\(^18\) In hypertensive humans, specific genetic polymorphisms are significantly associated with increased aortic stiffness, and some (like those involving the angiotensin II type 1 receptor gene), are associated with selective improvement of aortic pulse wave velocity after angiotensin-converting enzyme inhibition,\(^20\) thereby demonstrating the importance of selecting populations at risk for drug treatment. Now, research and therapeutic trials should imply a specific impact on conduit arteries. Perhaps the time has come to revise our conceptual approach to the clinical management of hypertension.

References


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