Natural History of Hypertension Subtypes

Paolo Verdecchia, MD; Fabio Angeli, MD

The relation between blood pressure (BP) and the risk of cardiovascular disease is direct, graded, and continuous over a wide range, apparently beginning at 115 mm Hg systolic and 75 mm Hg diastolic. Despite such a continuous relation, some working definitions, or subtypes, of hypertension have gained wide clinical acceptance. Experimental and clinical data support the notion that the hypertension subtypes defined by isolated or combined elevations of systolic and diastolic BP reflect distinct pathophysiological mechanisms, have different prognostic implications, and may require a different therapeutic approach.

Different Hypertension Subtypes

An increase in the stiffness of the aorta and large elastic arteries not accompanied by a rise in arteriolar resistance may lead to isolated systolic hypertension (ISH). In contrast, a predominant rise in arteriolar resistance may lead to combined systo-diastolic hypertension (SDH) if large artery stiffness also increases, or to isolated diastolic hypertension (IDH) if arterial stiffness is normal or low. Thus, IDH might be viewed as a marker of a good elasticity of aorta and large arteries, possibly because of a paucity of atherosclerotic lesions. In contrast, because the rigidity of the aorta and large arteries tends to increase with age, systolic BP also tends to increase with age, leading to an elevated frequency of ISH in the elderly. The decline of diastolic BP with age has been associated with progression of aortic atherosclerosis, defined in one study by the appearance of new calcifications or enlargement of old calcified areas. A confounding factor in the assessment of hypertension subtypes is the progressive amplification of the pressure wave during transmission from aorta to peripheral arteries, a phenomenon that is predominant in the young and decreases with aging. Thus, brachial diastolic BP may overestimate aortic BP, particularly in young subjects.

Although ISH is an important determinant of cardiovascular risk, possibly because it reflects diffuse atherosclerotic processes, IDH does not seem to be a condition of increased risk, perhaps because it might be a sign of a general paucity of atherosclerosis. The quite benign nature of IDH is further corroborated by the generally good response of elevated diastolic BP to antihypertensive treatment. According to the Third National Health and Nutrition Examination Survey (NHANES), treatment of hypertension normalizes diastolic BP (<90 mm Hg) in 89.7% of subjects, whereas it succeeds in normalizing systolic BP (<140 mm Hg) in only 49.0% of subjects. Similar results have been obtained from analysis of major intervention trials, which showed a greater degree of diastolic than systolic BP control. For example, in the Hypertension Optimal Treatment (HOT) study, more than 90% of subjects achieved diastolic BP normalization, whereas fewer than 50% achieved systolic BP normalization. In the Antihypertensive and Lipid-Lowering Trial to Prevent Heart Attack (ALLHAT) and the Controlled Onset Verapamil Investigation of Cardiovascular Events (CONVINCe) trials, approximately 90% of participants had their diastolic BP normalized after 2 years of treatment, whereas approximately 50% achieved systolic BP normalization. In treated hypertensive subjects, those with uncontrolled systolic BP were at greater risk of cardiovascular disease than those with uncontrolled diastolic BP after adjustment for confounding factors. Thus, effective systolic BP control is the real challenge and the main focus of treatment.

Because of the clear pathophysiological and clinical dissimilarities between the hypertension subtypes outlined above, a more precise knowledge of their natural history and clinical predictors may help to define and implement early, specific, and individualized prevention strategies.

In this issue of Circulation, Franklin and colleagues from the Framingham Heart Study report on the results of their categorization of hypertension subtypes in 3915 untreated participants who were free of previous cardiovascular events at the biennial examination carried out in the years 1953 to 1957. Subjects were followed up for 10 years up to biennial examination 9, performed in the years 1965 to 1967. The subjects who started an antihypertensive treatment during follow-up, as well as those with a new cardiovascular event, were censored at the corresponding dates. Thus, the Framingham investigators had the unique opportunity to track the natural history of the distinct hypertension subtypes over the long term, in the absence of the confounding effect of antihypertensive treatment and prior cardiovascular events.

The most interesting finding of the study is the following: compared with subjects with optimal BP (<120/80 mm Hg) at entry and after adjustment for several confounders, those with IDH were extremely more likely (ie, 23.1 times more likely) to develop SDH at follow-up. Furthermore, subjects with normal or high-normal BP at entry were 3.32 and 7.96 times more likely, respectively, than those with optimal BP to develop SDH at follow-up. Normal and high-normal BP at entry were also significant predictors of ISH at follow-up, with adjusted odds ratios of 3.26 and 4.82 compared with the...
Relation of different BP categories at baseline visit (years 1953 to 1955) to risk of developing different hypertension subtypes at follow-up visit 10 years later.18

Significance of Isolated Diastolic Hypertension
According to this Framingham report, the view that IDH is a low-risk condition should perhaps be reconsidered or reformulated. Unfortunately, no information on cardiovascular events associated with evolution of hypertension subtypes is available from the report. However, the subjects with IDH at entry had a cluster of features of increased risk. They tended to be more frequently men (65.3%) and smokers (57%) than the other groups. Their mean body mass index (BMI) was 28.0±4 g/m², and, although not reported, the metabolic syndrome might have been frequent in this group. It might be argued that the basic mechanisms of the frequent progression toward SDH in this group included an activation of atherosclerotic processes, with evolution toward progressive stiffening of the aorta and large arteries over time. Notably, both baseline BMI and the subsequent weight gain were significant predictors of subsequent development of SDH. These findings confirm the NHANES data, which showed that the increase in BMI contributes to explaining more than 50% (ie, 2% of the 3.6%) of the increase in hypertension prevalence in the United States from the years 1988 to 2000.9

Because the final visit in this study was carried out in the years 1965 to 1967, the modern clinical implications of these findings must take into account the current availability of potent and well-tolerated antihypertensive drugs. Implications may be subtle and double edged: The relatively easy control of IDH with current antihypertensive drugs, if not accompanied by an adequate control of other risk factors for atherosclerosis through appropriate health-promoting lifestyle modifications and pharmacological measures when needed, might ultimately fail to retard the progression of vascular lesions, with consequent possible evolution toward progressive arterial stiffening and superimposed systolic hypertension in the long run. Thus, the subjects with IDH, although possibly not at increased risk in the short or middle term,5,9–12 should be carefully monitored over time. In these patients, the goal of treatment should be the control of all cardiovascular risk factors, not solely the BP normalization.

One finding in the present report that is not easy to explain is the high likelihood of subjects with ISH at baseline to develop SDH at follow-up, with an adjusted odds ratio of 7.10 compared with the subjects with optimal BP at entry.18 The mean age of these subjects at entry was 54.4 years. These data suggest that a progressive rise in peripheral arteriolar resistance can occur over time even in middle-aged subjects with ISH, despite being, as a group, at the top of the age–diastolic BP relation.2 A large stroke volume might have been the driving mechanism of ISH in these subjects, with later superimposition of increased peripheral resistance possibly paralleled by a rise in central artery stiffness.

Significance of Prehypertension
The article by Franklin and colleagues provides additional data on the hotly debated issue of prehypertension (BP, 120 to 139 systolic or 80 to 89 diastolic).20 After adjustment for age and sex, the incidence of ISH (×100 person-years) was 22.8 and 35.4 among subjects with normal and high-normal BP, as opposed to only 6.6 among the subjects with optimal BP, with corresponding odds ratios of 3.26 and 4.82, respectively. Furthermore, 59% of subjects who developed ISH did not have diastolic hypertension at the baseline visit or at any other visit before ISH onset. Finally, the subjects with normal or high-normal BP at entry were significantly more likely than those with optimal BP to develop SDH.

These data provide further support to the argument that prehypertension, intended as the combination of normal plus high-normal BP categories, is a useful working definition in the setting of cardiovascular disease prevention because it identifies individuals at increased risk of developing progressive vasculopathy with stiffening of the aorta and elastic arteries over time. One should not forget that, because of the continuous nature of the relationship between BP and cardiovascular disease, most BP-associated cardiovascular complications occur in individuals with prehypertension. In a previous analysis of the Framingham Heart Study, compared with the subjects with optimal BP, those with high-normal BP showed a significantly increased risk of cardiovascular disease independent of other risk factors, and a nonsignificant trend toward an increased incidence of events was also noted in the group with normal BP.21 According to the Joint National Committee VII recommendations,20 the subjects with prehypertension are not necessarily candidates for drug therapy. Rather, they should be rechecked in 1 year20 and firmly advised to practice effective lifestyle modification22 to reduce their risk of developing future hypertension and associated cardiovascular disease.
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References


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