Brief Review

Unusual Hypertensive Phenotypes

What Is Their Significance?

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According to Webster,1 the terms “spurious,” “artifactual,” or “pseudo” denote false or deceptive resemblance. These terms when used specifically to hypertension refer to something that does not correspond with reality—a false perception; implicit in this definition is normalcy or a benign prognosis. Before discussion of the pros and cons of spurious, artifactual, or pseudohypertension, one should dispose of faulty technique (systematic error, terminal digit preference, or observer bias) in measuring blood pressure (BP), including cuff-inflation hypertension and failure to use the proper size cuff in obese arms as causes of erroneously high BP values. In this review, we limit our focus to the use of the terms “spurious,” “artifactual,” or “pseudohypertension” in relation to 3 unusual hypertensive phenotypes: (1) spurious isolated systolic hypertension (ISH) in late teenagers to young adults, defined as systolic BP (SBP) >140 mm Hg and diastolic BP (DBP) <90 mm Hg; (2) artifactual or benign isolated diastolic hypertension (IDH) in young to early middle-aged adults defined as a SBP <140 mm Hg and DBP ≥90 mm Hg; and (3) pseudohypertension in the elderly, presenting rarely with noncompressible artery syndrome and, more commonly, an elevated diastolic brachial artery pressure assessed indirectly with a cuff and sphygmomanometer, in the context of a “normal” intra-arterial pressure assessed invasively.

The purpose of this review is to present evidence for and against with regard to the validity of these 3 forms of unusual hypertensive phenotypes.

ISH in Late Teenagers to Young Adults

Although ISH is usually associated with the elderly, ISH is also the majority hypertensive subtype in adolescents2 and young adults.3 The phenomenon of spurious systolic hypertension in young individuals was first described by O’Rourke et al4 in 6 young males, aged 14 to 23 years. The investigators noted elevated brachial SBP (150–176 mm Hg) but normal brachial DBP (55–85 mm Hg), and all of these young subjects were relatively tall for their age. Using pulse wave analysis with the SphygmoCor system, a technique for measuring radial arterial waveforms and deriving central (aortic) pressure, they found a sharper-than-usual systolic peak and a normal mean arterial pressure and concluded that this was spurious (or pseudo-) hypertension secondary to exaggerated amplification of a normal central BP.

Mahmud and Feely5 identified ISH in 11 of 174 consecutively studied medical students (equally divided by sex), whose brachial BP averaged 147/70 mm Hg. All 11 of the subjects with ISH were tall men, nonsmokers, and active in sports. Using the SphygmoCor system, the difference between central and brachial SBPs was 31 mm Hg in those with ISH versus only 20 mm Hg in those with normotension. Following O’Rourke et al,4 they attributed this hypertension subtype to spurious systolic hypertension secondary to exaggerated pressure amplification in healthy, athletically active men with slow heart rates and highly elastic central arteries. Pickering,6 in reviewing the data on ISH in the young, concluded that this was probably a benign condition and perhaps in association with some degree of “athlete’s heart.”

More recent investigations dispute the view that ISH in young subjects is benign. McEniery et al3 studied 1008 young adult university students (mean age: 20 years) in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia Study. In keeping with previous investigations, they found that ISH in young adults had a 90% male predominance. However, in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia Study, ISH was associated with normal pulse pressure amplification but elevated brachial and central SBP, measured using the SphygmoCor technique. Hulsen et al7 studying a population-based Utrecht cohort of 750 young adults also with the SphygmoCor technique, found 57 young men with ISH (versus only 3 women) who had higher brachial and central SBP and DBP than in their normotensive counterparts.

A key question in interpreting the findings of these studies is, what should be considered a normal central pressure? Pulse pressure widens moving from central to peripheral arteries because of a rise in systolic pressure. This so-called pressure amplification is attributed mainly to differences in vessel stiffness and wave reflections within the arterial tree and is present in all but the very oldest individuals. Because of this disparity between brachial and central pressure, applying brachial BP thresholds to define normal values of...
central pressure is inappropriate and misleading. Indeed, McEniery et al.\(^8\) found that, for a healthy cohort of 4000 individuals, the brachial pulse pressure was, on average, 1.7-fold higher than aortic pressure in 20- to 30-year-old men (95% CI = 1.35 to 2.05). Using a brachial systolic pressure of <120 mm Hg as a reference, this would translate to a corresponding central SBP of \(\sim105 \pm 8\) mm Hg for men and \(\sim101 \pm 9\) mm Hg for women with a 95% CI of <110 mm Hg. In contrast, the mean central SBPs for subjects with ISH in the 4 studies mentioned above were 119, 116, 120, and 117 mm Hg,\(^7\) respectively. Moreover, the corresponding values in the normotensive controls in 3 of these studies were 100, \(\sim98,\) and 105 mm Hg,\(^7\) in keeping with the observations described above. Therefore, there is clear evidence that central SBP is elevated along with brachial SBP in young subjects with ISH (Figure 1), suggesting that these individuals may be at significantly increased cardiovascular risk.

McEniery et al.\(^3\) also observed that aortic stiffness and/or stroke volume was elevated in these young individuals, providing plausible physiological mechanisms underlyng the observed elevations in central pressure. Moreover, based on work by Lund-Johannson\(^9\) and Julius et al.\(^10\) an increased stroke volume associated with systolic hypertension in youth is highly likely to transform into sustained hypertension in the future, suggesting that these individuals are in the very early stages of developing “fixed” hypertension. Thus, the preponderance of evidence is strongly against the existence of spurious hypertension in young persons with significant ISH. Nevertheless, future longitudinal studies will be necessary to determine causative pathways in the development, evolution, and ultimate prognosis of ISH in adolescents and very young adults.

### Artifactual/Benign Isolated Diastolic Hypertension in Young Adults

The concept of artifactual or benign isolated diastolic hypertension arose from previous observations that individuals presenting with raised diastolic pressure and a narrow pulse pressure (by definition, isolated diastolic hypertension) had auscultatory BP measurements that overestimated the true, intra-arterial BP.\(^{11}\) In support of these observations, Fang et al.\(^2\) analyzed 1560 participants in a worksite hypertension control program and concluded that the relative risk of myocardial infarction was greater in those with systolic/diastolic hypertension than in those with IDH defined as SBP \(<160\) and DBP \(\geq 90\) mm Hg (5.20 versus 2.21 per 1000 person-years, respectively). When IDH was defined as SBP \(<140\) mm Hg, there were no myocardial infarctions recorded. However, the study was underpowered, with only 25 myocardial infarctions during a 4.5-year follow-up. However, subsequently, there have been 4 additional longitudinal outcome studies, which have largely concluded that IDH is benign and of minimal clinical importance. The Honolulu Heart Program\(^{13}\) and the Copenhagen City Heart Study\(^{14}\) defined IDH as SBP \(<160\) and DBP \(\geq 90\) mm Hg, which would include stage 1 IDH in the current classification. The Japanese Ohasama Study\(^{15}\) used home BP monitoring, defining IDH as SBP \(<137\) and DBP \(\geq 84\) mm Hg and with an 8.6 year follow-up, obtained a nonsignificant hazard ratio of 1.2 (95% CI: 0.16–8.96) for total cardiovascular disease events. All 3 of these studies were largely in middle-aged subjects. In contrast, in the Finnish Male Cohort Study,\(^{16}\) 3267 initially healthy individuals were evaluated at ages 30 to 45 years and followed for up to 32 years. IDH subjects were subdivided into SBP \(<160\) mm Hg and SBP \(<140\) mm Hg. When SBP was \(<140\) mm Hg, the hazard ratio was a nonsignificant 1.11 compared with the reference of 1.00 for normotensives. However, normotension was defined as SBP \(<160\) and DBP \(<90\) mm Hg, which would include subjects with stage 1 ISH, and, therefore, may have unfairly reduced the risk in the IDH group. Pickering\(^{17}\) reviewed all of the above studies and concluded that IDH, as currently defined, is either a measurement artifact or a benign state.

However, a number of lines of evidence suggest that IDH is likely to be associated with increased cardiovascular risk. The Framingham Heart Study showed that new-onset IDH
developed primarily from normal and high-normal BP during a 10-year follow up.18 Furthermore, 82.5% of participants with baseline IDH developed systolic/diastolic hypertension during the ensuing 10 years of follow-up, suggesting that IDH was a frequent precursor for systolic/diastolic hypertension and, therefore, potentially not a benign condition.18 Further compelling evidence comes from a large meta-analysis of BP values from >1 million middle-aged and older individuals (all aged >40 years) demonstrating a continuous, positive relationship between DBP and vascular and all-cause mortality.19 Interestingly, the authors could not detect any threshold for risk down to DBP values of 75 mm Hg. Recently, these observations were extended in a large cohort study of Swedish men in whom baseline examinations were undertaken at a mean age of 18 years, with 24 years of follow-up.20 The authors noted a continuous and steep relationship between values of DBP >90 mm Hg and cardiovascular and all-cause mortality, which was stronger than for SBP. In support of these observations, the Framingham Heart Study21 showed that DBP was a better predictor of future coronary heart disease events than SBP in adults <50 years of age; the reverse was true after 50 years of age.21 Finally, the Chinese Stroke Prevention Project,22 a community-based cohort study in 5 large cities across China, has provided a definitive answer to the importance of hypertension in general and IDH in particular in predisposing to stroke risk. A total of 26587 subjects without a history of stroke were recruited in 1987 and were followed for a mean duration of 9.5 years, during which time 1107 stroke events occurred. Stroke etiology was determined as follows: 55.5% ischemic, 40.7% hemorrhagic, and 3.8% unclassified. A major finding of this study was that the IDH subtype (defined as SBP <140 mm Hg and DBP ≥90 mm Hg) was not an uncommon cause of stroke in the Chinese population. Furthermore, IDH (hazard ratio: 2.35 [95% CI: 1.91–2.90]) and ISH (hazard ratio: 2.16 [95% CI: 1.69–2.76]) had similar predictive values for stroke incidence. Thus, we now have definitive evidence in an Asian population that the IDH subtype is an important predictor of cardiovascular disease risk and should be treated vigorously. These findings are supported by ambulatory BP monitoring (ABM) findings that show pulse pressure is the dominant predictor of cardiac events; in contrast, mean BP is the major predictor of stroke risk.23 The failure of the previous IDH outcome studies to predict risk may have resulted from insufficient statistical power as a result of the following: (1) a small sample size; (2) poor precision of BP measurements; (3) a low IDH relative risk for future cardiovascular disease events; and (4) the manner in which the data were analyzed statistically. In conclusion, the preponderance of evidence now strongly excludes IDH as an artifactual or benign form of hypertension.

Pseudohypertension in the Elderly

This is most commonly used to describe an elevated brachial artery pressure assessed indirectly with a cuff and sphygmomanometer, in the context of a normal intra-arterial pressure assessed invasively. The underlying pathophysiology is often cited as stiffening of the brachial artery, which is much more common in elderly subjects, hence the term pseudohypertension in the elderly.

In an extreme form, there may be true incompressibility of the brachial artery because of calcification. Ectopic calcification (also known as Monckeberg sclerosis) can specifically affect the muscular arteries of both the upper and lower extremities; rare involvement of the upper extremity results in a mechanical problem whereby BP cannot be measured by sphygmomanometry because of severely calcified brachial arterial walls rendering them noncompressible.24 Much more commonly, medial artery calcification involves the lower extremity arteries and is manifest by a decreased (<0.9) or incompressible increased ankle brachial index of ≥1.4.25 Importantly, incompressible arteries, whether the rare form in the upper extremities or the more common form in the lower extremities, are frequently associated with chronic renal disease, with or without diabetes mellitus, and, hence, with increased cardiovascular disease risk.24–28 However, curiously, individuals with ectopic medial calcification of the muscular arteries of the lower extremities with elevated ankle brachial indices (markedly elevated ankle and minimally elevated brachial pressure) do not have the traditional risk factors associated with atherosclerosis; indeed, their age-adjusted prevalence of hypertension is generally no greater than persons with normal or low ankle brachial index values.25–28 Thus, the incompressible artery syndrome is not a true representation of pseudohypertension.

Perhaps more common is the situation of compressible but stiffened arteries, which was thought to lead to an overestimation of diastolic pressure by sphygmomanometer in comparison with true intra-arterial pressure.29,30 To fully appreciate how this became a clinical entity, one must understand its historical context. This entity was defined by the simultaneous measurement of brachial cuff and direct intra-arterial measurement in the 1970s and 1980s at a time when hypertension was classified almost exclusively by elevation in DBP; SBP was considered significantly elevated only with values of ≥160 mm Hg.31,32 Furthermore, observational studies had not yet proven that SBP was a more important cardiovascular risk factor than DBP in the older-aged population, with risk beginning at SBP values >115 mm Hg.19 Therefore, pseudohypertension was defined as a diastolic cuff pressure >100 mm Hg and with an intra-arterial pressure <90 mm Hg.30 This entity was thought to occur as often as 4% to 7% in elderly individuals who presented with hypertension.30 It was often considered to have a benign prognosis but was never tested for cardiovascular risk in a population study.29,30 Although, described by Spence et al31–32 as diastolic pseudohypertension in subjects suspected of having pseudohypertension, with DBP frequently increased by as high as 20 mm Hg above normal values, intra-arterial SBP measurements were consistently elevated (frequently as high as stage 2 or 3 hypertension). These observations regarding diastolic pseudohypertension have been largely confirmed. As summarized by Smulyan and Safar,33 the Association for the Advancement of Medical Instrumentation34 in 1993 evaluated 5 studies that compared cuff auscultatory brachial artery with the gold standard intra-arterial brachial BP; for SBP (Figure 2A), intra-arterial was 3 to 4 mm Hg higher than cuff
auscultatory, whereas for DBP (Figure 2B), cuff auscultatory was \( \approx 10 \) mm Hg higher than intra-arterial readings, thus confirming diastolic pseudohypertension and ruling out systolic pseudohypertension.

Interestingly, Messerli et al.\(^3\)\(^5\) popularized the presence of pseudohypertension in older subjects by indicating that they could be identified on the basis of palpable thickening of the radial artery (Osler positive sign). Messerli et al.\(^3\)\(^5\) identified 13 persons with palpable radial arteries and falsely elevated DBP by 16.4 and falsely elevated SBP by 15.8 mm Hg as compared with intra-arterial measurements; however, with correction, the mean intra-arterial BP was 181/78 mm Hg, indicating that these individuals actually had ISH. Subsequent studies have shown that the Osler sign is not a useful diagnostic test because of low sensitivity and selectivity.\(^2\)\(^9\)

Therefore, the available evidence suggests that most individuals who have been labeled with the term pseudohypertension in the elderly actually have ISH, which is well accepted as a risk factor for cardiovascular events. The term pseudohypertension is, therefore, misleading in this context and ignores the considerable excess risk associated with ISH in older individuals. Moreover, stiffening of the brachial artery rarely occurs in isolation, and we now appreciate that aortic stiffening, which characterizes ISH in the elderly,\(^3\)\(^6\) is an independent predictor of cardiovascular events.\(^3\)\(^7\)\(^,\)\(^3\)\(^8\) Therefore, assessment of pulse wave velocity, the current gold standard measure of arterial stiffness,\(^3\)\(^9\) may be a better diagnostic test in these individuals. Furthermore, medial artery calcification of the elastic aorta and its branches may play an important role in the development of ISH in older persons. In this regard, quantitative high-resolution CT imaging has disclosed medial vascular calcification in the ascending, descending, and abdominal aortas in patients with ISH who are otherwise apparently healthy.\(^4\)\(^0\) Interestingly, the quantity of aortic calcification correlated with both the severity of ISH and with the resistance to

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**Figure 2.** A and B. References used by Association for the Advancement of Medical Instrumentation\(^3\)\(^3\) to validate cuff auscultatory vs intra-arterial systolic blood pressure (A) and diastolic blood pressure (B) measurements. Plotted values indicate average differences for each reference. Horizontal lines with brackets indicate the SD of differences (when available). Despite large standard deviations, these findings show a small decrease in auscultatory brachial systolic blood pressure as compared with simultaneous intra-arterial readings. In contrast, there was an \( \approx 10 \) mm Hg false elevation in auscultatory brachial diastolic blood pressure as compared with simultaneous intra-arterial readings. Adapted with permission from Smulyan and Safar.\(^3\)\(^3\)
achieving adequate control with antihypertensive therapy. Similar associations of calcification of thoracic aorta and ISH were noted in a study that evaluated large arteries for calcium content during routine health maintenance screening. Thus, it appears that vascular calcification, out of proportion to the normal aging process, may play an important role in the development of ISH.

During the past decade, validated devices for 24-hour ABM using the oscillometric method have become the gold standard for assessing and classifying hypertensive cardiovascular risk because of excellent correlation with target organ damage and with morbidity and mortality outcomes. Importantly, the use of ABM has identified the new hypertensive phenotypes of white-coat hypertension and white-coat effect, both of which are very common in the elderly and can simulate pseudohypertension. Indeed, white-coat hypertension is more likely to be observed in individuals with increased large artery stiffness, because the influence of the “alerting” or white-coat response on the measured BP is likely to be greater in individuals with stiffened arteries and a concomitant reduction in arterial buffering capacity. ABM is the ideal method of diagnosing both white-coat hypertension and white-coat effect, but other options are available that are less expensive and more easily repeatable for the additional assessment of the response to treatment, including home BP monitoring.

Despite these new developments in assessing hypertensive cardiovascular risk, the concept of pseudohypertension in the elderly has been perpetuated in textbooks, journals, and even in a recent consensus statement for hypertension in the elderly, suggesting that it should be suspected if measured SBP values are inappropriately high in the absence of target organ damage or if antihypertensive drugs provoke symptoms of hypotension despite the persistence of elevated SBP; in retrospect, these clinical states should raise the likely possibility of white-coat hypertension, white-coat effect in the absence of target organ damage, and occasionally of treatment-induced or worsening of orthostatic hypotension, all masquerading as pseudohypertension. Furthermore, central aortic BP assessment of cardiovascular risk should also be dissociated from pseudohypertension. Indeed, central aortic pressure measurement may not only be superior to brachial BP but may also be comparable to ABM in predicting cardiovascular risk. However, until we have more definitive morbidity/mortality studies, ABM monitoring remains the gold standard for assessment of hypertensive cardiovascular risk.

In summary, the term “pseudohypertension” in the elderly is misleading; it suggests a benign condition secondary to a false elevation in oscillometric or auscultatory DBP as compared with intra-arterial DBP, whereas, when white-coat hypertension and white-coat effect without target organ damage are ruled out, the finding of ISH with widened pulse pressure is associated with considerable cardiovascular risk. Thus, what has been perceived as false elevation in brachial BP, as compared with intra-arterial pressure, is the result of discrepancies in office/clinic BP versus home/ambulatory measurements. Indeed, “the emperor has no clothes” is an appropriate metaphor for the diagnosis of pseudohypertension in the elderly: there have been few if any further scientific reports of pseudohypertension in the elderly during the past 2 decades despite the continued inclusion of this entity as a hypertension phenotype in the medical literature. The myth lives on. Is it not time to give it a proper burial?

Perspectives
All 3 of the hypertensive phenotypic syndromes described in this review show mild-to-severe cardiovascular risk, and, therefore, cannot be described as having a benign cardiovascular prognosis. In young individuals, spurious systolic hypertension is actually associated with increased central and brachial SBP, rather than exaggerated central-to-peripheral BP amplification. Similarly, so-called artifactual isolated diastolic hypertension in young individuals is typically associated with additional cardiovascular risk factors and often precedes the development of systolic/diastolic hypertension in later life. In older individuals, the noncompressibility artery syndrome, predominately involving the lower extremities, is associated with severe medial calcification of muscular arteries, frequently an elevated ankle-brachial index, and typically no significant increase in age-adjusted BP. In contrast, diastolic pseudohypertension, representing wide pulse pressure ISH, is associated with calcification of the aorta and is accompanied by significantly increased cardiovascular risk. Indeed, using ABM as the new gold standard for assessing cardiovascular risk in the elderly, we conclude that white-coat hypertension and white-coat effect, in the absence of target organ damage, have been masquerading as pseudohypertension. In summary, there are no legitimate elevated BP phenotypes that should be labeled as spurious, artifactual, or as pseudohypertension.

Disclosures
None.

References


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Hypertension. 2012;59:173-178; originally published online December 19, 2011;
doi: 10.1161/HYPERTENSIONAHA.111.182956
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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