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REVIEW

The pathobiology of isolated systolic hypertension

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KEYWORDS
Isolated systolic hypertension;
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Abstract
Central artery stiffening with aging is the driving force that results in increased pulse pressure (PP) and ultimately the development of isolated systolic hypertension (ISH). Since diastolic blood pressure (DBP) rises with increased small arterial and arteriolar resistance and falls with increased large artery stiffness, DBP displays a J-curve pattern of CV risk; thus, PP is a stronger risk factor than systolic blood pressure (SBP) in patients with ISH when DBP is <70 mmHg. ISH can develop from either "burned-out" diastolic hypertension or de novo, secondary to increased arterial stiffness without going through a preliminary phase of essential hypertension. De novo ISH, the most frequent form of ISH, has multiple etiologies, which include a variety of conditions that impair synthesis of elastin protein and increase large artery calcification. The projected increase in ISH with aging of the US population and the often found resistance of ISH to antihypertensive therapy represent a potential worsening public health problem.

PALABRAS CLAVE
Hipertensión sistólica aislada;
Arteria central;
Presión de pulso;
Riesgo cardiovascular

La patobiología de la hipertensión sistólica aislada

Resumen
La rigidez de la arteria central con el envejecimiento es la fuerza principal que causa un aumento de la presión del pulso (PP) y finalmente el desarrollo de la hipertensión sistólica aislada (HSA). Ya que la presión sanguínea diastólica (PSD) aumenta con un aumento de la resistencia arteriola y de las pequeñas arterias y cae con un aumento de la rigidez de la arteria grande, la PSD demuestra un patrón de curva-J con riesgo cardiovascular. Por lo tanto, la presión del pulso (PP) es un factor con mayor riesgo que la PSD en pacientes con HSA cuando la PSD es de <70 mmHg. HSA puede desarrollarse de una hipertensión diastólica de "burned-out" ó de novo, secundaria a una rigidez arterial aumentada sin haber pasado por una fase preliminar de hipertensión esencial. La HSA de novo, la forma más común de HSA, tiene múltiples etiologías.
Estas incluyen una variedad de condiciones que impide la síntesis de la proteína elastina y que aumenta la calcificación de la arteria grande. El aumento estimado en HSA con el

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envejecimiento de la población de la USA y la resistencia que, a menudo, ocurre con la HSA a la terapia antihipertensiva representan un posible empeoramiento del problema de la salud pública.

Introduction

Once considered an inconsequential part of the aging process, the development of isolated systolic hypertension (ISH) represents a late manifestation of increased arterial stiffness in the middle-aged and elderly population.[1,2] Its inherent increased risk for vascular events highlights the importance of its control. Surprisingly, ISH is occasionally observed in adolescent and -young adults, but in association with an entirely different hemodynamic pattern than observed in the elderly. Previously, ISH was defined as a systolic blood pressure (SBP) $\geq$160 mmHg and a diastolic blood pressure (DBP) of $<$95 or $<$90 mmHg. With the recognition of its true risk, ISH was redefined as SBP$\geq$140 mmHg and DBP$<$90 mmHg in the 1990s. The purpose of this presentation is to provide a better understanding of epidemiology, pathophysiology, J-curve risk, diagnostic value and varied etiologies of ISH.

Epidemiology of ISH

Approximately 65 million individuals in the United States and 1 billion worldwide are affected by hypertension.[3] The National Health and Nutrition Examination Survey (NHANES III, 1988–1991)[2] showed that three out of four adults with hypertension were aged 50 or older. Beginning at age 50, the most predominant form of hypertension is ISH, accounting for more than three fourths of those with hypertension aged 50–59, approximately 80% of hypertension in those aged 60–69, and approximately 90% of those with hypertension aged 70 years or greater. Thus, ISH is the most common subtype of hypertension. Furthermore, a recent Framingham Study showed that normotensive persons reaching age 65 had a 90% lifetime risk of developing hypertension—almost exclusively of the ISH subtype—if they lived another 20–25 years.[4]

Pathophysiology of ISH

The two major physiologic components of blood pressure (BP) are mean arterial pressure (MAP) and pulse pressure (PP).[5] MAP is simply the interaction of cardiac output (CO) and peripheral vascular resistance (PVR), i.e., MAP=CO $\times$ PVR. PP depends on two major factors: (a) left ventricular ejection characteristics and (b) stiffness of the thoracic aorta and its branches. The peak SBP and minimum DBP represent a weighted sum and difference of MAP and PP, respectively. PP in older subjects represents a surrogate measurement of central elastic artery stiffness in the presence of a constant CO and heart rate. Thus, the central arterial stiffening is manifested by three factors: (a) a rise in PP leading to (b) a rise in SBP and (c) a fall in DBP, ultimately resulting in ISH.[5]

ISH in young adults: Although ISH is usually associated with the elderly, there is now firm evidence that ISH is also the majority hypertensive subtype in adolescents[6] and young adults.[7] McEniery et al.[7] studied young adult university students with a mean age of 20 years in the ENIGMA Study and confirmed that persons with ISH outnumbered those with essential hypertension (elevated SBP and DBP, or DBP alone) by a ratio of $\approx$2:1. Young adults presenting with ISH had a marked male predominance with heterogeneous hemodynamic patterns—increased stroke volume, increased aortic stiffness or a combination of both. By contrast, the major hemodynamic profile underlying essential hypertension was increased peripheral vascular resistance.[7] Furthermore, in comparison with normotensive individuals, those with ISH had higher central aortic SBP by more than 20 mmHg and an increased mean body mass index of 26 kg/m^2. Therefore, ISH in young adults is probably not a benign condition. Future longitudinal studies, however, will be necessary to distinguish between parallel and sequential causative pathways in the development, evolution and ultimate prognosis of ISH in very young adults.

ISH in the elderly: The Framingham Heart Study findings support the concept of an interaction between aging and established hypertension in the progressive fall in DBP and continued rise in SBP after age 50–60 years, which leads to the development of ISH.[8,9] These findings suggest a linkage between hypertension left untreated and the subsequent acceleration of large artery stiffness and pathologic aging—thus, creating a vicious cycle of accelerated aging. The most important clinical implications that can be derived from these studies are that after the sixth decade of life, (1) increased PP is a surrogate marker for large artery stiffness and for vascular aging (arteriosclerosis); (2) prehypertension and hypertension, left untreated, accelerate the rate of vascular aging by more than 15 years and (3) large artery stiffness rather than vascular resistance becomes the dominant hemodynamic factor in both normotensive and hypertensive subjects from age 50 onward.

PP as an independent risk factor

In middle-aged and older individuals with ISH, PP has been shown to be superior to SBP as an independent risk factor for predicting CV events. Indeed, ISH with increased PP has been associated with a variety of CV events.[5] Cardiac complications consist of left ventricular hypertrophy, atrial fibrillation, systolic and diastolic dysfunction, and heart failure. Large artery complications consist of myocardial infarction and both hemorrhagic and thrombotic stroke. Microvascular complications consist of white matter lesions, leading to cognitive impairment, and progressive chronic renal disease, frequently resulting in end-stage renal disease.

DBP as a J-curve risk factor

Because of nonlinearity, CV risk increases at both low and high extremes of DBP, when combined with increased SBP in a 2-compartment model.[10] At present, there are 3 postulated mechanisms for the J-curve of increased CV risk at the lower range of DBP. (1) Low DBP is an epiphenomenon resulting from increased arterial stiffness, but it is the latter that is the independent CV risk factor. (2) Low DBP, usually <70 mmHg, may be associated with myocardial ischemia secondary to compromised coronary blood flow during shortened diastole. Furthermore, reflected waves normally return during early diastole and thereby enhance coronary perfusion; this increased boost is absent in elderly persons with ISH. (3) *Coupling disease*,[11] resulting from stiffness of both the heart and arteries, often accompanied by left ventricular hypertrophy, interacts to produce diastolic dysfunction and heart failure; this results from the combination of an elevated cardiac afterload presented to a compromised left ventricle, which is unable to handle the load. The J-curve of increase in CV events has occurred both with and without antihypertensive therapy. Indeed, any one or combination of the 3 above postulated mechanisms, with or without antihypertensive therapy, may explain why a low DBP in combination with an elevated SBP is associated with increased CV risk.

Diagnostic value of BP components

Previous predictor of CVD risk examined a limited spectrum of the overall hypertensive population. The results of a recent Framingham Heart Study[10] confirm the importance of combining BP components, such as SBP and DBP or PP and MAP, to improve stratification of CVD risk. Indeed, when PP, a measurement of stiffness, was combined with MAP, a measurement of resistance, one could relate the 2 major physiologic components of hydraulic load to clinical outcome; single BP components cannot do this. These results have a bearing on the current US guidelines[12] that use both SBP and DBP, whichever is higher, for determining BP stage. While these guidelines take into account the importance of increased vascular resistance, they undervalue the importance of increased arterial stiffness (i.e., increased PP and low DBP), which is common in older persons, especially those with prehypertension and ISH with DBP <70 mmHg.[10]

Varied etiologies

As suggested by their age-dependent divergent patterns of onset, diastolic hypertension (essential or primary hypertension) and ISH may be two distinct disorders with significant overlap. The conversion from diastolic–systolic hypertension to ISH in the older age group has been attributed to "burned-out" diastolic hypertension. While some people who have had untreated or poorly treated diastolic hypertension at a younger age develop ISH as they become older, data from the Framingham Heart Study suggest that only about 4 out of 10 patients acquire ISH in this manner.[9] In contrast, 6 out of 10 people who develop ISH may show a slight rise in DBP over time, but do not go through a stage of diastolic hypertension. This de novo form of ISH may have many different causes that can be divided into at least 2 main categories: (1) impaired synthesis of elastin protein—abnormal elastic content of conduit arteries can result for intrauterine fetal growth retardation,[13] successfully repaired coarctation of the aorta[14] and perhaps from genetic predisposition to reduced aortic root diameter[15] and (2) increased aortic calcification. There appear to be many conditions where calcium is deposited abnormally in elastic containing conduit arteries in association with the development of ISH: (a) Type 1 diabetes,[16] (b) chronic kidney disease,[17] (c) osteoporosis[18,19] and (d) advanced aging.[20] McEniery et al.[20] have shown that aortic calcification, as measured by quantitative high-resolution CT imaging at the ascending, descending and abdominal aorta, correlated with aortic stiffness, as measured by carotid-to-femoral PWV (after correcting for age and MAP) in patients with ISH who are otherwise apparently healthy. In contrast, there was no association between aortic calcification and carotid-to-brachial pulse wave velocity or the augmentation index, suggesting that aortic calcification was not associated with more peripheral small vessel disease or with altered wave reflection. Furthermore, the magnitude of aortic calcification correlated with the severity of ISH and to the resistance of SBP control with antihypertensive therapy, after adjusting for potential confounding influences.[20]

Conflicts of interest

The author declares no conflicts of interest.

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