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Editorial

When Diastole Lets You Down: Clinical Relevance of a Widened Pulse Pressure

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See article by de Faria et al., pages 747–755 of this issue.

Pulse pressure (PP) is a piece of useful clinical information that every patient presents to you at each visit. It is like the unrequested chips and salsa that appear when you sit down at a Mexican restaurant. Do you pay any attention to it? The purpose of this editorial is to remind you that you should. PP is a measure of vascular health. It has prognostic significance for a wide range of important outcomes, and, in some instances, it may influence treatment decisions, as suggested by the report by de Faria et al. from the GLOBAL LEADERS trial in this issue.[1]

Pathophysiologic Consequences of an Increased Pulse Pressure

The arterial pressure waveform consists of a forward pressure wave during systole caused by ejection of blood into the aorta and a reflected wave backward toward the aortic arch from high-resistance arterioles, branch points, and other regions.[2] The pulse-wave velocity (PWV) is dictated by the relative stiffness, or elasticity, of the arteries. Normally, the PWV is relatively slow because compliant central arteries are able to distend during ventricular ejection, with the reflected wave arriving during diastole. However, in stiff arteries, the PWV is increased, so the reflected wave arrives during late systole, increasing afterload and thus cardiac work and systolic blood pressure (SBP). In addition, diastolic blood pressure (DBP) falls because the reflected wave is no longer present to support it.

The ratio of elastin, which is compliant, to the relatively stiffer collagen is a major determinant of vascular compliance. With aging and inflammation, the cross-linking elastin molecules are disrupted and fractured, become calcified, and are replaced by collagen. Aging and diabetes cause the accrual of advanced glycation end (AGE) products, which bind to elastin and degrade the vessel wall's elastic matrix. The increased mechanical stress induced by the pulsatile blood flow, along with the AGE products, promotes local inflammation and increases the release of inflammatory markers and cytokines, which increase vascular tone and prevent nitric-oxide–induced vasodilation. This contributes to formation of plaque, fibrosis, and calcification, which, in turn, decrease the diameter of the vessels, further reducing the ability of arteries to distend, therefore accentuating a vicious cycle. Diabetes accelerates atherogenesis through AGE products and chronic kidney disease (CKD) increases vascular calcification.

The stiffening vascular tree dramatically affects the rest of the body. An increase in PP to smaller peripheral arteries causes an uneven blood supply to target organs. Higher PP also increases mechanical stress on atherosclerotic plaques, potentially leading to plaque instability, rupture, and thus cardiovascular (CV) events.[3] Coronary arteries fill during diastole and may be hypoperfused because of the lower DBP, potentially leading to subendocardial ischemia. An increase in afterload leads to left-ventricular hypertrophy, risking heart failure (HF) and ischemic injury via myocardial supply–demand mismatch.[4]

Increased Pulse Pressure and Adverse Outcomes

Hypertension itself is associated with stroke and other adverse outcomes, so it can be difficult to assess the contribution of PP to these complications. In addition, other prognostic factors, such as advanced age and diabetes, are associated with widened PP. Nevertheless, widened PP has been linked to an impressive list of poor outcomes, as described below.

Widened PP has been demonstrated to increase risk of major adverse cardiac events (MACE) in different populations.[1,5,6] In patients with treated hypertension but without previous atherothrombotic events, high PP was an independent predictor of MACE.[5] In a registry of patients with risk factors or known cardiovascular (CV) disease, increased PP was associated with an increase in myocardial infarction and CV hospitalizations after adjustments but not

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with stroke or CV death.[6] In the GLOBAL LEADERS trial, patients with elevated PP following coronary intervention had higher rates of MACE regardless of antiplatelet treatment.[1] Peripheral arterial disease has also been linked to a widened PP.[7]

A widened PP is also associated with the development of HF. In a study of elderly subjects without HF at baseline, every 10-mm Hg rise in PP was associated with an adjusted 17% increase in incidence of HF and a 75% increase in risk in the highest compared with the lowest tertile.[8] In a study of patients hospitalized with HF, a U-shaped pattern for mortality was observed, with increased mortality at both low and high PP and best outcomes at a PP of 50 mm Hg.[9]

A widened PP may also contribute to dementia, including Alzheimer disease.[10-12] Subjects from the Framingham Study with no histories of stroke underwent neuropsychological testing at intervals, and those with higher PPs had greater declines in measurements of executive function.[10] Magnetic resonance imaging (MRI) evaluations of these patients showed that widened PP was associated with smaller cerebral volumes and hippocampal atrophy. Another study revealed that high PP in cognitively normal subjects 75 years or older is associated with development of Alzheimer disease.[11] Finally, dementia-free patients aged 55 to 65 years with elevated PP were more likely to have β-amyloid and phosphorylated τ proteins, known contributors to Alzheimer pathophysiology, in cerebrospinal fluid.[12]

Diabetes has been shown to contribute to widened PP, but, intriguingly, the reverse association is also true, with high PP linked to onset of diabetes. In a trial of high-risk Japanese hypertensive patients without diabetes randomized to candesartan or amlodipine and monitored for new-onset diabetes,[13] both elevated PP and low DBP were independent predictors of new-onset diabetes, whereas increased SBP was not. A stratification of new-onset diabetes per PP quartile revealed that candesartan-based regimens, when compared with amlodipine regimens, prevented new-onset diabetes but only at the highest PP quartile. This suggests not only that arterial stiffness contributes to the development of diabetes but that certain medications that decrease PP can be deployed to prevent the onset of diabetes. Another study revealed that PP is an independent risk factor for proteinuria in patients with diabetes, even with adjustments for SBP and DBP.[14]

Widened PP is also associated with worsening kidney disease. In an observational study of patients with CKD stages 2 to 4, an elevated baseline PP or SBP were correlated with declining glomerular filtration rate, whereas elevated DBP was not.[15]

Given the strong evidence for PP as an independent risk factor for both CV and non-CV disorders, it is not surprising that PP is a risk factor for mortality. In a meta-analysis of 14 studies involving 510,456 participants, increased PP was associated with an increased CV and overall mortality: specifically, pooled risk ratio of CV and all-cause mortality per 10 mm Hg PP increment was 1.13 (95% confidence interval [CI], 1.10-1.17) and 1.09 (95% CI, 1.07-1.11), respectively.[16] In a study of chronic hemodialysis patients, widened PP was an independent predictor of total mortality and was a superior predictor to SBP and DBP.[17]

Pulse Pressure in the GLOBAL LEADERS Study

The GLOBAL LEADERS trial compared 2-year ticagrelor monotherapy to standard 1-year dual antiplatelet therapy (DAPT) in patients who had undergone percutaneous intervention.[1] No significant differences were seen for the primary endpoint, all-cause death or Q-wave myocardial infarction, or for bleeding. When divided into high and low-PP groups, however, the low PP group had decreased rates of the primary endpoint compared with the high-PP group. Importantly, patients in the low-PP ticagrelor group had lower risks of the primary endpoint and of bleeding compared with DAPT. The high-PP group did not benefit from ticagrelor, either for the primary endpoint or for bleeding.

The authors of this study speculate that the pleiotropic effects of ticagrelor specifically increases in adenosine levels and endothelial progenitor cells and decreases in inflammatory cytokines, improve endothelial homeostasis in those with better endothelial function, as evidenced by a narrower PP, but not in those with wider PP.[1] This explanation seems reasonable but raises a broader question: Are there other clinical circumstances in which PP might influence treatment decisions?

When Pulse Pressure Might Influence Treatment

One would think that a higher PP would be associated with an increased risk of hemorrhage in patients receiving anticoagulants; however, there is little evidence in the literature to support this notion. In a recent clinical trial comparing the factor Xa inhibitor edoxaban with warfarin, high SBP and low DBP were both associated with an increased risk of bleeding, although the association with PP was not directly reported.[18]

A wide PP should influence treatment targets in hypertension. In the **S**ystolic Blood **Pr**essure **In**tervention **T**rial (SPRINT), in which a target SBP of <120 mm Hg improved CV outcomes compared with a goal of <140 mm Hg, patients with wide PP in the aggressive treatment arm suffered more serious adverse events than did those in the standard treatment arm.[19] These potential harms must be balanced against the potential benefits of treatment. In the **S**ystolic **H**ypertension in the **E**lderly **P**rogram (SHEP) trial of treatment for isolated systolic hypertension, in which PP is invariably wide, on-treatment DBP < 70 mm Hg was associated with increased CV risk with active treatment but not placebo.[20] Data from another large trial suggest that the increased event rate with an on-treatment DBP < 70 mm Hg is limited to subjects with concomitant CHD.[21] Hypertension should certainly be treated in patients with wide PP; however, these studies suggest possible danger from overtreatment.

Should a Widened Pulse Pressure Be a Treatment Target?

If a widened PP is not just a marker of increased risk but an actual cause, should we develop specific therapies to narrow PP? Treating isolated systolic hypertension usually narrows PP and has been shown to reduce CV events in multiple studies.

Nitrates reduce vascular smooth muscle tone, increase distensibility of the central arteries, and thus delay the wave reflection, lowering SBP while leaving DBP unchanged. These

BP changes were demonstrated in a small study of elderly patients with isolated systolic hypertension who were randomized to isosorbide dinitrate or placebo.[22] In clinical practice, nitrates would not be suitable for this purpose because of frequent side effects and the development of nitrate tolerance.

Preventing the development of a widened PP by preserving endothelial health through the lifelong control of CV risk factors is likely to be the best strategy. Perhaps as we munch on the chips and salsa, we should scrutinize the menu for healthy choices for our vasculature.

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