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Assessing Wide Pulse Pressure Hypertension:

Data Beyond the Guidelines*

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Aging changes vascular stiffness depending on one's genetic predisposition as well as the quality of blood pressure, cholesterol, and glucose management over the lifespan. Moreover, sodium intake over time markedly affects these changes, with very low sodium intake over a lifetime preventing hypertension (1). In Western population-based longitudinal studies, concomitant increases in systolic and diastolic blood pressure occur until ages 50 to 55 years.

Subsequently, systolic and diastolic blood pressures diverge, with systolic continuing to rise and diastolic stabilizing and then decreasing (2). These changes result in increased pulse pressure and ultimately isolated systolic hypertension. Although the precise pathophysiological mechanisms for the development of isolated systolic hypertension are not fully known, evidence suggests a combination of factors including elastin thinning, degradation, and replacement by collagen within the arterial wall, as well as medial calcification within larger arteries are contributory. These processes lead to increases in large artery stiffness and are accelerated by risk factors such as impaired glucose tolerance and renal insufficiency (3).

These changes in vasculature composition may contribute to changes in cardiovascular hemodynamics and are associated with increased left ventricular wall stress, myocardial oxygen consumption, and subsequent left ventricular hypertrophy (4). Very low diastolic

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pressures can limit coronary perfusion, resulting in ischemia, and widened pulse pressure is associated with worse cardiovascular outcomes as noted in the Framingham Heart Study, where every 10-mm Hg increase in pulse pressure was associated with a 23% increased risk of coronary artery disease (5). Additionally, in the SHEP (Systolic Hypertension in the Elderly Program) trial, every 10-mm Hg increase in pulse pressure in the active treatment group increased risk for heart failure by 32% and stroke risk by 24% (6). However, the incidence of coronary heart disease was not associated with pulse pressure in either the control or treatment groups in this trial.

In this issue of the *Journal*, using a prospectively collected registry, Warren et al. (7) retrospectively sought to determine if pre-procedural pulse pressure in patients undergoing percutaneous coronary intervention affected the incidence of short- and long-term adverse cardiovascular events, as well as mortality. The authors demonstrated that the presence of a wide pulse pressure should be considered an additional risk marker for subsequent cardiovascular disease in patients with existing coronary artery disease. Moreover, they demonstrated that individuals with narrow pulse pressure have significantly lower long-term mortality.

The authors are to be commended for using their large dataset of >10,000 patients to study this clinically underappreciated issue. They chose to divide the patient population into 4 groups based on different combinations of 2 factors: a systolic blood pressure above or below 120 mm Hg, and a diastolic blood pressure above or below 70 mm Hg. They termed these groupings high systolic, high diastolic blood pressure (HSHD); low systolic, low diastolic blood pressure (LSLD); high systolic, low diastolic blood pressure (HSLD) (wide pulse pressure); and low systolic, high diastolic blood pressure (LSHD) (narrow pulse pressure). Not surprisingly, patients in the HSLD grouping displayed characteristics that have previously been highly associated with increased pulse pressure, such as female sex, older age, and a greater prevalence of cardiovascular risk factors such as diabetes mellitus (8,9). In contrast, patients in the LSHD grouping were younger with less comorbid diagnoses.

These groups were then compared for 30-day and 12-month cardiovascular outcomes, and long-term mortality of a certain subset of patients whose records could be linked to a national death index. Although there was no difference in 30-day adverse cardiovascular outcomes between groups, there were differences in 12-month outcomes. Specifically, patients with HSLD demonstrated a higher incidence of myocardial infarction (5.9% vs. 4.7% in LSLD, 4.9% in HSHD, and 2.9% in LSHD; $p = 0.018$) and stroke (1.2%; $p = 0.013$).

The long-term follow-up of this cohort showed higher mortality in the wide pulse pressure group, and second highest mortality in the LSLD (where the mean pulse pressure was 45 mm Hg). Additionally, LSHD predicted the lowest risk of death. These findings are consistent with prior studies demonstrating a diastolic “J-curve” and worse cardiovascular outcomes with diastolic blood pressures <70 mm Hg in people with pre-existing heart disease (10,11).

The most contemporary attempt to address whether low diastolic pressure increases cardiovascular risk comes from a secondary analysis of the SPRINT (Systolic Blood Pressure Intervention Trial). This post hoc analysis demonstrated that all participants with a diastolic pressure <55 mm Hg had increased risk of cardiovascular events irrespective of coronary artery disease presence (12). Furthermore, a report from the CLARIFY registry of hypertensive patients with stable coronary artery disease found that a diastolic pressure <70 mm Hg was associated with high cardiovascular mortality (13).

The study by Warren et al. (7) is not without limitations. Pre-procedural blood pressures from a registry were used that were not obtained in the standardized fashion typical of hypertension trial protocols. Additionally, we increasingly recognize the role of white-coat and masked hypertension on cardiovascular outcomes, and registry-based studies using only office-based blood pressures cannot differentiate between individuals with truly sustained hypertension, sustained normotension, and white-coat or masked hypertension. Moreover, the method of measuring blood pressure may not be standardized.

The totality of the data coupled with findings by Warren et al. (7) suggest that a “J-curve” exists, especially in people with increased vascular stiffness and coronary disease, and the nadir for diastolic BP is somewhere between 55 and 70 mm Hg. Given these findings, the authors suggest that targeting a reduction in large artery stiffness may hold promise as a future therapy in patients with wide pulse pressures. Such a study was already attempted with a novel compound with no success (14). An alternative thought, however, would be to focus on identification of risk predictors of vascular stiffness and its prevention. Additionally, can we identify genotypic and phenotypic factors among patients with narrow pulse pressures that are protective or associated with less vascular stiffness? This is especially thought-provoking, because data suggest that pulse pressure may in fact be a heritable trait (15).

Findings regarding low diastolic pressure and cardiovascular risk must be put into clinical context. The sum of data suggests that we must not indiscriminately implement updated blood pressure guidelines that call for a more aggressive lowering of systolic blood pressure, particularly among those at highest cardiovascular risk. The most recent 2017 American blood pressure guidelines do not discuss the role of pulse pressure or low diastolic blood pressures when treating to the more stringent blood pressure goals (16). New guideline recommendations for lower blood pressure targets were driven predominantly by the results of SPRINT. SPRINT enrolled a relatively robust population with an average systolic blood pressure of 139 mm Hg, which is almost the same as the 138 mm Hg of the HSLD group in the study by Warren et al. (7); however, the average diastolic blood pressure in the SPRINT trial was 78 mm Hg, compared with 62 mm Hg in the HSLD group in the study by Warren et al. (7). These are 2 physiologically different groups of patients. There are multiple pharmacotherapies at our disposal to lower the systolic blood pressure, but in patients with such wide pulse pressures, we risk lowering the diastolic blood pressure excessively and inadvertently increasing coronary risk due to diastolic hypotension. How wide pulse pressure in older people can be incorporated succinctly into future cardiovascular risk calculators is yet to be determined (17). Therefore, clinical judgment must play a central role in physician decisions regarding the targeting of systolic in the context of diastolic blood

pressures. Lower systolic blood pressure targets (that are beginning to be thrust upon the clinicians under the guise of meeting “quality metrics”) must not blind us to a full and thorough evaluation of the individual patient, who may or may not be represented by evidence that drives clinical guidelines.

In contrast to the contemporary American blood pressure guidelines, the 2018 European blood pressure guidelines provide an expansive discussion of pulse pressure as a risk marker, affirming that a pulse pressure >60 mm Hg in hypertensive older persons increases cardiovascular risk. These guidelines also state that pulse pressure may be considered, and provide useful information in some circumstances (along with blood pressure variability, exercise blood pressure, and central blood pressure), but are not often used in routine clinical practice presently. This guideline was graded Class IIb, with a Level of Evidence: C (18).

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