Diastolic and Pulse Pressure: The Old and the New?

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The human aorta plays a major role in determining cardiac afterload and arterial hemodynamics. Therefore, alterations in aortic wall composition are likely to produce important circulatory changes. Aortic wall calcification, a common feature of the atherosclerotic process, is associated with reduced arterial distensibility (or increased arterial stiffness), higher systolic blood pressure, and lower diastolic blood pressure, hence an increase in pulse pressure. These hemodynamic changes impose a burden on the cardiovascular system: an increase in systolic blood pressure further increases cardiac afterload and promotes left ventricular hypertrophy whereas a reduction in diastolic blood pressure may critically reduce coronary perfusion, thus triggering ischemia.

Until recent years, the imaging of the aorta in atherosclerosis has received little attention if compared with the coronary and carotid arterial beds. Nevertheless, the burden of atherosclerosis in the aorta correlates well with the degree of atherosclerosis in other vascular beds. Moreover, aortic calcification is a strong and independent predictor of cardiovascular morbidity and mortality. This should prompt studies aimed at identifying the factors responsible for the presence and progression of aortic calcification to understand the underlying pathophysiological mechanisms and identify preventive pharmacological and non-pharmacological strategies. The data published so far have demonstrated a positive relationship between systolic blood pressure, and perhaps pulse pressure, and the presence of aortic calcification. However, the frequent coexistence of complex metabolic conditions, such as end-stage kidney failure, diabetes, and hyperlipidemia, potentially confounding this relationship, the relative small sample size, the lack of serial assessment of aortic calcification progression, and the retrospective or cross-sectional nature of some of these studies curtail data interpretation.

In this issue of Hypertension, Miwa et al present the results of a study started in 1988 involving 116 Japanese subjects with controlled hyperlipidemia and hypertension undergoing 6 monthly computed tomography examinations of the abdominal aorta for more than 6 years, on average. The percentage of calcified areas against the whole wall area was calculated from images of four consecutive slices above the iliac bifurcation using dedicated software. In a univariate analysis, age, baseline body mass index, systolic blood pressure, and pulse pressure were positively and significantly related with the yearly increase in aortic calcification. However, in a multiple regression analysis including age, gender, body mass index, lipid profile, history of smoking, antihypertensive treatment, and follow-up period, pulse pressure was found to be the most powerful predictor of aortic calcification progression whereas diastolic and mean blood pressure failed to show any significant relationship. Trivial increases in aortic calcification were observed in subjects with pulse pressure less than 50 mm Hg, whereas increases between 0.5% and 1.0% per year occurred in patients with higher pulse pressure values.

This enlightening article contains several features worthy of discussion. To start with, this is the first study to prospectively assess the role of different blood pressure components on the progression of aortic wall calcification, an established marker of atherosclerosis, over a reasonable period of time. It is must be emphasized that the project was started in the late 1980s, when physicians were focused on achieving satisfactory diastolic blood pressure values as the main target for the treatment for their hypertensive patients. A clear merit of the investigators was to foresee the emerging role of systolic and pulse pressure in cardiovascular risk stratification, which started to come to light some years later, when designing their trial. Another important element that facilitates data interpretation was the pharmacological treatment of hypercholesterolemia and hypertriglyceridemia with regular follow-up visits to ensure satisfactory lipid and blood pressure control. This strategy minimized the confounding effect of these factors on the progression of aortic calcification. However, in my opinion, the major achievement of this study, unlike many other prospective trials, was to demonstrate a nearly linear progression of aortic calcification over 5 years in a subgroup of subjects. This enabled the investigators to consider the yearly changes in percent calcified volume as a reliable marker of calcification progression, thus strengthening its statistical power in the regression model.

These data, although providing new information on an important topic, must be interpreted with caution for various reasons. Firstly, the drugs used for the treatment of dyslipidemia and hypertension might have affected, to some extent, the progression of aortic wall calcification. A number of studies in animals and humans have demonstrated that hydroxymethylglutaryl CoA reductase inhibitors and probucol possess significant antiinflammatory and antioxidant effects, in addition to their cholesterol-lowering effects. Similar antioxidant effects have been observed with angiotensin-converting enzyme inhibitors and calcium channel blockers.
of the dihydropyridine type.\textsuperscript{10,11} The absence of a significant treatment effect on the progression of aortic calcification in the study by Miwa et al could be merely secondary to a sample size effect, because this was not the primary endpoint. Secondly, the study relies on serial blood pressure readings obtained in the office with a sphygmomanometer. Quantification of the overall blood pressure loading by using ambulatory blood pressure monitoring would have provided more robust data to enter into the regression model. The authors can be easily forgiven for this pitfall, though. Again, the study was conceived during a time when the physiological, clinical, and prognostic significance of ambulatory blood pressure monitoring was far from being established. Thirdly and more importantly, the study was conducted in a single-racial group of people with a relatively low cardiovascular risk, ie, Japanese subjects with no previous cardiovascular events or diabetes, controlled hyperlipidemia, and with satisfactory blood pressure on study entry (132/77 mm Hg, on average). Whether these findings can be extrapolated to populations with different dietary lifestyles, anthropometric characteristics, genetic make-up, and cardiovascular risk factors remains to be demonstrated.

Cardiovascular scientists with an interest in this area are likely to face a tough job in the years to come. A number of novel and potential biomarkers of cardiovascular risk have been recently identified [homocysteine, C-reactive protein, Lp(a) lipoprotein, P-selectin, interleukin-6, tumor necrosis factor-\alpha, and soluble intercellular adhesion molecule-1, to cite a few]. Most of these substances exert strong inflammatory effects, thus facilitating the onset and progression of atherosclerosis, and are likely to further confound the relationship between traditional hemodynamic, biochemical, genetic, and environmental factors and arterial wall calcification. Although some of these markers might just represent an epiphenomenon rather than true atherosclerosis promoters, larger prospective studies will be required to gain enough statistical power and to better-understand the mechanisms underlying the progression of atherosclerosis in humans.

Notwithstanding these issues, the study by Miwa et al provides important and timely pathophysiological back-up to the recent observations clearly demonstrating the stronger role of systolic and pulse pressure, compared with diastolic and mean pressure, in predicting cardiovascular outcome in populations with different cardiovascular risk. Should we start to introduce pulse pressure as a meaningful and reliable tool for cardiovascular risk stratification in tables, equations, and software programs when managing our hypertensive patients? There is still a long way to go to solve this conundrum, perhaps; but the signs are there.

References

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