B-Type Natriuretic Peptide and Artery Stiffness

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Arteries stiffen with age, largely as a consequence of structural alteration of the collagen and elastin content of the artery wall. Circulating B-type natriuretic peptide (BNP), secreted predominantly from the heart, also increases with age, probably as a consequence of left ventricular wall stress induced by a rise in impedance to ejection or structural changes in the myocardium including age-related loss of myocytes. It is not surprising, therefore, that arterial stiffness and BNP are correlated. Indeed the very low correlation coefficient \( r = 0.12 \), \( r^2 = 0.014 \) suggests that the measurements are mechanistically related to a minimal extent at most.

The methods used in this study require further analysis. Artery stiffness can refer to any segment of the arterial tree from the root of the aorta to the capillary beds. The arterial system is obviously complex, with multiple parallel channels; and the stiffening that may occur has quite distinct causes in different segments. In the aorta and large conduit arteries, in which pulse-wave velocity is measured, the main cause of stiffening is a structural change related to fragmentation of elastin, which is very compliant, and to growth of collagen, which is stiff. These changes are related to the aging process. The large arteries are not very responsive to vasoactive substances secreted by the endothelium. In contrast, the small arteries that characterize branch points and the precapillary microcirculation are particularly sensitive to nitric oxide secreted from the endothelium. Stiffening of these vessels is characteristic of endothelial dysfunction that eventually will facilitate structural changes in the small arteries as well as the large conduit arteries. The pulsewave velocity studies reported by Yambe et al \(^1\) were derived by an unusual method of identifying the difference between aortic-to-femoral and aortic-to-brachial time delays. These velocities nonetheless define a stiffness parameter limited to the proximal conduit arteries.

The BNP levels in blood can be assessed by a number of methods. The Shionogi assay and the BNP point-of-care assay are the most widely used. It has been traditional to use cut-off points for BNP, with levels <50 pg/mL reported as normal and those >50, but especially those >100 pg/mL, reported as abnormal. It is important to keep in mind that values for the Shionogi assay are generally as much as 30% lower than values from the Biosite Triage assay. In addition, BNP values are influenced not only by age but also by factors such as gender, renal function, and body mass index. How these cofounders relate to the known ventricular wall–stress mechanism of BNP release remains conjectural.

These considerations make understandable both the significance and the weakness of the statistical relationship between large artery stiffness and BNP release; but the data also should stimulate more intense consideration of vascular–cardiac interactions. Are these two measurements correlated physiologically because artery stiffening increases left ventricular work and raises wall stress and myocardial mass? Or do the data suggest that structural change in the arteries and heart occur concordantly, perhaps as a consequence of systemic determinants of the aging process? Although the authors report that correcting for chronological age did not abolish the statistical relationships between the two variables, it is well known that biological and chronological age are imperfectly related. Even more challenging is to consider the prognostic value of these two measurements of cardiovascular health. Large artery stiffness as a marker for the severity of the aging and atherosclerotic processes is correlated with morbidity and mortality risk. \(^2\) Similarly recent data suggest that BNP levels, even within the so-called normal range, are powerful determinants of cardiovascular morbidity and mortality. \(^3\) Does the remarkable predictive value of these two measurements suggest that both are markers for advancing disease in asymptomatic individuals? Or that both are merely correlated with the aging process, which is certainly a powerful determinant of how long we live? Or that these two measurements are mechanistically related and somehow detectors of a pathologic process of unknown origin? It also should be apparent that even if these...
markers have prognostic value they are probably late manifestations of a disease process that began much earlier with endothelial dysfunction and that could have been identified and treated long before irreversible structural changes led to stiffening of the large arteries and secretion of excess BNP.

There is also some room for a touch of cynicism in this analysis. The more measurements we evaluate the more we find that they correlate with outcome. Blood pressure, cholesterol, C-reactive protein, blood sugar, plasma renin activity, plasma norepinephrine, hemoglobin, and now BNP are just some of the markers that appear to be linearly related to life expectancy. Are these mechanistically related or epiphenomena? Do they provide some insight into human disease or are they mere markers—such as age, which always emerges as a powerful determinant—of our limited time left on earth?

References