Perioperative Blood Pressure Management: Does Central Vascular Stiffness Matter?

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Two studies[1,2] in this issue of the journal are important because they shed light on the prognostic and possible therapeutic implications of age-related changes in the cardiovascular system. The multicenter study by Fontes et al.[1] describes the relationship between pulse-pressure and postoperative neurological and cardiac complications in patients undergoing coronary artery bypass graft (CABG) surgery. Aronson et al.[2] report on the multicenter "ECLIPSE" trial that was designed to assess the safety of the short-acting calcium antagonist, clevidipine, in controlling perioperative arterial blood pressure in patients undergoing cardiac surgery. Its implications, however, may extend beyond that of the safety of clevidipine. To understand the potential implications of these two studies requires an understanding of age-related vascular properties, the potential discord between chronological and vascular age and the potential mechanisms underlying cardiovascular complications, and morbidity and mortality in the aging vasculature. Furthermore, an understanding of the utility of predictors of cardiovascular events in the nonsurgical and surgical populations, and an appreciation of the concept that similar management approaches to patients with disparate vascular pathophysiologies may have implications that are currently under-recognized.

In 1898 William Osler wrote that "Man is as old as his arteries." Interestingly, this observation antedated the still increasing epidemic of cardiovascular disease in Western culture. Although much of this increase is attributable to lifestyle and risk factor-associated variables, the simple or not so simple matter of just living longer is itself associated with cardiovascular changes that confer risk. Although age, *per se*, has long been recognized as a powerful predictor of cardiovascular events, including those occurring perioperatively, the accrual of age-associated cardiovascular changes is highly variable. Thus, researchers have long attempted to identify markers of vascular health which might have the capacity to identify individuals of similar chronological age but different likelihood of future cardiovascular events.[3,4] In effect, one is attempting to differentiate vascular age from chronological age.

Arterial blood pressure is the most commonly measured index of vascular health. However, it is a somewhat insensitive index, a fact that also has long been recognized. Jarish in 1928, lamented that "The development of our knowledge of the circulation has been bedeviled by the fact that the measurement of blood flow is so complicated, whereas that of blood pressure is so easy: hence the blood pressure manometer has exerted an almost hypnotic influence, though bodily organs don't need pressure but flow." Regional blood flow measurements fall well outside the scope of routine clinical practice. Moreover, techniques that evaluate vascular structure (for example, stenosis assessed with angiography or by Doppler, intimal medial thickness) generally imply advanced disease. Thus, investigators have focused on indices of vascular function in efforts to detect disease in its earlier stages. Such indices include the reactive hyperemic response assessing endothelial function, microalbuminuria, and vascular stiffness.

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The mechanisms underlying vascular stiffness development are multifactorial, complex, and incompletely understood. They include changes not only in structural elements of the vessel wall (for example, quality and quantity of collagen, irreversible glycation of proteins, and formation of advanced glycation end-products), but also changes in functional properties. Stiff vessels transmit pulse waves (generated by distension of the ascending aorta during ejection of blood by the left ventricle) with increasing velocity compared with compliant or nonstiff, vessels. Pulse waves transmitted toward the periphery are reflected back to the central circulation at points of functional or anatomical discontinuity as occurs at branch points or points with abrupt changes in vessel diameter. In a compliant vasculature, the reflected waves return to the central circulation following aortic valve closure augmenting diastolic perfusion to the heart. In contrast, in a stiff vasculature, the higher velocity of both the antegrade and reflected pulse waves results in the latter returning to the central circulation during systole, augmenting systolic pressure, decreasing diastolic pressure, and increasing systolic loading conditions for the left ventricle. Hence, the basis of the two most widely used techniques to access central vascular stiffness, that is, the measurement of pulse wave velocity (PWV) and the measurement of the augmented central systolic pressure [the latter calculated as the augmentation index (AI) and obtained using application tonometry].[5,6] In the absence of PWV or AI measurements, pulse pressure and systolic blood pressure (both increased in a stiff vasculature) have been used as surrogates of vascular stiffness. In the setting of a stiff vasculature, myocardial changes develop not only because of altered vascular-ventricular coupling, but also because mechanisms underlying vascular stiffness changes affect the myocardium.[7] The overall result is that intrinsic myocardial systolic and diastolic stiffness properties are increased. This, in addition to increased loading conditions and compromised coronary blood flow secondary to decreased diastolic blood pressure, contributes to the increased cardiac mortality and morbidity in populations with increased vascular stiffness. In addition, increased vascular stiffness compromises flow to other vital organs (for example, the brain and kidney)[8] due at least, in part, to disturbances in autoregulation.

It is now well established in the general medicine population[9–11] that indices of vascular stiffness (PWV, AI, pulse pressure, systolic blood pressure) confer additional, independent value in predicting cardiovascular morbidity and mortality over and above that provided by established risk factors, including age. For example, The Health ABC,[12] Rotterdam,[13] and Monica[14] studies all used PWV to access vascular health, whereas the Dublin Outcome Study[15] used a derived index (the Ambulatory Arterial Stiffness Index). All these studies were prospective, had large numbers of subjects, including those without clinical disease at enrollment, and had commendable follow-up periods (for example, Rotterdam Study 4.1 yrs, Monica Study 10 yrs). Moreover, although the Health ABC and the Rotterdam studies investigated older subjects, the Dublin Outcome and Monica studies included subjects who were distinctly middle-aged. All these studies stratified their subjects using an index of vascular stiffness/health (for example, quartiles of PWV) and all demonstrated that increased vascular stiffness was independently predictive of adverse cardiovascular outcomes (death, myocardial infarction, stroke, congestive heart failure, sudden death). Moreover, in multivariable analyses incorporating established cardiovascular risk factors, including chronological age, vascular stiffness indices retained their significant predictive value.

The study by Fontes et al.[1] in this issue of the journal, in addition to two other recent studies, indicate that this paradigm may also be applicable to cardiac surgical outcomes. Fontes et al. conducted a prospective observational study investigating the relationship between pulse pressure and both cerebral/neurological and cardiac outcomes in patients undergoing cardiac surgery. They demonstrated that increased pulse pressure was independently associated with an increased incidence of postoperative neurological complications and cardiac failure. This work is an extension of previous work by the same group who demonstrated a relationship between pulse-pressure and adverse renal outcomes.[16] It also corroborates results of the study by Benjo et al.,[17] who demonstrated that pulse pressure was an independent predictor of stroke development after cardiac surgery. Although there were differences between the two studies (multicenter versus one center, CABG only versus CABG plus valve surgery, prospective versus retrospective, neurological complications encompassing those beyond focal deficits versus focal deficits only), some of the similarities in the neurological results of these two studies are striking. Both identified similar pulse-pressures (80 and 72 mm Hg) as cut-off values above which complications were significantly increased. Moreover, in multivariate models, both Fontes et al. and Benjo et al. demonstrated that pulse-pressure was an age-independent predictor of adverse neurological outcomes. Regarding the cardiac results of Fontes et al., pulse-pressure did not retain its predictive value in their multivariate model, but a pulse-pressure of more than 80 mm Hg was associated with an increased incidence of heart failure and death from cardiac causes.

The mechanisms underlying the evolution of complications in patients with increased vascular stiffness are incompletely understood. Stiff vessels have altered vascular smooth muscle cell phenotypes with arterial remodeling of the blood vessels in vital organs. Importantly, the influence of vessel stiffness on organ autoregulation is unknown. It is entirely possible,

perhaps even likely, that the autoregulatory range is distinctly different across individuals with different vascular properties and with different types of superimposed surgery and anesthesia. An altered autoregulatory range might lead to organ hypoperfusion in some individuals despite what might be deemed to be a "clinically acceptable" blood pressure. Aronson et al.'s[2] study may be important in this latter regard. They demonstrated the safety of clevidipine by recording the frequency with which systolic blood pressure did or did not remain within a predefined desirable range, and examined the clinical outcomes by comparison with the established drugs, sodium nitroprusside, nitroglycerin, and nicardipine. Although their results demonstrated the safety of clevidipine, they also found that sodium nitroprusside was associated with longer time periods outside the predefined systolic blood pressure range and that this group of patients exhibited a tendency toward increased mortality. This result may have a number of explanations but could involve blood pressure excursions outside the autoregulatory range. The problem for the clinician is that one is unable to identify the limits of the autoregulatory range in an individual patient because this would require simultaneous measurements of pressure and flow and the absence of a correlation. Recent animal work[18] and work in pediatric head trauma[19] have attempted to do exactly that, and suggest that this approach to identifying the limits of an individual's autoregulatory curve may become clinically feasible.

At a minimum, the concept that indices of vascular stiffness have independent predictive value, not only in nonsurgical populations but also in surgical populations (at least those undergoing cardiac surgery), should add precision to the models currently used to predict operative risk. Moreover, there is considerable evidence from other arenas which indicate that these vascular stiffness changes are potentially modifiable. In a human study, breakdown of advanced glycation end-product cross-links significantly decreased systolic blood pressure and significantly increased compliance compared with placebo in individuals with pulse pressures more than 60 mm Hg and systolic blood pressures more than 140 mm Hg.[20] Furthermore, the CAFÉ Study[21] (an antihypertensive trial) showed clearly that a pharmacological regimen (angiotensin converting enzyme inhibition and a calcium antagonist) that preferentially decreased central vascular pressures (and presumably central vascular stiffness) resulted in lower long-term cardiovascular event rates, compared with a regimen (β-blockers and diuretics) that did not decrease central pressures. Importantly, both regimens had identical effects on peripheral/brachial blood pressure measurements. In the acute perioperative setting, we do not have the capacity to access these indices of vascular function and thus cannot determine the influence of such interventions. It is likely, however, that the vascular changes that accrue with age do modulate vital organ blood flow and that this may have implications for perioperative blood pressure management. The studies by Fontes et al. and Aronson et al. are important in that they further our understanding of the implications of age-related vascular changes in the perioperative period. Moreover, these studies each represent a large body of work and organization for which all concerned should be complimented.

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