Editorial Comment

Aortic Regurgitation: The Need for an Integrated Physiologic Approach*

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The present study, the investigation by Starling and coworkers (1) underlines the diagnostic and therapeutic relevance of an integrated and sophisticated physiologic assessment of left ventricular function in patients with aortic regurgitation. Their effort to differentiate net "left ventricular performance" from "myocardial performance" is, we believe, a step in the right direction. However, specific concerns with the study should be noted. 1) The left ventricular end-systolic wall stress-ejection fraction relation, which was used as an index of contractile state, has been shown previously to be variably preload dependent. This could act as a confounding variable and may help explain some of the disparity in the myocardial mechanics data acquired in the group 2 patients with aortic regurgitation. 2) A controversial method was employed to normalize left ventricular maximal elastance (Emax) for ventricles of different sizes. 3) The autonomic nervous system remained intact at the time that pharmacologic manipulation of left ventricular loading conditions was used to generate Emax. Although this may not have affected the results of this study, it is always an issue of concern when acute changes in afterload are produced by drugs such as nitroprusside or methoxamine. 4) Left ventricular pressure was used to estimate wall force in the left ventricular force-length (Fmax) relation. A more appropriate measurement of myocardial fiber load, especially in a dilated ventricle, would have been wall stress. It is important to emphasize that left ventricular systolic pressure-volume and stress-volume assessments of cardiac performance are not conceptually interchangeable. Within this context, analysis of "Fmax" using stress instead of pressure may have given added insight into the interpretation of the authors' data. All of these issues, however, do not significantly detract from the important overall message of the report. Importantly, the approach of Starling et al. (1) can be developed further by consideration of the role the systemic circulation plays in an integrated analysis of cardiovascular function. This concept is expanded on in the discussion that follows.

Proposed physiologic framework for chronic aortic regurgitation (Fig. 3). The insidious onset of myocardial contractile dysfunction in patients with chronic aortic regurgitation may be clinically masked by compensatory factors that maintain overall left ventricular systolic performance (2,3). This scenario has important implications regarding the timing of aortic valve replacement which, ideally, should be delayed until the surgical risk is at least balanced by the likelihood of irreversible damage to the left ventricular contractile mechanism (3-5). Recently, long-term vasodilator therapy was compared with placebo administration in patients with moderate to severe aortic regurgitation and was shown (6,7) to reduce the size of the left ventricle and improve its function. This finding raises the possibility that nonsurgical interventions targeted specifically at the peripheral vasculature can alter the natural history of aortic regurgitation and influence the surgical option. This issue takes on more relevance when one considers that the only drugs known to increase survival in patients with left ventricular contractile abnormalities are those that primarily act on the systemic circulation (8,9). Thus, it seems reasonable that any attempt to develop an operational framework for evaluating the cardiovascular system in aortic regurgitation must include considerations of left ventricular peripheral vascular interaction. Figure 1 schematically outlines such an approach.

Measurements of overall left ventricular systolic performance such as ejection fraction and cardiac output reflect the net effect of preload, afterload, contractility and heart rate (10,11). Preload and afterload, the forces acting on the left ventricular fibers at end-diastole and end-systole, respectively, are best quantified (as in the study of Starling et al.) as circumferential wall stress (12,13). Unlike other clinical measurements of left ventricular load, wall stress incorporates chamber geometry and wall thickness as well as pressure and volume. Traditionally, compensated aortic regurgitation is thought of as a preload-augmented state with left ventricular dilation, increased left ventricular stroke volume and normal or increased ejection fraction (4,14). In reality, however, the physiology of aortic regurgitation is far more complex than this, with multiple variables acting to counterbalance the pump-related effects of preload augmentation. These include 1) increased afterload (end-systolic wall stress) with or without afterload mismatch (1,15,16); 2) depression of contractile state (4,14,15); and 3) the inverse relation between left ventricular diastolic filling time and regurgitant volume such that an increase in heart rate can reduce left ventricular preload, regurgitant fraction and ejection fraction despite constancy of contractile state (17,18).

During systole, the left ventricular cavity and the systemic arterial system are in continuity (Fig. 1). Flow and pressure are the only direct mechanical means of communication...
between the heart and the systemic circulation. Cardiac systolic load is, therefore, a function not only of cardiac but also of vascular factors which, by impeding the forward flow of blood, influence arterial pressure and flow. The best known of these vascular variables, and the only one that currently enjoys extensive clinical use, is systemic vascular resistance. However, attempts to correlate systemic vascular resistance with left ventricular load have not proved meaningful (19). This reflects the fact that the vascular contribution to cardiac load is the product of a complex interaction among several variables external to the heart that, in addition to systemic vascular resistance, include arterial compliance and viscoelasticity as well as blood inerterance (20,21). These factors, acting directly and through reflected waves originating at branch points in the arterial tree, produce the arterial pressure waveform, in turn, the left ventricular pressure generated during ejection acts with systolic chamber geometry to determine afterload. Similarly, systemic venous and pulmonary venous blood returning to the heart in conjunction with diastolic chamber geometry contribute directly to the generation of preload. Superimposed on these events are coronary blood flow and myocardial perfusion, which are dependent on the magnitude of aortic pressure and flow.

Within this framework, patients with aortic regurgitation demonstrate multiple flow- and pressure-related abnormalities that could significantly affect left ventricular-peripheral vascular interaction (3,5,6,7,22). These include 1) the increased rate and volume of blood flow into the aorta during early to mid systole; 2) the wide pulse pressure that augments pulsatile load on the aorta; 3) the presence of antegrade and retrograde pathways for exit of blood from the aorta during diastole with their concomitant effects on the timing and amplitude of reflected waves; and 4) the possible adverse effects of high systolic pressures and flows on aortic compliance and operant stiffness leading to important stimuli for increased left ventricular wall stress, mass and chamber volumes.

The concept of left ventricular-peripheral vascular coupling just described differs from the time-varying elastance concept of coupling developed by Sagawa and others (23,24). These authors have used the ratio of E\textsubscript{max} to arterial elastance (E\textsubscript{a}) as an index of ventricular-vascular coupling, defining the optimal ratio as that associated with maximal efficiency of left ventricular mechanical energetics. However, the E\textsubscript{max}/E\textsubscript{a} ratio does not identify or even attempt to address the individual arterial properties that influence left ventricular performance. Rather, it evaluates the net effect of both ventricular and vascular properties on myocardial mechanics and energetics. Furthermore, this approach assumes the accuracy of a vascular model that does not incorporate such properties as aortic wall viscosity and blood inerterance.

**Future directions.** More precise modeling of the cardiovascular system is needed to identify and quantitate each of the physiologic factors intrinsic and extrinsic to the heart that determine myocardial function in normal and pathologic states. Recently, noninvasively obtained calibrated external pulse tracings recorded in conjunction with Doppler echocardiographic data have been used to accurately measure instantaneous aortic pressures and flows as well as calculate vascular compliance in humans (25–27). Perhaps application of these techniques to obtain serial data will assist in the further clinical development of the concepts of left ventricular-peripheral vascular coupling and lead to more appropriate guidelines for the timing of pharmacologic and surgical interventions in patients with aortic regurgitation.
References


