Editorial:
Acute Displacement of the Diastolic Pressure-Volume Curve of the Left Ventricle: Role of the Pericardium and the Right Ventricle

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IN CHRONIC CARDIAC DISEASE, the left ventricular diastolic pressure does not provide a reliable guide to the diastolic left ventricular volume, and measurement of chamber volume, shape, and wall thickness are necessary to identify changes in the myocardial stress-strain relation. Under acute conditions, the stiffness of the left ventricular chamber progressively increases as passive diastolic filling occurs, but whether a single equation can describe this non-linear pressure-volume curve in the human heart is not settled; this topic and the chronic adaptations that affect diastolic compliance have been examined in two recent reviews and will not be discussed here. Rather, certain factors that may be involved in acute displacements of the entire left ventricular pressure-volume curve will be considered, a phenomenon which is investigated in two clinical papers appearing in this issue of Circulation — one concerned with pharmacologic interventions, the other with acute ischemia.

Pharmacologic and Hemodynamic Influences

Many experiments in animals, in which the pericardium was absent, have indicated that the pressure-volume curve of the left ventricle studied at end-diastole, or during slow filling (diastasis), is not displaced significantly in the steady state by most pharmacologic agents, or by acute hemodynamic interventions within the physiologic range. However, both experimental and clinical work have shown that viscous effects can influence this relation during the early and late phases of rapid ventricular filling. In fact, the use of an equation which includes a parallel viscous component recently has been shown to describe the left ventricular diastolic stress-strain relation better than a simple exponential function, when complete single diastolic cycles are analyzed. In addition, shifts upward of the curve during tachycardia, hyperosmolality or hypothermia may occur, probably due to early incomplete ventricular relaxation. Such an effect also has been examined by studying the time constant (T) for the fall in left ventricular pressure during isovolumetric relaxation. This constant is altered by pharmacologic and hemodynamic interventions for example, increased left ventricular end-systolic size and pressure increase T, and it has been suggested that such an effect could influence the filling relation well into diastole. Thus, in contrast to analyses of the slow phase of filling, or end-diastolic points over a range of filling pressures, the influence of the viscous factor and incomplete relaxation become important when single, dynamic diastolic cycles are used to determine pressure-volume relations, as is usually the case in clinical studies. Finally, as shown in figure 1, alterations in right ventricular filling, in the absence of the pericardium, also substantially affect the diastolic left ventricular diastolic pressure-volume curve.

The work of Holt suggested an effect of the pericardium on the diastolic pressure-volume relation of the ventricles, and studies on the isolated heart in which the left ventricle alone was filled showed that the diastolic pressure-volume relation was shifted to the right by removal of the pericardium, particularly at high left ventricular filling pressures. Other studies with the pericardium intact suggested a significant effect of the right ventricle and indicated that the shape of the left ventricle at end-diastole was distorted at elevated right ventricular end-diastolic pressures; it was suggested in the latter study that direct displacement of the interventricular septum toward the left ventricle, together with stiffening of the septum, rather than an influence of the pericardium, was primarily responsible for the accompanying shift of the left ventricular diastolic pressure-volume relation. Recent studies in our laboratory have indicated that acute volume loading of the whole heart with the pericardium intact shifts the entire left ventricular pressure-volume relation upward (fig. 2), primarily because of a rise of intrapericardial pressure; nitroprusside infusion in the presence of such acute cardiac distension displaced the entire pressure-volume relation downward (fig. 2), accompanied by a drop of intrapericardial pressure. These acute shifts of the curve were abolished when the experiments were repeated in the same dogs after removal of the pericardium (fig. 2). Recent independent studies by Glantz et al. have revealed similar conclusions.

In patients undergoing cardiac catheterization, Alderman and Glantz showed displacement upward of the entire pressure-volume relation during infusion of a vasopressor, angiotensin, with a displacement downward of the entire curve during nitroprusside...
Infusion in some patients; based on theoretical calculation, they suggested that the elasticity of the ventricular wall itself had not changed during these interventions. Such effects of nitroprusside on the diastolic pressure-volume curve were confirmed by Brodie et al. and nitroglycerin also was found to displace the entire pressure-volume relation of the left ventricle downward without a significant change in slope. An article in this issue of Circulation by Ludbrook and co-workers produces further evidence in this connection; it was found that amyl nitrite, despite production of a fall in systemic arterial pressure similar to that after nitroglycerin, caused no displacement of the diastolic pressure-volume curve, a finding which was attributed to amyl nitrite's failure to reduce the right atrial pressure (average reduction was 5 mm Hg after nitroglycerin). These data suggest that shifts in the left ventricular diastolic pressure-volume relation during such pharmacologic interventions in man may be related to alterations in filling of the right ventricle, and/or to changes in intrapericardial pressure in man.

Effects of Acute Ischemia

Alterations in the left ventricular diastolic pressure-volume relations during acute myocardial ischemia are complex, since changes occur in regional systolic and diastolic myocardial dynamics, as well as in regional coronary blood flow. In the absence of contracture, hypoxia and anoxia have little effect on the diastolic stress-strain relation of isolated cardiac muscle. Global ischemia does not appear to alter the end-diastolic pressure-volume relation of the left ventricles.
tricle in dogs placed on right heart bypass. Forrester et al. found, in the dog heart, increased left ventricular compliance early after myocardial infarction. These investigators also found the segment length-pressure relation in the ischemic region to be shifted to the right without a change in slope, and suggested that segmental compliance was also increased. In our laboratory we have consistently found, both in open-chest dogs and in conscious animals, that soon after acute ischemia the diastolic

FIGURE 2. Relations during diastole between a segment of the left ventricle and the left ventricular diastolic pressure (LVDP). Points were obtained during slow cardiac filling (diastasis). The upper panel shows this relation with the pericardium intact before (open symbols) and after the intravenous infusion of dextran to produce acute cardiac dilatation (upper curve); the middle curve shows the effects of an intravenous infusion of nitroprusside in the presence of such acute cardiac dilatation. In the lower panel the same dog is later studied again, but without (W/O) the pericardium. The same interventions, volume loading and nitroprusside, are produced. The ventricle now appears to be operating on a single diastolic pressure-length relation. (Reproduced by permission from Shirato K, Shabetai R, Bhargava V, Franklin D, Ross J Jr).
pressure-segment length relation in the ischemic zone is shifted to the right, but its slope is steepened;\textsuperscript{35, 36} moreover, diastolic sarcomere lengths are longer in the ischemic segment than in normal regions.\textsuperscript{37} These findings suggest that creep has occurred and that the ischemic segment is stiffer than normal. Other studies on regional function early after experimental coronary occlusion have shown that late systolic expansion in ischemic zones coincident with late systolic shortening in normal regions can profoundly affect the isovolumetric relaxation period.\textsuperscript{38, 39} Also, incomplete ventricular relaxation appears to follow ischemia.\textsuperscript{40} How such abnormalities may affect the pressure-volume relation of the entire ventricle during various degrees of experimental ischemia remains to be defined.

Clinical studies have demonstrated an upward shift of the left ventricular diastolic pressure-volume relation during angina pectoris, obtained from single cardiac cycles after cessation of cardiac pacing. Barry et al.\textsuperscript{41} measured left ventricular pressures and volumes at endsystole and end-diastole and found that during angina the logarithmic relation connecting these two points was displaced upward, to the left, and flattened; they attributed this finding to increased muscle stiffness secondary to sustained contraction (or failure of relaxation) in a portion of the left ventricle. A shift upward of the entire diastolic pressure-volume relation during postpacing angina, plotted throughout single cycles, has been documented without an apparent change in the slope of this relation.\textsuperscript{42} Based on a reduction in peak \( -\frac{dP}{dt} \), other investigators have suggested that left ventricular relaxation is incomplete during angina pectoris.\textsuperscript{43} In this issue of Circulation, Mann et al.\textsuperscript{7} extend earlier studies in reporting that during angina after pacing there was no significant change in the average right ventricular end-diastolic pressure; this finding, coupled with a fall in peak \( -\frac{dP}{dt} \) and a rise in the time constant (T) for isovolumetric relaxation, lead them to conclude that impaired ventricular relaxation contributes significantly to the observed upward displacement of the diastolic pressure-volume relation; altered myocardial turgor due to increased coronary blood flow\textsuperscript{44} was also considered a possible factor, but based on the absence of a significant rise in right ventricular end-diastolic pressure it was concluded that constraint by the pericardium could not explain the shift, since diastolic pressures in both ventricles should have been affected.\textsuperscript{7}

Based on these experimental and clinical studies, it appears certain that several factors aside from an alteration in the end-diastolic pressure-volume relation, or that during diastasis, of the left ventricular myocardium, may be involved in acute displacements of the entire pressure-volume curve observed with pharmacologic interventions and ischemia. These include:

1) An effect of right ventricular filling on the left ventricle. This effect can occur whether or not the pericardium is intact, and when the influence of the pericardium is not important such an effect could be due to an influence of right ventricular filling on circumferential fibers shared by both ventricles, or to effects on the interventricular septum. In addition, direct involvement of the right ventricle by ischemia could be associated with alteration of its function and diastolic filling characteristics.

2) Alterations of intrapericardial pressure. Experimentally, it seems clear that such an effect can be operative when the left ventricle alone is distended to a filling pressure above approximately 12 mm Hg, while more marked shifts of the entire left ventricular pressure-volume curve occur when the right-sided chambers also are distended or emptied. Experimental studies are needed in which the relative contributions of all four cardiac chambers are examined, since it seems likely that the magnitude of the displacement, as well as the slope of the pressure-volume relation, may be different when the left ventricle and left atrium alone, the right ventricle and right atrium, or all four cardiac chambers are distended or emptied.

Experimental studies on possible changes in intrapericardial pressure during acute ischemia have not yet been reported, and it may be predicted that the degree of any such changes would depend on the severity of ischemia (i.e., whether left atrium and the right-sided chambers are distended as well as the left ventricle).

3) An effect of post-pacing coronary hyperemia to increase muscle stiffness in the ischemic region through augmented myocardial turgor.\textsuperscript{44} More recent experimental studies have indicated, however, that changes in coronary perfusion pressure and flow do not significantly affect the diastolic pressure-volume characteristics of the entire left ventricle.\textsuperscript{45}

4) Effects of altered viscous properties during rapid ventricular filling. Study of such effects may require different models for computation of stress-strain relations. In this connection, the left ventricular ejection fraction drops during post-pacing angina, resulting in an increased residual left ventricular volume and pressure\textsuperscript{46} which, in turn, would cause movement upward on a single diastolic pressure-volume relation (producing decreased chamber compliance); increased end-systolic pressure and volume induced either by ischemia or pharmacologically also could affect subsequent viscous behavior.

5) Incomplete ventricular relaxation. Particularly during ischemia, regional contraction abnormalities may occur in early diastole, and Weiss et al. have described prolongation of the time constant (T) for isovolumetric relaxation after restoration of blood flow following experimental ischemia.\textsuperscript{49}

How each of these factors may have affected the findings in the study reported by Mann et al.\textsuperscript{7} in which average left ventricular end-diastolic pressures increased in post-pacing angina without a significant change in the right ventricular end-diastolic pressures, is not clear. However, it should be noted that while there was no significant change in the average right ventricular end-diastolic pressure, the average value actually increased from 9.7 to 11 mm Hg, the pressures rose in eight of the 10 patients, and in three
patients the pressure rise was between 2-4 mm Hg; thus, the authors' suggestion that the intrapericardial pressure could not have risen because right ventricular diastolic pressure did not rise does not yet seem established. Since the right ventricle is more compliant than the left, a small change in right ventricular filling pressure could reflect a substantial alteration in right ventricular volume, and factors such as septal displacement, increased septal stiffness, or stretching of common fibers could have played a role in elevating the left ventricular end-diastolic pressure even without a clear role for the pericardium. Moreover, the influence of right ventricular ischemia on left ventricular diastolic properties, if any, is unknown. For these reasons, although the authors' tentative conclusion that impaired ventricular isovolumetric relaxation due to ischemia must have been important may be correct, the potential role of these other factors requires further investigation.

In studying the diastolic properties of the diseased human left ventricle, consideration must be given to how that chamber interacts with the right ventricle, as well as with the pericardium and other cardiac chambers. From the evidence presented above, acute displacements of the diastolic pressure-volume curve under some circumstances appear to be related to alterations of intrapericardial pressure, while in other instances it is possible that alterations in the size or function of the right ventricle produce such changes. A shift of the diastolic curve due to such factors would imply that changes in left ventricular diastolic pressure can occur without a change in the relation between diastolic left ventricular volume and sarcomere length; hence, certain types of displacement of the ventricular function curve, e.g., during afterload reduction, may be only apparent. Finally, viscous effects and incomplete relaxation must be considered, particularly when dynamic filling is analyzed during single cardiac cycles. Much more information is needed in man, particularly in the setting of ischemia, before we can assign definite mechanisms to alterations in the shape or position of left ventricular diastolic pressure-volume curves observed under acutely changing conditions.

References

CATEGOLAMINE RESPONSE TO ANGINA/Schwartz et al.

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Catecholamines in Coronary Sinus and Peripheral Plasma During Pacing-Induced Angina in Man

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SUMMARY We measured aortic and coronary sinus dopamine (DA), epinephrine (E), and norepinephrine (NE) in eight patients with cardiac ischemia (I) and eight control subjects (C). Samples were taken at rest (73 ± 3 beats/min in C and 68 ± 3 beats/min in I) and during coronary sinus pacing to peak rates (144 ± 4 beats/min in C and 136 ± 6 beats/min in I). Arterial NE was higher in the ischemic patients at rest (254 ± 25 pg/ml in C and 324 ± 21 I; p < 0.05). There were no differences in arterial E and DA. Neither pacing nor angina affected peripheral catecholamine concentrations. Resting myocardial NE flux was similar for both groups. With pacing, coronary sinus flux and net myocardial NE release increased significantly in both groups. The maximum relative increase in net myocardial NE release was less in the ischemic patients than in the controls (575 ± 145% in C and 255 ± 40% in I; p < 0.05). Thus, angina induced by pacing does not augment peripheral sympathetic activity. Furthermore, pacing-induced angina appears to be associated with a decrease in cardiac sympathetic tone compared with that found in paced controls.

AN INCREASE IN sympathetic activity has been postulated to be a significant determinant for some of the pathophysiological events associated with angina pectoris. With a compromise in regional myocardial blood flow, an increase in circulating catecholamines, by increasing myocardial oxygen consumption, would be expected to have deleterious effects on the jeopardized myocardium. Though an increase in peripheral plasma catecholamine concentration has been well-documented as a result of acute myocardial infarction,1 4 the plasma catecholamine response to angina is not clear.

The classic studies cited to support an association between an increase in circulating catecholamines and angina pectoris are those of Raab6 and Gazes.6 These studies, performed a generation ago, used techniques to measure plasma catecholamines which are now known to be imprecise. Raab could not differentiate between "cortical sterols" and "adrenalin," and the resting levels of plasma catecholamines reported by Gazes were greater than those now known to be valid. These early investigators based their conclusions on an increase in plasma catecholamines during exercise.

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