Medical Staff Conference

The Pathogenesis of Acute Left Ventricular Failure
The Role of the Pericardium

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Measures of pulmonary capillary wedge pressure are sometimes used as estimates of left ventricular filling pressure and, therefore, as estimates of left ventricular end-diastolic volume. Knowing the filling pressure is only half of the story, however, for end-diastolic volume is determined by the pressure difference across the ventricular wall. The pressure outside the ventricle is, of course, the pericardial pressure, and the importance of the pericardium in acute left ventricular failure is increasingly recognized. Dr Eldon Smith, Professor and Chair of the Department of Medicine at the University of Calgary, will update us on this subject.*

ELDON R. SMITH, MD†: Acute left ventricular failure, characterized by elevated pulmonary venous pressures and excessive transudation of fluid into the alveolar spaces, complicates many cardiovascular disease processes. Although there has been a great improvement in our understanding of the pathophysiology involved—particularly related to the importance of diastolic dysfunction—we remain uncertain as to the exact mechanism(s) in many situations. In this conference, the focus will be on recent experimental and clinical evidence that suggests that the pericardium may play a more central role in the mediation of acute left ventricular failure than was previously thought.

The Clinical Problem

Let us examine the case of a patient with acute anterior wall infarction. A few hours after admission, the patient had a flow-directed catheter inserted and the hemodynamics were measured (Table 1). Of note is the fact that the stroke volume and cardiac output were normal—values indexed to surface area were also normal—although the mean pulmonary capillary wedge pressure was elevated. Traditionally, we have ascribed the elevated filling pressure in this clinical setting to reduced compliance of the infarcted myocardial segment. Experimental evidence, however, suggests that acutely infarcted myocardium is more, rather than less, compliant than normal myocardium[1]; impaired distensibility does develop over days to weeks, presumably secondary to the developing fibrosis. Thus, although diastolic compliance was apparently reduced in this patient, it is not clear that changes in myocardial stiffness were responsible.

The patient subsequently received an infusion of nitroglycerin and after stabilization, the values shown in the right column of Table 1 were determined. There was no significant change in the heart rate, cardiac output, or stroke volume despite a major reduction in the left ventricular filling pressure. Given our traditional concepts of physiology, this is also somewhat difficult to understand. Based on Sarnoff's adaptation of Starling's law of the heart, we might expect that such a major decrease in the left ventricular filling pressure would effect a decrease in left ventricular volume and be associated with a decrease in stroke volume. It is generally recognized, however, that administering nitroglycerin to such patients usually does not result in a major reduction in left ventricular volume. This is well illustrated in Figure 1, taken from the work of Ludbrook and co-workers.[2] Here, nitroglycerin produced a major decrease in diastolic pressure, with only a minimal change in left ventricular volume. Thus, there was a parallel downward shift in the diastolic pressure-volume relation with an apparent improvement in left ventricular compliance in response to the nitroglycerin.

Traditionally, acute alterations in apparent diastolic compliance would be attributed to changes in myocardial relaxation or to altered distensibility. In vitro studies of cardiac muscle, however, have not shown any alteration in these variables in response to nitroglycerin. Major upward displacement in the diastolic pressure-volume relation such as that shown in Figure 1 would be expected to occur primarily in response to processes such as hypertrophy, fibrosis, or infiltration. Acute myocardial ischemia is a possible exception,

TABLE 1.—*Hemodynamics Before and During Nitroglycerin Infusion*

Measured	*Control*	*With Nitroglycerin*
Heart rate, beats/min	96	95
Systolic arterial pressure, mm/mercury	110	105
Right atrial pressure (mean), mm/mercury	8	2
Wedge pressure (mean), mm/mercury	17	10
Stroke volume, ml	64	61
Cardiac output, liters/min	6.2	5.8

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during which ischemia-induced calcium influx might alter the distensibility of the myocardium.[3] In view of these considerations, it is not surprising that the mechanism of such parallel shifts in the left ventricular pressure-volume relation as illustrated for nitroglycerin has remained controversial.

The Role of External Constraint

One possible explanation for such load-mediated shifts in the left ventricular pressure-volume relation is unappreciated alterations in pericardial pressure.[4] Figure 2 shows a simple model of the two ventricles enclosed in a semirigid pericardium. In **B,** the left ventricular intracavitary pressure is 15 mm of mercury at end-diastole, while pressure in the pericardium is 5 mm of mercury. The left ventricular transmural pressure, therefore, is 10 mm of mercury; this represents the true distending pressure (preload) on the left ventricular myocardium. The effects of dilatation of the right ventricle in this model are illustrated in **A** (Figure 2). This results in more of the (potential) space in the pericardium to be occupied by the right ventricle, with a subsequent increase in pericardial pressure to 15 mm of mercury. For the left ventricular volume to remain the same as in **B,** diastolic pressure must rise to 25 mm of mercury; transmural pressure remains unchanged at 10 mm of mercury.

Given the poorly compliant nature of the pericardium,[5] one can readily appreciate how minor changes in total cardiac volume could effect significant changes in pericardial pressure. Of course, a change in volume of any of the cardiac chambers—not just the ventricles—or an alteration in the amount of pericardial fluid would alter pericardial pressure and, therefore, shift the left ventricular diastolic pressure-volume relation.

Although this model is simple and compelling, a major impediment to its acceptance has been that our conventional understanding of pericardial pressure (in the absence of effusion) is that it is similar to intrathoracic pressure and varies little in response to alterations in cardiac volume. This concept is based primarily on the experimental observations of Kenner and Wood,[6] who showed that pericardial pressure measured with a fluid-filled catheter system varied insignificantly in response to constriction of the aorta and pulmonary artery, interventions that resulted in substantial increases in the right atrial pressure and that presumably increased the total volume of the heart. Whereas these findings have been widely accepted, the possibility exists that the method used to measure pericardial pressure was not appropriate. Of note is the observation that Agostoni and Permutt and colleagues,[7,8] in addressing the subject of pleural pressure, have been careful to distinguish between "liquid pressure" such as might be measured with a fluid-filled catheter system and "surface pressure." It is this latter pressure—actually a compressive contact stress—that is of importance to this discussion.

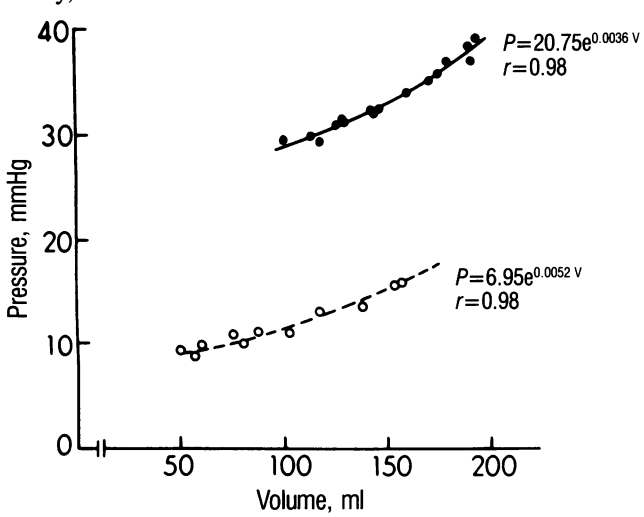

Figure 1.—Diastolic pressure-volume relations before (●) and after (O) nitroglycerin (NG) administration. Volume data points represent consecutive frames from a cine angiogram (based on data from Ludbrook et al[2]).

The Measurement of Pericardial Pressure

As long ago as 1960, Holt and co-workers[5] reported measuring pericardial pressure with a liquid-containing balloon and showed that vascular volume expansion resulted in substantially increased pericardial and intracavitary left ventricular pressure. Using a similar balloon, Smiseth and colleagues[9] working at the University of California, San Francisco, showed significant alteration in pericardial pressure occurring secondary to changes in preload and afterload in a model of left ventricular failure. Thus, these two techniques, a fluid-filled catheter and a liquid-containing balloon, when used to measure pericardial pressure, provide very different results.

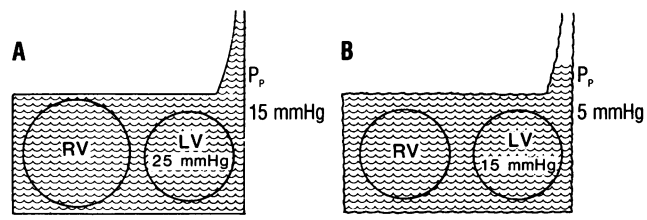

Figure 2.—Schematic model of the ventricles in the pericardium. RV = right ventricle; LV = left ventricle; P_P = pericardial pressure (from Smith et al,[16] with permission).

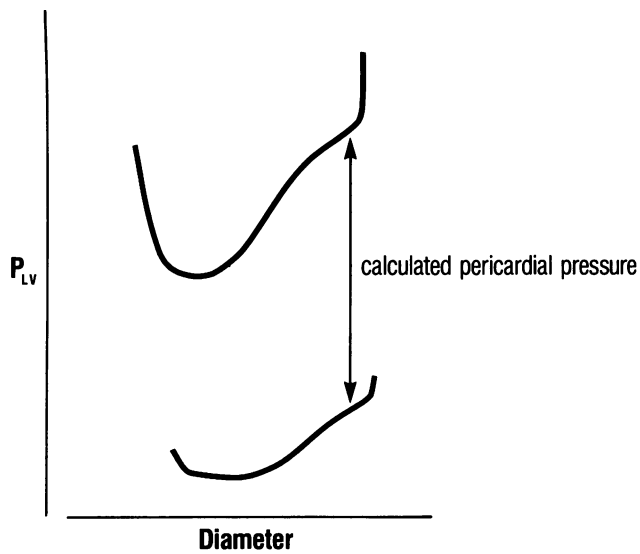

Figure 3.—The diagram shows the "calculated" pericardial pressure concept, with the upper curve representing left ventricular diastolic pressure (P_{LV}) versus diameter with the pericardium intact and the lower curve representing the relationship after the pericardium had been removed, the lungs retracted, and cardiac volume adjusted to be equal at end-diastole to that in the upper curve. The lower curve, therefore, represents transmural pressure (from Smiseth et al,[10] with permission).

To develop a "gold standard" for pericardial pressure to which these two measurement techniques might be compared, we used a simple, static equilibrium concept. At the instant of end-diastole when all movement in the left ventricle has stopped, the blood within the cavity exerts a pressure against the endocardium that must be exactly opposed by the sum of the transmural pressure and the external (pericardial) pressure. This concept is illustrated schematically in Figure 3. Transmural pressure can be directly measured experimentally by opening the chest, removing the pericardium and retracting the lungs so that the external surface of the left ventricle is exposed to atmospheric pressure. Under these circumstances, transmural pressure is equal to intracavitary pressure. Thus, at any given left ventricular end-diastolic volume, the correct pericardial pressure is the pressure that must be added to the transmural pressure to equal left ventricular intracavitary pressure.

Using these concepts, we were able to compare the data from both the fluid-filled catheter and a carefully calibrated liquid-containing balloon to "calculated" pericardial pressure in a series of dogs.[10] The results showed that the liquid-containing balloon transducer correctly reflected pericardial constraint despite the presence or absence of fluid within the pericardial space. Conversely, the fluid-filled catheter system grossly underestimated pericardial pressure when the pericardium was completely empty of fluid and recorded the same pressures as those recorded by the balloon transducers only when approximately 30 to 40 ml of fluid had been infused into the pericardial space. Even when the pericardium had four or five slits made in the ventral and lateral surfaces, allowing all the fluid to drain, the balloon transducer accurately reflected pericardial pressure, whereas liquid pressure as measured by the fluid-filled catheter fell to zero.

On the basis of these experiments, we concluded that pericardial pressure can be accurately measured by a balloon transducer, whereas the traditional catheter system for measuring intravascular pressure seriously underestimates pericardial constraint unless there is excessive fluid within the pericardial space.

Pericardial Pressure in Humans

Unfortunately, balloon transducers cannot easily be used to measure pericardial pressure in humans. An empiric observation in the animal laboratory, however, was that right-sided filling pressure did not differ significantly from pericardial pressure measured with a balloon transducer.[11] This suggests that right atrial and right ventricular transmural pressures are normally quite low and hardly detectable by noting the difference between right ventricular filling pressure and pericardial pressure.[12] To determine if this relationship held true in humans, we did a study in patients undergoing cardiac surgical procedures.[13] Following thoracotomy in nine patients, a flat, liquid-containing balloon transducer was inserted into the pericardial space over the lateral left

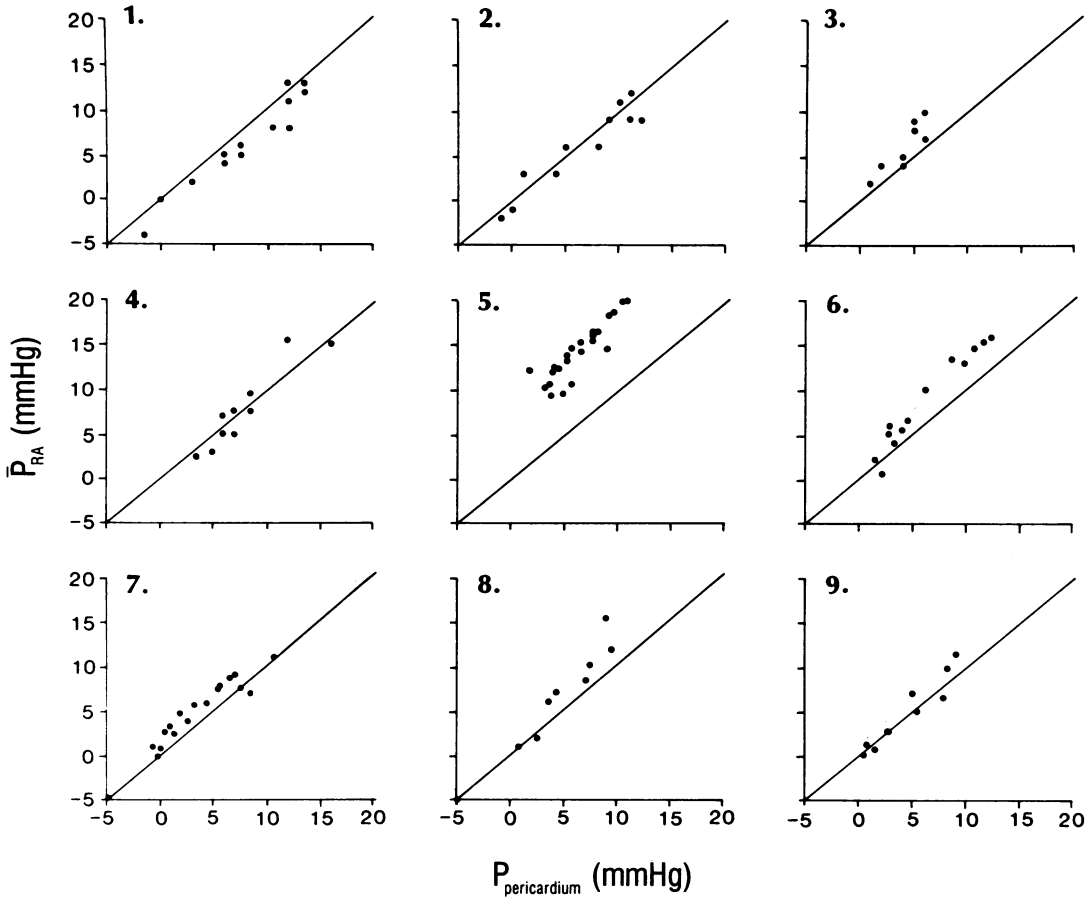

Figure 4.—Individual patient plots of mean right atrial pressure (P_{RA}) on the ordinate *v* pericardial pressure ($P_{pericardium}$) on the abscissa. Pericardial pressure was measured with a liquid-containing balloon transducer. In patient 5, the correlation coefficient was 0.94, although data are shifted upward from the line of identity; this probably reflects an undetected error in baseline (from Tyberg et al,[13] with permission).

ventricular wall through a small transverse incision. Mean right atrial and pericardial surface pressures were then compared over a large range of right atrial pressure effected by intravenous infusion. In each patient there was a close linear relationship (mean $r = 0.94 \pm 0.03$) with slopes not different from unity between mean right atrial and pericardial pressures (Figure 4).

More recently, similar findings have been reported by Boltwood and co-workers.[14] These workers studied 20 patients undergoing cardiac surgery and compared mean diastolic right atrial pressures with pericardial pressures measured with a balloon transducer. In the patient group without cardiac enlargement, there was no difference between right atrial pressures and pericardial surface pressures measured over either the right-sided chambers or over the left ventricle. In the subgroup with cardiac enlargement, however, the group mean right atrial pressure significantly exceeded the mean pericardial pressure. Much of this difference was accounted for by two patients with pulmonary hypertension who presumably had right ventricular hypertrophy. It is reasonable to expect that as the thickness of the right ventricle increases, so does transmural pressure. That the pericardial pressure was being accurately reflected by the balloon transducer was suggested by the observation that following pericardiotomy, right atrial pressures either decreased or were unchanged despite an increase in stroke volume; this result would only be expected if left ventricular transmural pressures had increased after pericardiotomy.

On the basis of these data, it seems clear that pericardial constraint in humans is much greater than previously thought and that it represents a significant fraction of left ventricular intracavitary diastolic pressure even at normal volumes, at least in anesthetized supine patients. Moreover, a clinically useful estimate of the pericardial surface pressure can be obtained from a right atrial or right ventricular diastolic pressure measurement, at least in the absence of right ventricular hypertrophy. These data suggest that a clinically useful estimate of the left ventricular diastolic transmural pressure might be available from commonly used hemodynamic monitoring data by subtracting right atrial from pulmonary capillary wedge pressures.

The Pericardium and Load-Mediated Shifts in the Left Ventricular Pressure-Volume Relation

Let us return to our earlier postulate that the nitroglycerin-induced downward shift in the left ventricular diastolic pressure-volume relation might be explained by an unappreciated decrease in pericardial pressure. To test this hypothesis, we studied patients undergoing routine diagnostic cardiac catheterizations.[15] Pressures were measured in the left and right ventricles by micromanometer-tipped catheters, with the left ventricular volume estimated by two-dimensional echocardiography studies. Recordings were obtained before and approximately five minutes after the sublingual administration of nitroglycerin. Figure 5 shows the results from one patient.

We concluded from this study that the nitroglycerin-induced downward shift in the left ventricular diastolic pressure-volume relation was due to an undetected decrease in pericardial pressure. Moreover, the fact that the transmural diastolic pressure-volume relation was unaffected by nitroglycerin provides further evidence that the elastic properties of the myocardium were unaltered. Finally, we concluded that pericardial pressure was substantial, even in this group of patients in whom left ventricular intracavitary pressures were not particularly elevated nor the left ventricle dilated. We postulated that the nitrate produced this effect by causing venous dilatation with a resultant decrease in venous pressure and a decrease in right heart volume, which led to the decrease in pericardial pressure.[16]

Pericardial Pressure in Left Ventricular Failure

Let us now return to the data in Table 1 and explore the possible effect of the pericardium on the observed hemodynamics. The left ventricular transmural diastolic pressure before administration of nitroglycerin was 9 mm of mercury

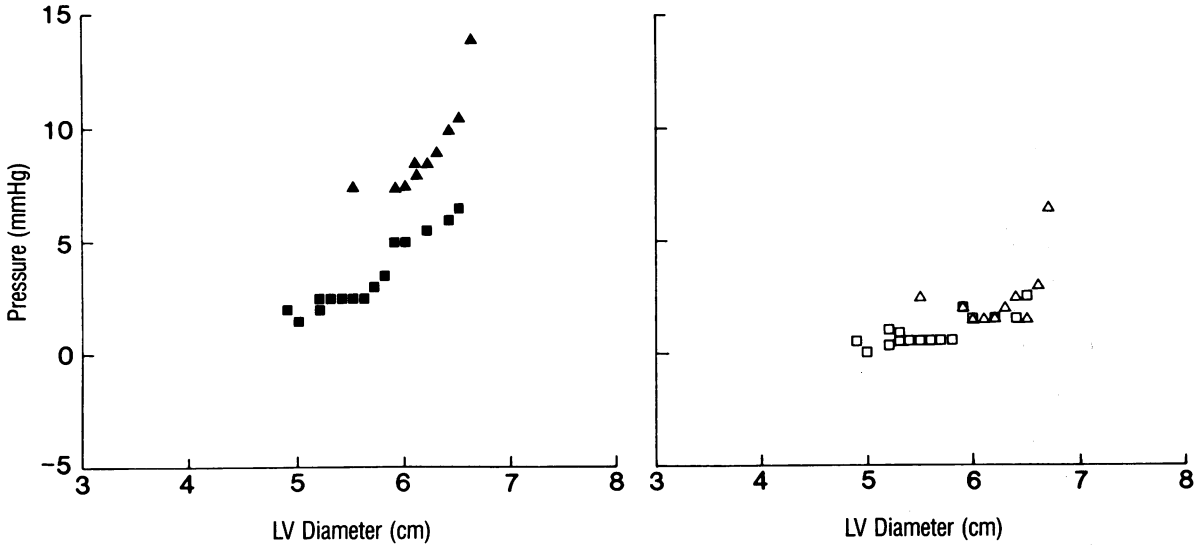

Figure 5.—Left Panel: Left ventricular (LV) intracavitary diastolic pressure-diameter relation before (▲) and after (■) sublingual administration of nitroglycerin in a patient undergoing routine cardiac catheterization. Note the parallel downward shift in the pressure-diameter relation after nitroglycerin was given. **Right Panel:** The same two cardiac complexes are depicted but transmural pressure—left ventricular minus instantaneous right ventricular pressure—has been plotted. The transmural pressure-diameter curve before (△) and after (□) administering nitroglycerin defines a single curve (from Smith et al,[16] with permission).

(pulmonary capillary wedge minus right atrial pressure). Following the initiation of the nitrate infusion, the estimated transmural pressure was still 8 mm of mercury, despite the rather significant decrease in left ventricular filling pressure. Since transmural diastolic pressure (preload) was maintained, we should not be surprised that the left ventricular stroke volume and cardiac output were also maintained. Obviously, a nitrate-induced decrease in afterload might have also contributed to the maintenance of stroke volume observed in this patient.

These data suggest that the acute elevation in left ventricular intracavitary diastolic pressure so characteristic of acute myocardial infarction is at least partially due to an unappreciated increase in pericardial pressure. In turn, nitroglycerin is very efficacious in the treatment of such patients because of its ability, through an action on the venous system, to decrease the pericardial pressure and thereby lower left ventricular intracavitary and pulmonary venous pressures. It seems likely that other vasoactive substances that shift the diastolic pressure-volume relation of the left ventricle act via a similar mechanism. Thus, sodium nitroprusside has an action similar to nitroglycerin, whereas angiotensin, which shifts the diastolic pressure-volume curve upward, probably increases the cardiac volume through its action on left ventricular afterload as well as on venous tone.[17]

Although it seems likely that substantial increases in left ventricular intracavitary diastolic pressure can be explained by the constraining effect of the pericardium on diastolic filling, one might not so readily accept that a similar mechanism would be operative in chronic heart failure. It is well recognized that the pericardium and heart both are capable of dilatation in patients with chronic heart failure; however, a recent study by Carroll and co-workers[18] suggests that the pericardium may affect diastolic filling in some of these patients. These workers studied 12 patients with dilated cardiomyopathy, all of whom had abnormal left ventricular diastolic properties. Administering nitroprusside produced a significant decrease in the left ventricular end-diastolic pressure; in five patients this was associated with a decrease in the left ventricular end-diastolic volume (diameter). In the remaining seven patients, however, sodium nitroprusside caused a parallel downward shift of the pressure-diameter relationship. Of importance is that this downward shift occurred in those patients with elevated right atrial pressures, and the magnitude of the downward shift corresponded to the magnitude of the decrease in right atrial pressure. Thus, it seems likely that even in patients with chronic biventricular heart failure and pronounced cardiomegaly, pericardial pressure accounts for a significant proportion of the elevated left ventricular intracavitary pressure.

Summary and Conclusions

Contrary to the conventional view, recent studies have documented that pericardial pressure both in animals and in humans is substantial and nearly equal to right atrial and right ventricular diastolic pressures. This observation provides a clinically reliable means to calculate effective left ventricular preload—pulmonary capillary wedge minus right atrial pressures. With this approach, our data suggest that the parallel downward shift in the left ventricular pressure-volume relation caused by nitroglycerin is due to an unappreciated decrease in pericardial pressure. It seems likely, therefore, that in most instances the substantially elevated left ventricular pressure noted in patients with acute left ventricular failure is due to an unappreciated increase in the pericardial pressure. Finally, recent data suggest that even in patients with chronic heart failure with notable cardiac enlargement, the pericardium can affect left ventricular diastolic filling. Our improved understanding of the hemodynamic importance of the pericardium promises to provide new insight into the pathogenesis of acute and chronic heart failure and may lead to new therapeutic options.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *If nitroglycerin works by this mechanism, it obviously involves some reduction in cardiac size. If we say that right ventricular size is reduced, how is performance of the right ventricle maintained?*

DR SMITH: This is a very difficult question, and we do not yet have a completely satisfying answer. Most important is the fact that the pericardium has a very steep pressure-volume relationship, so that a minor change in volume can result in a major alteration in pressure. Moreover, the atria probably also become smaller, perhaps even more so than the right ventricle. Also, we have shown that the pleural surface pressure in the cardiac fossa is elevated during congestion, and alleviation of this congestion by nitroglycerin might reduce the pleural component of the pericardial pressure, thereby increasing the transmural pressure in both ventricles at any given cardiac volume. Finally, we know that the nitroglycerin-induced afterload reduction helps to maintain left ventricular performance. How important this is to the right ventricle is unclear. Certainly, this question deserves further study with careful measurement of chamber dimensions and transmural pressures.

KANU CHATTERJEE, MD*: *You have attributed all of the effects from acute left ventricular failure and from nitroglycerin to an alteration in pericardial pressures. Do you think that ventricular interaction via the septum might also be involved?*

DR SMITH: There is no question that any intervention that alters the pressure-volume relation of one ventricle will also alter the pressure-volume relation of the other because of a shift in the position of the ventricular septum. Any degree of ventricular interaction via the septum is magnified by the presence of the pericardium. It is difficult to be certain of the relative contributions of the two mechanisms in any given situation. I accept your point that it is possible that the septum is involved to a greater extent than we are aware of in these particular studies.

DR ROOT: *We are told that the traditional management of right ventricular infarction is to give adequate fluid to maintain a cardiac output. I can see by invoking your mechanism that if we are too enthusiastic in our fluid administration, we could actually have a negative effect on cardiac output. Is this an accurate interpretation?*

DR SMITH: That is a very perceptive remark. The whole question of fluid administration in right ventricular infarction is one that I think merits reexamination. Such an approach clearly results in improved cardiac output in experimental animals in which the right-sided filling pressures are not

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particularly elevated over the preinfarction values and in humans when intravascular volume has been depleted by the inappropriate use of diuretics. The literature is not so clear concerning the efficacy of administering fluids to those patients with high right-sided filling pressures and low cardiac output. One can easily envision how such therapy in these patients might cause a decrease in left ventricular transmural pressure by increasing pericardial pressure and could further compromise cardiac output.

DR BOUSHEY: *Is there any evidence that the pericardium can vary its volume?*

DR SMITH: Not that I am aware of. The histologic appearance of the pericardium does not suggest that active changes would be likely—that is, there are no muscle cells. Of course, the pericardium does undergo stress relaxation, although this occurs only slowly and with changes that are so small that they do not seem to be important with respect to the phenomena we have been discussing.

PHYSICIAN IN THE AUDIENCE: *Could alterations in pericardial pressure be accounted for by vascular turgor?*

DR SMITH: We do know that the vascular supply to the pericardium is sufficient to allow rapid absorption of fluid from the pericardial space. I personally doubt that there is enough turgor induced by the vascularity of the pericardium to explain a 20 mm-of-mercury downward shift in the diastolic pressure-volume relation. Admittedly, this possibility has not been adequately examined.

PHYSICIAN IN THE AUDIENCE: *In those situations in which cardiac performance is compromised by chronic left ventricular failure, would it be a reasonable hypothesis to suspect that pericardiectomy might be beneficial?*

DR SMITH: It is an interesting hypothesis. It is widely believed that greyhounds can run faster if the pericardium has been removed, presumably because they develop a larger stroke volume, and it has been shown recently that a pericardiectomized dog has greater exercise capacity and myocardial oxygen consumption. I am aware of only one report of pericardiectomy being used in humans to manage dilated cardiomyopathy. It was an uncontrolled observation, although the author suggested that improvement occurred.

PHYSICIAN IN THE AUDIENCE: *Why don't patients who have pericardiectomy have pronounced cardiac enlargement?*

DR SMITH: This probably reflects a number of factors. There is probably some scarring, which tends to replace pericardial function. In addition, the lungs, esophagus, and other chest structures also contribute to extracardiac constraint. In a recent study in dogs, we showed that the addition of positive end-expiratory pressure to ventilated animals caused an increase in the pericardial pressure. Conversely, expanding the cardiac volume by administering intravenous fluid caused an increase in the pleural pressure measured adjacent to the heart. Overall, approximately a third of external constraint to the left ventricle was contributed by the lungs. Thus, cardiac dilation is likely limited by the constraint provided by extrapericardial structures.

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