

Early Increase in Left Ventricular Compliance after Myocardial Infarction

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ABSTRACT The left ventricular (LV) pressure-volume (P-V) relationship is a resultant of several determinants, including initial ventricular volume, geometry, and wall stiffness. A quantitative index of one of these determinants, LV wall stiffness, was developed from a mathematical analysis of the isolated P-V relationship. Since this relationship was exponential, stiffness (dP/dV) could be expressed by the equation $dP/dV = aP + b$, where a and b are constants. The a constant, termed the passive elastic modulus, was independent of both pressure and volume, was modified only slightly by changes in geometry, and thus was primarily affected by changes in wall stiffness. LV wall stiffness was assessed by determination of the passive elastic modulus in eight normal canine hearts and in five hearts 1 hr after acute myocardial infarction. The value of the passive elastic modulus for the normal canine LV was found to be $0.099 \pm 0.006 \text{ cc}^{-1}$. In the five infarcted hearts there was a modest, but statistically insignificant, shift of the P-V curves from control, such that for the same pressure the infarcted hearts contained greater volume. However, the passive elastic modulus decreased 41% to $0.057 \pm 0.006 \text{ cc}^{-1}$ ($P < 0.001$). Thus, although LV wall stiffness may increase later in the course of myocardial infarction, it is concluded that it was significantly decreased 1 hr after infarction. Calculation of the passive elastic modulus provided a sensitive means of detecting such changes, whereas P-V curves alone were generally insensitive.

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INTRODUCTION

Recently, there has been increasing interest in the pressure-volume (P-V)¹ relation of the left ventricle (LV) in coronary artery disease and after acute myocardial infarction (1-8). This interest stems from the observations that an elevation of LV filling pressure may be due not only to failure and dilatation, but also to a decrease in ventricular compliance (5). Although significant alterations of the LV P-V relationship are known to occur several days after acute myocardial infarction (2, 7), early changes have not been studied.

Recent experiments (9) have provided a more quantitative description of the P-V relationship of the LV. In these studies, the P-V relation in dogs could be closely approximated by an exponential curve. Thus the reciprocal of compliance, dP/dV , could be defined as a linear function of the pressure (P) for pressures above 5 mm Hg by the equation: $dP/dV = aP + b$. The slope, a , of this linear relation, termed the passive elastic modulus, was shown to be independent of alterations in intrinsic LV size or pressure, only slightly changed by altered geometry, and predominantly and primarily affected by changes in wall stiffness. The purpose of the present study was to utilize the passive elastic modulus to evaluate the early effects of acute myocardial infarction on LV muscle stiffness.

METHODS

13 mongrel dogs weighing from 17 to 32 kg were anesthetized with i.v. pentobarbital 30 mg/kg. In eight dogs, the chest was rapidly opened and the heart dissected free of the pericardium and intrathoracic organs. In five dogs, acute

¹ Abbreviations used in this paper: dP/dV , LV wall stiffness; LV, left ventricle; P-V, pressure-volume.

myocardial infarction was first induced by the injection of 0.2 cc of elemental Hg into the left circumflex coronary artery via a small pericardial incision. Infarctions so produced resulted in gross absence of contraction over approximately 25% of the LV surface. Exactly 1 hr after infarction, these hearts were removed in a similar manner. P-V curves were obtained on each heart according to a method previously described (9). Each heart was washed free of blood with Ringer lactate, and two 40-cm non-distensible 10F plastic tubes were passed into the LV chamber across the aortic and mitral valves. These catheters were secured by a heavy cotton tie about the atrioventricular groove. One of these catheters was connected to a double-track Harvard constant infusion pump (Harvard Apparatus Co., Inc., Millis, Mass.) calibrated to deliver 5.50 cc/sec $\pm 1\%$, and the second was connected directly to a Statham P23Db pressure transducer (Statham Instruments, Inc., Oxnard, Calif.). The heart was immersed in a bath of Ringer lactate at 23°C to equalize stresses across its wall. The transducer was positioned at the surface of the immersion bath, level with the superior surface of the LV to establish a zero pressure reference. The LV was then filled with Ringer lactate and allowed to drain to atmospheric pressure. The chamber volume at this pressure (V_0) was determined to the nearest 0.5 cc by siphon drainage into a graduated cylinder. The ventricle was then refilled to V_0 and 3-5 P-V curves were obtained in each heart, by constant infusion of Ringer lactate from the Harvard pump to a pressure of 30 mm Hg. Absence of leakage of fluid across the occluded valve orifices and complete emptying of the ventricular cavity was documented by comparison of volume of infusion to volume withdrawn. Evacuation of the ventricular cavity routinely results in differences of less than 0.5 cc between these two volumes. The pressure-time relationships were recorded on an Electronics for Medicine photographic recorder (Electronics for Medicine, Inc., White Plains, N. Y.) at 25 mm/sec paper speed with 0.1-sec time lines. The time required for determination of each P-V relation was less than 30 sec. Total study time from removal of the heart to completion was less than 40 min, thus avoiding changes in wall stiffness secondary to rigor mortis (10-11). At the completion of study, the right ventricle, atria, and great

vessels were trimmed away and the LV was weighed to the nearest gram.

Several theoretical and practical limitations of the above methodology are apparent. The relationship between the in vivo and in vitro P-V relationships is not well established. It seems reasonable to assume that the physiologic determinants of compliance in the two preparations is similar. Nonetheless the effects of the pericardium and intrathoracic location on the in vivo P-V relationship probably produce quantitative differences in the two preparations. In addition, use of a ligature around the annulus fibrosis clearly results in some distortion of ventricular geometry. When all studies are performed in a similar manner, this artefact is minimized. Other methods of in vitro study, such as placement of a button in the valve orifices, on the other hand, introduce infinitely stiff material of variable dimension into the ventricular cavity. Finally, a basic assumption of the study is that the injection of 0.2 cc Hg into a major epicardial vessel will not in itself induce changes in left ventricular compliance. This assumption is based upon the fact that the mass of solution injected represents only about 3% of the LV mass.

Previous studies have demonstrated that the P-V relationship of the canine ventricle is a precisely exponential function fitting the equation $dP/dV = aP + b$ (reference 9), where a is a constant directly related to ventricular wall stiffness (passive elastic modulus) and b is inversely related to initial size of the ventricular chamber. The constants a and b were derived as follows: pressures and volumes were measured directly from the recorded curves and instantaneous dP/dV was approximated by determination of $\Delta P/\Delta V$ at 0.1-sec intervals corresponding to increments of added volume of 0.550 cc. A plot of dP/dV against simultaneous pressure produced a precisely linear function, the slope of which was the constant a , and the y intercept, b . The reproducibility of the method is illustrated in Fig. 1.

Mean LV wall thickness (h) was calculated, assuming a spherical geometry and a specific gravity of muscle of 1.0, as follows:

$$h = 0.62(\sqrt[3]{LV \text{ wt} + V_0} - \sqrt[3]{V_0}).$$

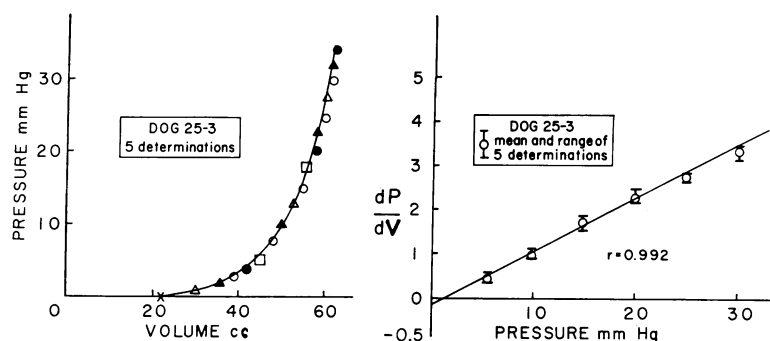


FIGURE 1 Reproducibility of serial P-V determinations. On the left, are plotted data points from five separate determinations (different symbols) in a single normal heart. On the right, the relationship of the derived function, dP/dV , is plotted against pressure. This relationship is precisely linear. The accuracy of the method is illustrated by the small range of values of dP/dV at each pressure. Similar reproducibility of the P-V curve is obtained during withdrawal of fluid from the ventricle.

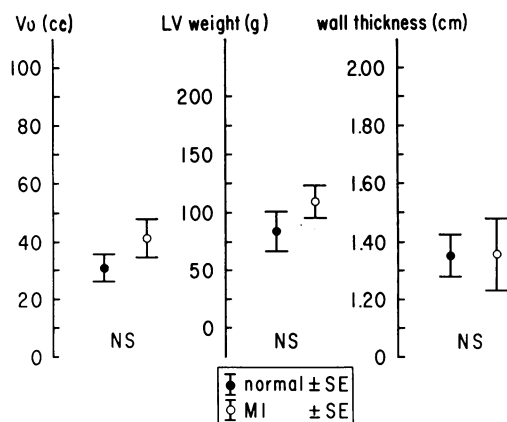


FIGURE 2 Comparison of ventricular volume at zero pressure (V_0), LV weight, and wall thickness in the normal and infarct group. The groups are well matched for these variables. (SE = standard error of the mean).

RESULTS

Since resting ventricular chamber size and LV wall thickness may affect the P-V relationship, these factors were analyzed separately for both the normal and infarcted hearts. The two groups were not statistically different in terms of initial ventricular volume (V_0), LV weight, and mean LV wall thickness (Fig. 2). Ventricular volume was averaged at pressures of 0, 5, 10, 20, and 30 mm Hg for the normal and infarcted group. The resulting mean P-V curves (\pm SEM) for the two groups are illustrated in Fig. 3. The average P-V curve of the infarcted group falls somewhat to the right of the normal group, but the difference is not statistically significant.

A variety of modes of data normalization were employed (Fig. 4). Ventricular volume was normalized for initial chamber size ($V - V_0$, $V - V_0/V_0$), LV mass ($V/100$ g LV wt) and the multi-variant LaPlace relationship h/r ($V - V_0$). These methods produced an overlap of the curves, with no significant difference

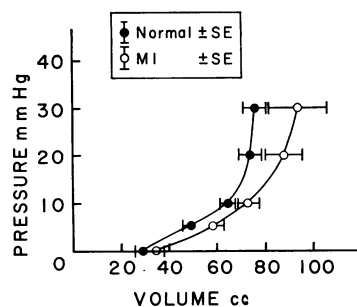


FIGURE 3 Mean P-V curves for the normal and infarct (MI) groups. There is a slight shift of the curve for the infarct group to the right of the control group.

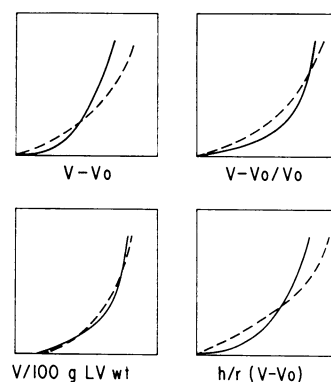


FIGURE 4 Mean P-V curves in control (solid line) and infarct (dashed line) hearts, normalized for initial volume ($V - V_0$), per cent increase from initial volume ($V - V_0/V_0$), LV weight ($V/100$ g LV wt), and the LaPlace relation ($h/r \times [V - V_0]$). In each case pressure is shown on the ordinate and volume normalized on the abscissa. The illustrative curves represent a pressure range of 0–30 mm Hg. There was no significant difference between the two groups by any of the methods of normalization. Standard errors and data points were therefore omitted for simplicity. There were statistically significant differences in the passive elastic modulus regardless of the method of normalization. Thus, when normalized for 100 g LV wt, $a = 0.103$ before infarction, and 0.071 after infarction. Similarly when normalized for 100 cc initial volume, $a = 0.029$ before, and 0.021 after infarction.

between control and infarcted groups ($P > 0.05$). Calculation of the passive elastic modulus, however, demonstrated a statistically significant difference between the two groups. In comparison to the normal group, there was a 41% mean decrease in the passive elastic modulus 1 hr after acute myocardial infarction (Fig. 5) from 0.099 ± 0.006 to 0.057 ± 0.006 cc^{-1} ($P < 0.001$). Normalization of the passive elastic moduli for differences in LV weight and volume maintained this difference, although to a lesser degree of significance ($P < 0.01$). There was no significant change in the b constant (y intercept).

DISCUSSION

Since diminished compliance during the healing phase of acute myocardial infarction probably is the result of fibrocellular infiltration, one might expect that changes in compliance immediately after infarction would not be demonstrable. Thus, Forward demonstrated no change in ventricular systolic stiffness immediately after infarction (12), and Hood was unable to observe any gross change in ventricular compliance over the first two hours after infarction in open-chested dogs (2). Although data in the present study demonstrated a modest shift of the P-V relationship to the right—an increase in ventricular compliance—the shift was not

statistically significant. Utilizing a more specific index, the passive elastic modulus, however, it was found that LV wall stiffness was significantly diminished in the first hour after acute myocardial infarction.

This early decrease in LV wall stiffness may be related to an interaction of normal and infarcted muscle. If one assumes that acutely infarcted muscle initially loses its ability to contract but does not change its passive length-tension relations, then the muscle will be passively stretched during systole (paradoxical systolic expansion) by adjacent contracting tissue (13). Such passive stretch would repeatedly raise the muscle to a much higher point on its passive length-tension curve that had ever been achieved when it was capable of contracting. This condition was simulated in a noncontracting isolated cat papillary muscle by performing repetitive length-tension curves (Fig. 6), using methods previously described (14). The muscle was passively stretched and shortened over a range of force representative of that which it would experience if it were in series with normally contracting muscle. Each length-tension curve exhibited the characteristic hysteresis loop common to most physical and biologic systems (15, 16). The muscle, undergoing this repetitive stretch, rapidly assumed a longer resting length. Thus, the passive length-tension curve of the noncontracting muscle was shifted to the right, such that its compliance was increased. Since levels of tension achieved by contracting LV muscle may be sufficient to produce microscopic fiber slippage of noncontracting muscle segments, increased muscle length and compliance may reflect passive disruption of the myofibers or supporting elements within the noncontracting infarct segment.

This hypothesis assumes changes occur only in the noncontracting segment undergoing intense, repetitive passive stretch. It is possible, however, that the increased LV end diastolic pressure which follows in-

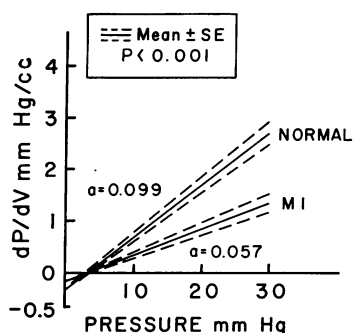


FIGURE 5 Differences in passive elastic modulus (a constant) for control and infarct (MI) hearts, indicating a significant decrease in LV wall stiffness 1 hr after acute myocardial infarction. The b constant (y intercept) is similar in the two groups.

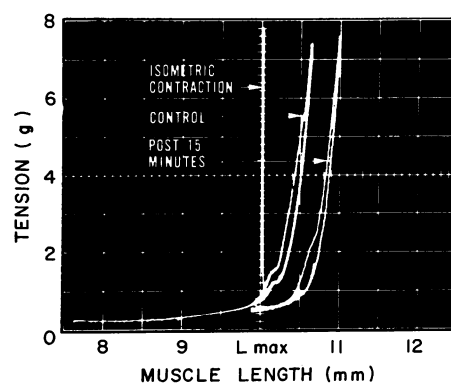


FIGURE 6 Alteration in length-tension curves of a cat papillary muscle during repetitive passive stretch. Peak active developed force during isometric contraction before passive stretch was 7.8 g. Passive stretch was then applied to a tension closely approximating that developed during active contraction, at a frequency of 30 per min for 15 min. There was a progressive shift of the passive length-tension curve to the right of control, suggesting increased compliance of the noncontracting muscle, possibly secondary to stress relaxation.

fraction may exert a less marked but directionally similar effect upon normal, contracting myocardium, which would contribute to decreased ventricular wall stiffness.

In the intact heart, during the first hour after infarction, an analogous mechanism would result in an increased ventricular volume at the same pressure, secondary to stress relaxation or actual anatomic disruption of the infarcted segment of myocardium, and thus an increase in ventricular compliance. As cellular infiltration and tissue edema occur over time, this segment would progressively stiffen. Thus, although serial observations of LV compliance were not possible in this study, the data implies that LV wall stiffness may be a continuously changing variable during the first few hours or days after acute myocardial infarction.

The clinical implication of altered ventricular compliance in acute myocardial infarction has not been established with certainty. Diminished LV compliance several days after acute myocardial infarction has been demonstrated in both animals (2) and man (7). Increased LV stiffness with unchanged right ventricular stiffness may explain the wide discrepancies between filling pressures of the two ventricles which have been observed in acute myocardial infarction (5). Furthermore, increased LV filling pressure is transmitted retrograde to the pulmonary venous and capillary system, and may result in pulmonary congestion. Thus, in the presence of increased LV stiffness, it is possible to have classic physical signs of congestive heart failure, e.g. rales and gallop sounds, in the presence of normal

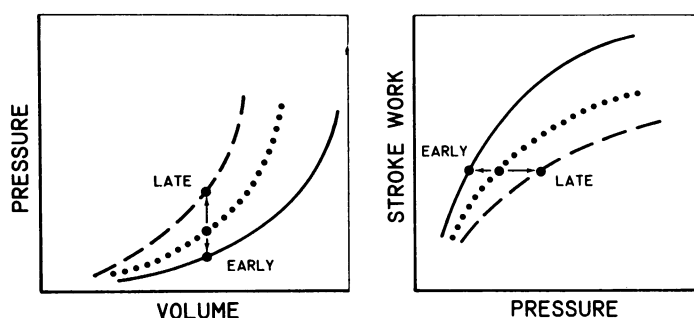


FIGURE 7 Apparent shift in ventricular function in acute myocardial infarction, secondary to alterations in ventricular compliance. On the left is illustrated the change in compliance from normal (dotted line) that occurs during the early (solid line) and late (dashed line) phases of acute myocardial infarction. The small arrow illustrates that at a constant volume, pressure may vary directly in response to changes in compliance. Thus, assuming true Starling function (stroke work vs. LV volume) to remain constant, alterations in compliance alone would result in shifts of ventricular function curve derived from the use of pressure as an index of volume, as shown in the right panel.

cardiac function as judged by the relationship between stroke work and ventricular end diastolic volume.

The effect of an early decrease in LV wall stiffness after acute myocardial infarction is of importance in at least two respects. First, traditional evaluation of LV performance by Starling function curves involves use of LV filling pressure, plotted against a measure of performance such as stroke volume or stroke work. When either patient groups or serial changes over time in a single individual are commonly evaluated in this manner. A basic assumption concerning such analysis is that LV end diastolic pressure is a valid indicator of LV end diastolic volume, or conversely that compliance is similar in all patients and does not change with time. Immediately after acute myocardial infarction, however, LV end diastolic pressure may be lower for any given end diastolic volume, resulting in a relative overestimation of cardiac function (Fig. 7). Second, the systolic tension generated by contracting myocardium, when applied to noncontracting elements, may lead to progressive stretch and ultimate anatomic disruption of the noncontracting fibers. It seems likely that this constitutes an important mechanism in aneurysm formation after acute myocardial infarction.

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