Influence of Reduction of Preload and Afterload by Nitroglycerin on Left Ventricular Diastolic Pressure-Volume Relations and Relaxation in Man

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With the technical assistance of Frank R. Reed

SUMMARY To clarify the mechanisms of afterload reduction on left ventricular diastolic function, the influence of nitroglycerin upon ventricular diastolic pressure-volume relations was studied in 22 patients during catheterization. After nitroglycerin, average ventricular systolic pressure declined by 25 mm Hg (18%) and end-diastolic pressure by 7 mm Hg (28%) (P < 0.005). End-systolic and diastolic ventricular volumes decreased by 37% and 23% respectively (P < 0.005). Although peak negative dP/dt fell by 22% (P < 0.0005), "T," an index of the time course of isovolumic diastolic ventricular relaxation, was insignificantly changed.

SALUTORY EFFECTS of reduction of left ventricular afterload using vasodilator therapy in acute myocardial infarction and left ventricular decompensation are well recognized. Subsequently, such benefits are thought to be associated with improvement in the ratio of myocardial oxygen supply to demand, resulting in part from reduced left ventricular afterload, and in part from relatively enhanced coronary perfusion of the subendocardial regions critically prejudiced by reduction of left ventricular diastolic pressures.

Although changes in the systolic function of the left ventricle after vasodilator therapy have been described,

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adheres to a specific pressure-volume curve, which has been characterized experimentally in the canine heart, and empirically in man by a monoexponential function unique to each ventricle.\textsuperscript{4,5} Acute alterations of ventricular preload and/or afterload reflecting changes in systolic or diastolic pressures, or volumes, have been considered to result in translation of the pressure-volume relation along this specific curve,\textsuperscript{6} implying that the diastolic pressure-volume relation is attributable solely to elastic forces within the myocardium.\textsuperscript{7} Some authors have observed an upward shift in the position of the entire pressure-volume curve in the presence of acute myocardial ischemia induced by rapid pacing.\textsuperscript{7,8} and have suggested the occurrence of sustained contraction, or failure of relaxation of a portion of the left ventricular myocardium, as the cause of this shift.\textsuperscript{9}

Accordingly, this study was designed to examine the effects of reduction of left ventricular afterload by nitroglycerin upon left ventricular diastolic pressure-volume relations and rate of diastolic ventricular relaxation in man. Our purposes were to determine the influence of this hemodynamic intervention upon ventricular diastolic properties and to ascertain whether primary or secondary effects of preload and/or afterload reduction on the left ventricle are responsible for the reported beneficial influence of nitroglycerin on ventricular function.

Methods

Patient Selection

Twenty-two male patients, with a mean age of 41.2 years (range 29–58), were selected from those scheduled for routine diagnostic cardiac catheterization for evaluation of chest pain suggestive of coronary artery disease. An additional six patients were studied as controls without administration of nitroglycerin. Selection of patients for study was based upon absence of significant valvular disease, cardiomyopathy, hypertension, or ventricular hypertrophy. Normal sinus rhythm was present in all cases. Signed informed consent was obtained in all cases. No complications developed.

Catheterization Procedure

Right and left heart catheterization were performed with patients in the fasting state. All cardioactive medications except nitroglycerin were withdrawn for at least 18 hours before the procedure. Premedication with 50–100 mg of hydroxyzine hydrochloride was administered intramuscularly 60 min before the study. Right and left heart catheterizations were performed using standard techniques, via the brachial or femoral artery approach. Cardiac output was measured by the Fick and/or indicator dilution (indocyanine green) techniques. Left ventriculography was performed in the basal state and following sublingual nitroglycerin, or without drug administration in those patients studied as controls. Contrast injection was performed via a 7 French pigtail catheter introduced percutaneously from the left femoral artery. Selective coronary arteriography was then performed using either the brachial\textsuperscript{10} or femoral\textsuperscript{10} artery approach.

Ventricular Pressure

High fidelity left ventricular pressures were measured with 5 or 7 French micromanometer tip catheters (Millar Instruments, Inc.) introduced via the right femoral artery using a percutaneous arterial introducer (Desilets-Hoffman, USCI, Inc.), or via a right brachial arteriography. After initial experience with 7 and 8 French micromanometer tip angiographic catheters revealed artificial displacement of the recorded ventricular diastolic pressure when contrast injection was performed via the transducer tip catheter, an additional left ventricular catheter (7 French pigtail), inserted percutaneously via the left femoral artery, was used for contrast injection. This artifact has also been noted by other investigators and has been attributed to the pressure of the contrast injection on the atmospheric reference air tube of the micromanometer catheter.\textsuperscript{11} Although fluid-filled catheter systems have been used for the study of ventricular diastolic pressure-volume relations by some authors,\textsuperscript{6,9} it has recently been emphasized that micromanometer tip catheters should be utilized for this purpose to avoid resonance artifacts observed with fluid-filled systems.\textsuperscript{4,12} In addition, accurate measurement of the first derivative of left ventricular pressure with respect to time (dp/dt) requires high frequency response obtainable only with micromanometer systems.\textsuperscript{12} Left ventricular systolic and diastolic pressures were recorded on suitable low gain (0–200 mm Hg) and high gain (0–40 mm Hg) scales respectively via the micromanometer catheter system. Catheter tip transducers were calibrated electronically (TCB 100 Control Unit, Millar Instruments, Inc.) after equilibration against the pressure recorded via the fluid-filled catheter system. Instantaneous dp/dt was obtained by direct differentiation of the left ventricular pressure signal (Accudata 132; Honeywell, Inc.). High and low gain ventricular pressures, dp/dt, electrocardiogram, cine frame pulse, and angiographic injector pulse were recorded simultaneously at a paper speed of 200 mm/sec using a multichannel recording system (Honeywell, Inc.) (fig. 1).

Experimental Protocol

After routine measurement of resting right and left heart hemodynamics and cardiac output, patients were positioned precisely in the 45° RAO projection, and left ventricular pressures measured by the micromanometer and fluid-filled catheter systems were equilibrated. To observe the effects of radiographic contrast injection upon resting hemodynamics, ventricular pressures were recorded initially during held submaximal inspiration for a period of time similar to that required for ventriculography (“mock run”). Avoidance of the Valsalva maneuver was ensured by prior careful instruction of the patient, fluoroscopic observation of the diaphragm, and monitoring of left ventricular pressures. Left ventriculography was then performed under similar respiratory conditions, injecting 30 ml of sodium and meglumine diatrizoate (Hypaque 76) into the ventricle over a three second interval by means of an ECG triggered injector (Contrac; Siemens Corp.) via the pigtail catheter, ventricular pressures being measured simultaneously by the micromanometer catheter. After the first ventriculogram, a pause of 20 min was permitted, for dissipation of the hemodynamic and myocardial effects of the contrast agent.\textsuperscript{13} When baseline systolic and end-diastolic left ventricular pressures and heart rate were restored, sufficient nitroglycerin (0.6 to 1.2 mg) was administered sublingually to obtain a reduction of left ventricular systolic pressure of 20–30 mm Hg. A second “mock run” and left ventriculogram were
then performed under similar respiratory conditions. The pressure measured with the micromanometer catheter system was equilibrated with that obtained via the fluid-filled catheter immediately before and after each ventriculogram to exclude drift in the micromanometer system. Both the patient and the X-ray equipment were maintained in precisely the same position and projection between the two ventriculograms. In six patients investigated as controls, two ventriculograms were performed 20 min apart using the same recording protocols, but without administration of nitroglycerin, to examine the effects of the contrast injection alone upon diastolic pressure-volume relationships.

Data Analysis

Ventricular pressure-volume relations were analyzed from the peak of the rapid filling wave to the “a” wave of the first well opacified beat. This period is considered to reflect most closely the elastic properties of the ventricle, with minimal influence of myocardial viscous and inertial properties, and incomplete relaxation, whose effects appear to be predominant during the rapid filling phase.  

Ventricular volume was determined serially from consecutive cine frames throughout diastole, using standard area length techniques. Volume analysis was performed using the earliest adequately opacified sinus beat in each instance, excluding premature contractions and the first or second subsequent sinus beats. All analyses were performed within the first three beats of the commencement of injection, when the effects of the contrast agent on myocardial function are negligible. Serial high fidelity diastolic pressures were measured at 16.7 msec intervals from the high gain (0–40 mm Hg) ventricular pressure tracing at intervals corresponding precisely with each cineventriculographic frame.

Observed left ventricular pressure-volume data were analyzed by fitting (by the least squares technique) to:

i) the linear function
\[ P = aV + b \]
where \( P \) = pressure in mm Hg; \( V \) = volume in cc; \( a = \Delta \) pressure, \( b \) is a constant.\(^{18}\) \( \Delta \) volume

ii) the first order exponential function
\[ P = be^{av} \]
where \( P \) = pressure in mm Hg; \( b \) = data constant; \( e \) = base of natural log; \( V \) = volume in cc; \( k \) = rate constant of the exponential function\(^{15,6,8,19-21}\)

The linear analysis was chosen initially since it is difficult statistically to compare exponential curves in valid manner.\(^{18}\) The slope “\( a \)” (\( \Delta P / \Delta V \)), of the linear function,\(^{18}\) and the rate constant “\( k \)” of the exponential function\(^2\) have previously been considered to reflect ventricular chamber diastolic stiffness in individual patients.

To define the relative “position” of the curve on the pressure-volume plot, the extrapolated pressure intercept at zero volume was derived for both linear and exponential pressure-volume functions. Since actual measurements of the pressure intercept of the pressure-volume curve are impracticable in the clinical situation, the extrapolated value of this intercept reflects a purely mathematical expression and is intended solely to define the position of the pressure-volume curves under varying hemodynamic conditions.

Left ventricular early diastolic relaxation was analyzed according to the method of Weiss et al.\(^{23}\) using “\( T \),” an index of the time course of left ventricular relaxation derived from the rate constant of the exponential pressure decline during the isovolumic period of diastole subsequent to the occurrence of peak negative \( dP/dt \). Since “\( T \)” has been shown to be independent of peak systolic pressure, and end-systolic volume and fiber length,\(^{23}\) it would appear a suitable parameter for analysis of ventricular relaxation in association with administration of nitroglycerin, which may be expected to induce changes in these hemodynamic conditions.

Statistical comparisons between data recorded at rest and after nitroglycerin were performed by means of the paired \( t \)-test, using each patient as his own control. No statistical comparison of pressure-volume relations between individual patients was performed, due to the unresolved question of appropriate normalization factors.

Results

Diagnostic Findings

Significant coronary artery disease was documented by coronary arteriography in 16 patients. Mild mitral valve prolapse was present as the only abnormality in three patients, while in the remaining three, no cardiovascular abnormality was demonstrated at catheterization. No patient with coronary artery disease developed symptomatic, electrocardiographic, or hemodynamic evidence of acute myocardial ischemia during this study.

Effects of Ventriculography on Hemodynamics

The effects of contrast injection during left ventriculography (before administration of nitroglycerin) on baseline intracardiac pressures, peak positive and negative \( dP/dt \),
and R-R intervals are listed in table 1. Average changes in peak negative dP/dt, and R-R interval varied in direction and were not statistically significant. However, consistent, statistically significant increases occurred in all intracardiac pressures and in average peak positive dP/dt with contrast injection. These increases in pressure emphasize the necessity for recording pressure and volume simultaneously when ventricular pressure-volume relations are examined using angiographic techniques. Pressures recorded prior to ventriculography are not dependable for comparative studies.8, 11

Effects of Nitroglycerin on Hemodynamics

A significant reduction was observed in peak systolic, minimal diastolic, peak “a” wave, and end-diastolic pressures in all patients after nitroglycerin (table 2). Although the average R-R interval decreased slightly (average of 6%), changes in heart rate were inconsistent and were not statistically significant.

Effects of Nitroglycerin on Early Diastolic Ventricular Relaxation

Left ventricular peak negative dP/dt fell significantly in all patients after nitroglycerin by an average of 22% (table 2). Use of peak negative dP/dt as an index of left ventricular relaxation8 has, however, recently been criticized10 due to its sensitivity to concomitant changes in peak systolic pressure and end-systolic volume. In accordance with this observation, the decline in peak negative dP/dt in the present study correlated with the fall in systolic pressure (r = 0.64). Conversely, “T” was not significantly changed after nitroglycerin, implying that at any specific level of pressure at the time of peak negative dP/dt, the rate of pressure decline during the isovolumic period of diastole is unchanged. Since “T” has been proposed as an index of the time course of left ventricular diastolic isovolumic relaxation which, unlike peak negative dP/dt, is relatively insensitive to changes in hemodynamic factors which are changed by nitroglycerin, the absence of a significant change in “T” suggests the absence of any significant relaxation changes in response to nitroglycerin.

Effects of Nitroglycerin on Left Ventricular Volume

Substantial and statistically significant reductions were observed in mean left ventricular end-diastolic and end-systolic volumes after nitroglycerin (table 2). Left ventricular stroke volume fell in 13 patients and increased in nine; thus while the mean stroke volume for the group fell slightly, the change was not statistically significant.

Effects of Nitroglycerin on Ventricular Diastolic Pressure-Volume Relationships

Although the diastolic pressure-volume relationship for the period between minimal diastolic, and peak “a” wave pressures conformed generally to a monoexponential function, during the brief period analyzed between peak rapid filling wave and peak “a” wave, which averaged 190 ± 14 (SE) msec, the pressure-volume relationships could be approximated by a linear function, with an average coefficient of determination of 0.93 (range of r = 0.82 to 0.99). Fitting the pressure-volume data to the exponential function

Effects of Nitroglycerin on Right Ventricular Hemodynamics and Volume after Nitroglycerin

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<th>TABLE 1. Changes in Left Ventricular Hemodynamics During Ventriculography</th>
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<td>&quot;Mock Run&quot;</td>
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<td>Minimal diastolic pressure (mm Hg)</td>
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<td>RR interval (msec)</td>
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*mean = ± standard error of the mean.
†mean = ± standard error of the difference.
 §Statistical significance determined by paired t-test.
 NS = not statistically significant.
 Δ = change in each parameter (absolute units ± SE).

<table>
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<th>TABLE 2. Changes in Left Ventricular Hemodynamics and Volume after Nitroglycerin</th>
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<td>&quot;T&quot; (msec)</td>
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<td>End-diastolic volume index (cc/m²)</td>
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<td>End-systolic volume index (cc/m²)</td>
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*mean = ± standard error of the mean.
†mean = ± standard error of the difference.
 §Statistical significance determined by paired t-test.
 NS = not statistically significant.
 "T" = rate of isovolumic relaxation.
Comparison of the linear and exponential fits to the pressure-volume functions before and after nitroglycerin in a representative patient is depicted in figure 2. Prominent downward and leftward displacement of the pressure-volume function is evident; in particular, substantial reduction of diastolic pressure after nitroglycerin is documented within a constant range of volume common to both pre- and post-nitroglycerin states. This phenomenon was observed in all patients, the relative magnitude of the displacement downward and leftward being apparently related to the changes in ventricular pressure and volume respectively. In all patients, the downward shift of the pressure-volume function was confirmed by a statistically significant decline in the extrapolated pressure intercept of the pressure-volume function using both linear and exponential approximations (paired t-test) (table 3). No significant difference in the magnitude of the displacement of the pressure-volume function was observed between patients with and without coronary artery disease.

For the whole patient group, the average slope of the linear fit and rate constant of the exponential fit to the pressure-volume functions before and after nitroglycerin are compared in table 3. For all patients, despite significant downward displacement of the pressure-volume function, no significant change was observed in the average slope of the linear fit, or rate constant of the exponential fit to the observed pressure-volume data (table 3).

By comparison, pressure-volume curves obtained during serial ventriculograms were virtually superimposable in all six patients studied as controls without administration of nitroglycerin. Thus, left ventricular pressure-volume relations obtained during contrast injection were unaffected by ventriculography per se when adequate time was permitted for dissipation of the direct effects of the contrast agent on myocardium.¹⁶

**Discussion**

Controversy exists regarding the most appropriate technique for assessment of ventricular diastolic chamber stiffness and relaxation in man and is further compounded by the technical difficulties associated with simultaneous measurement of pressure and volume. Several investigators have utilized ventricular pressures measured immediately prior to ventriculography, in conjunction with ventricular volumes determined angiographically shortly thereafter.⁶ ⁸ ¹¹ Although changes in ventricular contractile function within the first five beats after commencement of angiographic injection have been shown to be insignificant,¹⁷ our results indicate a small, though significant increase in both systolic and diastolic ventricular pressures during injection. Although it was not possible to assess the effects of the contrast injection upon ventricular volumes in this study, Vine et al. have shown that no significant changes in left ventricular end-systolic or end-diastolic volume occur during contrast injection in man.⁹ Thus, in view of the documented changes in ventricular pressure during injection, simultaneous measurement of ventricular pressure and volume appears essential when left ventricular pressure-volume relationships are examined using angiographic techniques.

Several mathematic models have been proposed to describe the pressure-volume function during diastole. Thus, McCullagh et al. described an "index of diastolic stiffness" defined as the slope of the linear fit to a series of determinations of end-diastolic pressure-myocardial segment length,
over a range of loading conditions in conscious dogs. Likewise, Grossman et al.27, 28 have analyzed left ventricular pressure-diameter relations during mechanical left atrial systole, using Δ pressure/Δ diameter as an estimate of "operational" left ventricular chamber stiffness during late diastole. The observation by Noble et al.4 and by Diamond et al.29 that diastolic left ventricular pressure-volume relations in the intact dog heart could be reasonably fitted to an exponential function receives theoretical support from the proven exponential nature of the length-tension curve in isolated cardiac muscle.30 Although application of exponential analysis to the human situation has not been fully validated,14, 22 it has recently been used by several authors for the description and quantification of diastolic left ventricular pressure-volume relations in the clinical setting.8, 11, 22

Clearly, the optimal function for expression of ventricular chamber diastolic stiffness in man is at present uncertain.40 However, it was not the object of this study to develop an expression of ventricular stiffness which would serve as a basis for comparison between different individuals, for which some means of normalization for ventricular wall thickness, volume and/or mass is necessary.19, 21, 30 Rather, it was our purpose to quantify ventricular chamber pressure-volume relations in individual patients to permit observation and statistical comparison of the effects of an acute alteration of ventricular loading conditions on that relation. For these purposes, use of a simple linear or monoeexponential fit to the pressure-volume data seemed appropriate, and provided statistically satisfactory approximation of the observed data in this study. Although such simple expressions do not quantitate muscle stiffness or provide a basis for comparison between patients due to the lack of appropriate normalization for individual heart size, they have been considered to represent a useful descriptor of ventricular pressure-volume relations in the intact ventricle in individual patients.6, 22

The nature of early diastolic ventricular relaxation, and its assessment are controversial. Recently, peak negative dP/dt, which approximates the rate of decline of ventricular wall tension during the isovolumic relaxation period, has been utilized by McLaurin et al.24, 31 as a convenient index of ventricular relaxation in the intact heart. However, aware of the dependence of peak negative dP/dt upon aortic peak systolic pressure and end-systolic left ventricular volume,32 and of its limitation to the description of relaxation at only one point of time, Weiss et al. have recently proposed a function "T," derived from the rate constant of the exponential left ventricular pressure fall during isovolumic relaxation, as an index of the time course of isovolumic diastolic ventricular relaxation, and thus of the activity of the myocardial relaxing system.33 This function, which was shown to be independent of peak systolic pressure, end-systolic volume and fiber length and minimally dependent upon heart rate, was found to be significantly more sensitive than peak negative dP/dt for detection of myocardial ischemia during rapid atrial pacing in patients with coronary artery disease.34 Although acute myocardial ischemia in patients with coronary heart disease has been reported to result in an increase in the slope of the left ventricular pressure-volume curve reflecting decreased compliance,4, 6 other authors have recently demonstrated an upward shift of the entire pressure-volume function,7, 8 suggesting that an alteration of the relaxation process, or sustained contraction of a portion of left ventricular myocardium during angina may be responsible for such elevation of the pressure-volume function.8 Thus, much evidence attests to the importance of early diastolic relaxation in the determination of diastolic pressure-volume relations, and it was considered important to examine early diastolic relaxation directly, in addition to mid and late diastolic pressure-volume relations. Since "T" appears to be an index of left ventricular relaxation that is relatively insensitive to changes in hemodynamic factors induced by nitroglycerin, the lack of change in "T" observed in the present study suggests that alterations of relaxation are not the major explanation for the documented shift in the pressure-volume relationships.

The mechanisms responsible for the displacement of the pressure-volume function observed in this study are conjectural. Downward displacement of the left ventricular pressure-volume function has also been reported by Alderman et al.11 and Brodie et al.28 in response to reduction of left ventricular loading conditions by nitroprusside, and has been attributed to an effect of nitroprusside upon myocardial relaxation.33 In the present study, however, "T," an index of the time course of left ventricular isovolumic relaxation which, unlike peak negative dP/dt, is insensitive to hemodynamic changes induced by nitroglycerin, was not significantly altered. Thus relaxation changes do not appear to constitute the major explanation for the shift in the pressure-volume relationship observed after nitroglycerin.

Further, using a theoretically derived mathematical function validated in dog studies for evaluation of myocardial elasticity, Alderman et al. showed the absence of significant change in myocardial elasticity in man during shifts of the pressure-volume curve induced by nitroprusside.15 Hence, the observed displacement of the pressure-volume function in response to pre- and afterload reduction under these circumstances would not appear to be attributable to any direct effect of these hemodynamic changes upon either ventricular diastolic elastic properties or relaxation per se.

Changes in the behavior of the anatomical constraints to left ventricular distension including the right ventricular chamber, the pericardium, and the pleural cavity13 associated with altered pressure and volume loading conditions have also been suggested to contribute to the observed displacement of the pressure-volume curves. Thus, increased right heart filling pressures have been shown experimentally to increase left heart filling pressures in perfused dog heart preparations with intact pericardia by Bemis et al.24 Since the constraint to left ventricular distension exerted by the right ventricle via the interventricular septum is at least partially determined by right ventricular filling pressures and volumes, reduction of venous return associated with the prominent peripheral venous pooling effect of nitroglycerin may be expected to reduce the constraint to left ventricular filling exerted by the right ventricle, thus reducing left ventricular pressures and volumes and shifting the pressure-volume relation downward without altering chamber stiffness directly. Yet another constraint to left ventricular distension is the perfusion pressure within the coronary vascular bed. Bacaner et al.36 demonstrated that coronary blood flow is a critical determinant of cardiac size and cardiac performance in dogs. Further, Salisbury et al.36 showed
that alteration of coronary perfusion pressure in canine hearts was associated with directionally similar changes in left ventricular end-diastolic pressure. These authors attributed the observed inverse relationship between coronary vascular perfusion pressures and ventricular distensibility to an increasing volume of blood retained within the coronary circulation when coronary arterial pressures are increased, concluding that such turgor of the coronary vessels directly influenced ventricular distensibility.

Pleural pressures were not measured in the present study. However, Alderman et al. indicated that while changes in pleural pressures may affect pressure-volume relations slightly between patients, in individual patients under identical respiratory conditions, pleural pressures are similar and would not be expected to account for a significant shift of the pressure-volume relation.11

In summary, significant downward shifts in the position of the left ventricular pressure-volume function, without alteration either of the slope of the function or of “T,” an index of the time course of isovolumic ventricular relaxation, occur both in normal subjects, and in patients with coronary artery disease after reduction of pre- and afterloading conditions by nitroglycerin. Such changes do not appear to be attributable to changes in the elastic properties of the myocardium, but may be due to alteration of the physical constraints to left ventricular distension proffered by the right ventricle, pericardium, and/or perfusion pressure within the coronary vascular tree. Such changes contradict the concept of a single pressure-volume curve, specific to each ventricle and suggest the existence of a family of pressure-volume curves with similar slope but variable position, dependent upon the immediate loading conditions. The occurrence of shifts of the pressure-volume function make substitution of end-diastolic ventricular pressure for end-diastolic volume, or fiber length, invalid when changes in ventricular systolic function in response to hemodynamic interventions are evaluated using classical ventricular function curves. These results suggest an indirect beneficial effect of afterload reduction on ventricular function, namely, the downward displacement of the left ventricular pressure-volume curve with the resulting diminution of myocardial oxygen consumption associated with the smaller ventricular volume.

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References

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