Is τ a Preload-Independent Measure of Isovolumetric Relaxation?

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Several studies have been performed in patients with a variety of myocardial diseases that have identified a prolongation of τ. However, it is not clear whether prolongation of τ represents abnormal myocardial physiology or the effect of excessive load associated with a particular disease process. Accordingly, we evaluated the effect on τ of an isolated decrease in preload induced by inferior vena cava occlusion before the appearance of reflex changes in six patients designated as normal by catheterization criteria. A computer-based digitization routine identified cardiac contractions in all patients early after inferior vena cava occlusion where left ventricular end-diastolic pressure decreased (18.3±6.3 to 9.3±5.8, p<0.05) while left ventricular systolic pressure (113.3±13.8 to 111.8±14.0, p=NS) and heart rate (66.0±10.0 to 65.9±10.3, p=NS) did not change. After this alteration in preload, no change in τ from baseline, as calculated by the logarithmic (T1), derivative (T_D), or method of Mirsky (T_1/2), was noted: T_1, 47.4±6.5 to 44.6±7.6; T_D, 39.3±8.1 to 39.8±8.4; T_1/2, 33.0±4.0 to 31.8±4.6; all p=NS. The baseline pressure extrapolated from isovolumetric relaxation did not change in these preload beats compared with baseline (+4.26±6.20 to -0.80±4.87, p=NS). Subsequent beats were identified where left ventricular systolic pressure showed a numeric decrease compared with baseline (113.3±13.8 to 100.8±14.3, p=NS) despite no change in heart rate (66.0±10.0 to 66.8±10.5, p=NS). The extrapolated baseline pressure decreased in these subsequent beats compared with baseline (+4.26±6.20 to -3.90±4.26, p<0.05) despite no change in τ (T_1, 47.4±6.5 to 41.6±8.4; T_D, 39.3±8.1 to 40.8±11.1; T_1/2, 33.0±4.0 to 31.7±4.2; all p=NS). Visual display of the individual natural log of left ventricular pressure versus time values used to calculate T_1 were consistent with exponential pressure decay as an appropriate model for isovolumetric relaxation. This study demonstrates that τ is a preload independent measure of isovolumetric relaxation. (Circulation 1989;80:1757-1765)

The relaxation of isolated papillary muscle is dependent on the total load imposed on the muscle. This concept was first demonstrated by Parmley and Sonnenblick and more recently expanded by Brutsaert et al. The muscle preparations used in these studies included both isometric and afterloaded isotonic contractions. Because of the nonphysiologic sequence of relaxation during an afterloaded isotonic contraction (isotonic before isometric relaxation), the load dependence of relaxation has been examined by "physiologically sequenced" relaxation. With this method the load dependence of relaxation was reconfirmed although at a temperature of 28°C. More recently, Gaasch et al demonstrated that variable preload, with constant total load, did not produce a change in isometric relaxation. Relaxation of isolated papillary muscle is, therefore, independent of preload but dependent on total load.

Similar observations have been extended to the intact animal heart. Karliner et al found that primary changes in afterload produced changes in the time constant of isovolumetric left ventricular pressure (LVP) decline (τ), but volume infusion did not produce such changes. Gaasch et al also found that modest changes in left ventricular preload did not influence τ, but when volume loading was sufficient to produce an increase in aortic pressure, τ increased. Gaasch et al recently extended this observation to an isolated increase in left ventricular preload, finding no associated change in τ. In contrast, Raff and Glantz found that volume loading slowed τ, and they concluded that this effect was a reflection of both preload and afterload. Therefore, these conclusions were reached on the basis of...
multiple linear regression analysis and not pure preload changes. Most data in the intact animal heart favor \( \tau \) being independent of preload but dependent on afterload.

The present study was designed to determine whether \( \tau \) is a preload-independent measure of isovolumetric relaxation in patients undergoing cardiac catheterization. Several studies have been performed in patients with a variety of myocardial diseases and have identified a prolongation of \( \tau \). However, it is not clear whether prolongation of \( \tau \) represents abnormal myocardial physiology or the effect of excessive load associated with a particular disease process. Accordingly, we evaluated the effect on \( \tau \) of an isolated decrease in preload induced by inferior vena cava occlusion before the appearance of reflex changes in six patients without documentable cardiac disease by catheterization criteria.

**Methods**

**Study Group**

Inferior vena cava occlusion with simultaneous hemodynamic monitoring was performed at the time of cardiac catheterization in eight patients. One patient developed transient atrial fibrillation, and a second had simultaneous falls in preload and afterload. These two patients were excluded from data analysis. Among the remaining six patients there were five men and one woman with an age range of 29–52 years. All medications were withheld for at least 18 hours prior to catheterization. These patients all had atypical chest pain syndromes and normal physical examinations, electrocardiograms, right and left-heart pressures, cardiac outputs, coronary arteriography, and biplane left ventriculography. All patients gave written consent to a protocol approved by the Human Investigation Committee of the University of Virginia. There were no complications as a result of this study.

**Cardiac Catheterization and Angiography**

Routine left-heart catheterization was performed from the left groin and right-heart catheterization from the right groin, leaving the latter for the inferior vena cava balloon. Right-heart catheterization was performed with a 7F flow-directed, balloon-tipped catheter (Critikon, Tampa, Florida). Coronary angiography was performed by the Judkins technique. Left ventriculography was performed through a pigtail catheter with biplane cine recordings. Nonionic contrast (Iopamidol, Squibb, New Brunswick, New Jersey) was used to minimize the myocardial depressant effects of contrast. Pressures were measured with thoroughly flushed disposible air reference transducers (Spectramed, Oxnard, California). Recordings were inscribed by means of a Honeywell Electronics-for-Medicine VR-16 Recorder.

**Inferior Vena Cava Occlusion Protocol**

After completion of coronary angiography and left ventriculography, the deflated SF 40-mm occlusion balloon catheter (OBW 40/8/2/100, Mansfield Scientific, Mansfield, Massachusetts) was introduced percutaneously into the right femoral vein, positioned in the right atrium over an 0.035-in. guidewire, and inflated. A 7F micromanometer pigtail catheter was subsequently introduced into the left ventricle and balanced. Analog data from the electrocardiogram (ECG), micromanometer LVP, and on-line dP/dt were stored on a nine-channel cassette FM recorder (MR-40, TEAC, Montebello, California).

Thirty minutes passed between the last injection of nonionic contrast and data collection. All patients were instructed on breath-holding before the catheterization, and all data were collected at midexpiration. Analog recordings of ECG, LVP, and online dP/dt were continuously made throughout the research portion of the catheterization. The 40-mm balloon was pulled to the right atrial–inferior vena cava junction. The occlusion was maintained until left ventricular systolic pressure fell no lower than 80 mm Hg, at which point the balloon was readvanced into the right atrium. The baseline systolic LVP for these six patients was 113 ± 14 mm Hg, and the nadir pressure in response to inferior vena cava occlusion was 95 ± 17 mm Hg. The goal of this study was to obtain a decrease in preload and not afterload; therefore, the occlusions were often released before obtaining a true maximal fall in pressure. Six occlusions were performed in each patient, of which only one was used for data analysis. The occlusions not analyzed had either ectopy, inability of the patient to hold his or her breath at midexpiration, or no preload beats.

**Data Analysis**

The analog data recorded during the inferior vena cava occlusion were played back to the computer-based digitization routine we developed. This routine digitized each waveform and stored the data to be analyzed. By handling the analog data in this manner, we eliminated the errors for off-line hand digitization of the analog signal traces. The sampling rate for digitizing the analog signals was 1-msec intervals (1 kHz), thus providing greater accuracy than the 5-msec (200 Hz) digitization rates previously reported. 5–8, 10–11, 14–16 The computer-based digitization hardware consisted of an LSI 11/23+ computer with an on-board 12-bit analog-to-digital converter (Andromeda Systems ADC11, Orange, California), a video display, and our software.

\( \tau \) was calculated by three methods. The first used a plot of \( \ln(LVP) \) versus time, as derived by Weiss et al \( (T_\alpha) \). 17 This approach assumed that LVP during isovolumetric relaxation decays in a monoeponential manner to zero. The second method assumed a variable asymptote to LVP decay, taking into
account the effects of pleural and pericardial pressure. This method, developed by Raff and Glantz, used a plot of negative dP/dt versus LVP (T1/2) and allowed calculation of extrapolated, residual LVP, assuming diastole to be infinite in duration (Pb). The preload dependence of Pb was therefore also determined in this study. The third method computed the time needed for LVP to fall to one half of its value from peak negative dP/dt, using the method of Mirsky (T1/2). T1/2 is similar to TL in that the latter is the time it takes for pressure to fall from maximum negative dP/dt to 1 eth that pressure, and T1/2 uses one half instead of 1 eth. The use of T1/2 advocates not going through the exercise of the exponential fit but simply determining τ from the pressure fall itself.

Statistical Analysis

Mean values and SDs were calculated at baseline, after preload reduction, and after total load reduction. The three groups of data were compared by analysis of variance (ANOVA). Duncan’s multiple-range test was used to directly compare data at baseline versus preload reduction, baseline versus total load reduction, and preload versus total load reduction. A p value less than 0.05 was considered significant.

Results

Hemodynamics

The mean hemodynamic data at baseline, after reduction of only preload, and after a subsequent reduction in total load (preload and afterload) with inferior vena cava occlusion are shown in Table 1. An example of hemodynamic data from a patient is shown in Figure 1. The heart rate was not altered after a reduction in preload or after a reduction in total load (66.0±10.0 to 65.9±10.3 to 66.8±10.5 beats/min, respectively; p=NS). The systolic LVP was not altered after a reduction in preload (113.3±13.8 to 111.8±14.0 mm Hg; p=NS). Although there was a numeric decrease in systemic LVP in the total load beats from 113.3±13.8 to 100.8±14.3 mm Hg, statistical significance was not achieved. The left ventricular end-diastolic pressure (LVEDP) decreased after a reduction in preload and decreased further with a reduction in total load (18.3±6.3 to 9.3±5.8 to 6.3±6.4 mm Hg, respectively; p<0.05). Peak positive dP/dt decreased with a reduction in preload (+1,576±129 to 1,462±80 mm Hg/sec; p<0.05). With a reduction in total load, there was a numeric decrease that did not achieve statistical significance from preload (+1,462±80 to 1,399±126 mm Hg/sec, p=NS). Peak negative dP/dt was not altered with a reduction in preload (-2,027±160 to -1,943±196 mm Hg/sec; p=NS) but decreased with a reduction in total load (-1,808±264 mm Hg/sec; p<0.05 vs. baseline and preload).

Effect of Preload and Total Load Changes on τ

TL, Tp, and T1/2 are presented in Table 1 at baseline, after a reduction of only preload, and after a subsequent reduction in total load with inferior vena cava occlusion. There were 46.7±6.2 points used to calculate τ at baseline. The number of points increased in the preload and total load beats (54.2±5.5, 60.4±2.0, respectively; p<0.05). There was no change in Tp with a reduction in preload or total load (47.4±6.5 to 44.6±7.6 to 41.6±8.4 msec, respectively, p=NS). The correlation coefficient (R) for T1 was similar at baseline, after a reduction in preload, and after a reduction in total load (−0.996±0.004 to −0.995±0.005 to −0.996±0.005, respectively; p=NS).

There was no change in Tp from baseline with a reduction of only preload and after a subsequent reduction in total load (39.3±8.1 to 39.8±8.4 to 40.8±11.1 msec, respectively; p=NS). R for Tp was similar at baseline, after a reduction in preload, and after a reduction in total load (−0.862±0.038 to

<table>
<thead>
<tr>
<th>Table 1. Mean Patient Data</th>
<th>Baseline</th>
<th>Preload</th>
<th>Total load</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>66.0±10.0</td>
<td>65.9±10.3</td>
<td>66.8±10.5</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>113.3±13.8</td>
<td>111.8±14.0</td>
<td>100.8±14.3</td>
</tr>
<tr>
<td>LVEDP (mm Hg), visual</td>
<td>14±2</td>
<td>8±2*</td>
<td>3±3*†</td>
</tr>
<tr>
<td>LVEDP (mm Hg), computer derived</td>
<td>18.3±6.3</td>
<td>9.3±5.8*</td>
<td>6.3±6.4†</td>
</tr>
</tbody>
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*p<0.05 vs. control, †p<0.05 vs. preload.

HR, heart rate; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; n, number of points used to calculate τ; TL, τ logarithmic; Tp, τ derivative; T1/2, τ method of Mirsky; R, correlation coefficient; Pb, pressure baseline.
Figure 1. Tracings of left ventricular pressure fall in response to inferior vena cava occlusion in one patient. The double hatch mark notes the onset of occlusion. ○, Baseline beat; ●, preload beat; ▲, total load beat. As is evident, a fall in end-diastolic pressure precedes a fall in systolic pressure.
Effect of Preload and Total Load Changes on $P_b$

Determination of $T_o$ provided a calculation of the extrapolated residual LVP ($P_b$). At baseline $P_b$ was $+4.26\pm6.20$ mm Hg. After a reduction in preload with inferior vena cava occlusion, there was a numeric decrease in $P_b$ that did not achieve statistical significance ($-0.80\pm4.87$ mm Hg; $p=0.20$ vs. baseline). With a reduction in total load, $P_b$ did decline to $-3.9\pm4.26$ ($p<0.05$ vs. baseline).

Linearity of lnP Versus Time

In Figure 2 the natural log of left ventricular pressure versus time is depicted for each of the six patients during inferior vena cava occlusion. The open circles represent the baseline beat, the closed circles a reduction in preload, and the closed triangles a reduction in total load. Each symbol is a lnP versus time value digitized at a frequency of 1 kHz. In all patients, there was a parallel downward shift from baseline to preload to total load beats, consistent with no change in the slope of the ln(P) versus time relation (or $T_o$) despite a visibly evident decrease in preload and total load. In addition, the exponential nature of the pressure decline during isovolumetric relaxation is visibly evident.

Biexponential Pressure Decay of Negative $dP/dt$ Versus Left Ventricular Pressure

In Figure 3 negative $dP/dt$ versus LVP is depicted for each of the six patients during inferior vena cava occlusion. The open circles represent the baseline beat, the closed circles a reduction in preload, and the closed triangles a reduction in total load. Each symbol is a negative $dP/dt$ versus $P$ value digitized at a frequency of 1 kHz. The preload and total load values separated from the baseline values only during the first half of isovolumetric relaxation. There was the appearance of biexponential pressure decay, as previously described by Brower et al.

Discussion

This study altered preload in six patients with inferior vena cava occlusion before the appearance of reflex increases in heart rate. After this alteration in preload, no change was noted in $T_o$ as calculated by the logarithmic, derivative, or method of Mirsky. Although there was a decreasing trend for $P_b$, statistical significance was not achieved. Subsequent beats were also identified where systolic LVP decreased although without reaching statistical significance. $T_o$ calculated by the three methods above still did not change, but $P_b$ decreased. Visual display of the individual ln of LVP versus time values used to calculate $T_o$ by the logarithmic method were consistent with exponential pressure decay as an appropriate model for isovolumetric relaxation.

A strength of this study was the ability to alter loading conditions in patients before the appearance of reflex changes without the use of an intravenous drug infusion. The technique used was transient occlusion of the inferior vena cava, popularized in the animal laboratory by Rankin and coworkers. However, traditional muscle mechanic studies in patients have not taken advantage of this technique but, rather, have used drug infusions to alter load. For instance, Starling et al recently demonstrated that $T_o$ was a load-independent measure of isovolumetric relaxation. They altered load by infusing methoxamine and nitroprusside while performing atrial pacing to maintain a constant heart rate. However, their study was weakened by the cardiovascular effects of these drugs. Methoxamine is a relatively specific $\alpha_1$-adrenoceptor agonist. Human myocardium contains $\alpha$-adrenergic receptors in both the atrium and the ventricle. Methoxamine infusion has both inotropic and chronotropic effects, mediated by increased influx of calcium through calcium channels. Scholz et al confirmed these results, demonstrating an increased magnitude of the slow inward calcium current and associated inotropic effect. However, a decreased rate of decay of the slow inward calcium current was also noted by these same workers. Methoxamine can also increase coronary resistance, override intrinsic coronary regulatory influences, and produce ischemia in dogs with normal coronary arteries. The variety of cardiovascular effects mentioned above can have opposite effects on $T_o$ and explain, in part, the load independence of $T_o$ demonstrated by Starling et al.

A second strength of this study was accurate calculation of $T_o$. Several hemodynamic studies performed in both the animal and cardiac catheterization laboratories determined $T_o$ by reentering hand-traced LVP recordings into a computer. Human error could be introduced into the raw data before computer calculation of $T_o$. We stored analog left ventricular pressure signals on a tape recorder and, with an analog-to-digital converter, reentered the pressure signal into a computer for calculation of $T_o$. Because no human error or bias was introduced when converting the analog LVP signal to a digital format, the data were digitized every 1 msec in the current study, fivefold faster than previously reported in the literature. $T_o$ was calculated from a mean of 54±8 points for the logarithmic and derivative methods.

In addition to its preload independence, $T_o$ may be independent of total load within a physiologic range. There have been several clinical studies of hypertrophy and ischemia equating a prolongation of myocardial relaxation (or $T_o$) with abnormal left ventricular diastolic function. These studies were weakened by increased systolic LVP, LVEDP, or both imposed on the myocardium when $T_o$ was
FIGURE 2. Plots of ln of left ventricular pressure versus time for each of six patients during inferior vena cava occlusion. ○, Baseline beat; ●, reduction in preload; ▲, reduction in total load. (See text for discussion.)

prolonged. Our findings support the assumptions of the above studies that alterations in \( r \) are independent of load changes. Although the goal of the current investigation was to produce pure preload beats, total number of load beats was identified as well. No change in \( r \) was noted with simultaneous falls in systolic and diastolic LVP. To avoid a reflex increase in heart rate, the total load beats produced with inferior vena cava occlusion did not achieve a significant change in left ventricular systolic pressure from baseline (113.3±13.8 to 100.8±14.3 mm Hg), although the trend was clear. However,
Starling et al produced greater alterations in load with drug infusions and confirmed the load independence of \( \tau \) in humans over a physiologic range in the cardiac catheterization laboratory.\(^{14}\) The present investigation, in conjunction with the work of Starling et al, argues that given the physiologic constraints of hemodynamic studies performed in patients, \( \tau \) is a load-independent measure of isovolumetric relaxation.

To determine the preload dependence of \( \tau \), the current study decreased filling of the left ventricle, while work by Gaasch et al\(^5\) and Karliner et al\(^6\) used volume infusion. Occlusion of the inferior vena cava to alter preload was the opposite of these canine studies using volume infusion. In all of these studies, \( \tau \) was found to be independent of preload. However, increasing preload enough to raise systolic LVP in the studies of Gaasch and Karliner did...
produce an increase in τ. These studies imply that τ may be dependent on preload only to the extent that changes in preload affect systolic loading. In the present study and the work of Starling et al.,14 decreases in load sufficient to decrease systolic LVP did not change τ. Thus, increasing as opposed to decreasing load may change the rate of isovolumetric relaxation. For instance, when load is increased, isovolumetric relaxation may be prolonged. Conversely, a decrease in load may have no effect. However, in the study of Starling, an increase in load did not prolong isovolumetric relaxation. These data must temper the notions of the type of systolic load (i.e., increasing load and prolonging τ versus decreasing load and not affecting τ).

Unlike τ, the baseline pressure (Pb) extrapolated from isovolumetric relaxation, which represents a baseline to which pressure would fall if decay continued infinitely, was found to be load dependent in the present study. Pb may reflect a basal level of diastolic myocardial tone, but its physiologic meaning has been unclear. Carroll et al, for instance, attached important physiologic significance to Pb and believed that exercise-induced ischemic increases in Pb represented an important influence of slowed isovolumetric relaxation on elevated pressures late in diastole.25 In contrast, Thompson et al did not demonstrate pacing-induced ischemic alterations in Pb despite prolongation of isovolumetric relaxation and elevation of LVEDP.15 The present study demonstrated a downward trend in Pb with decreasing preload and a significant fall in Pb with a fall in both preload and afterload (Table 1). Future studies in patients designed to examine physiology with Pb in the cardiac catheterization laboratory will have to be tempered by the load dependence demonstrated in this study.

In their original description Weiss et al believed τ was a reflection of the “active cardiac relaxation system.”17 Several investigators have since identified a prolongation in τ in several disease states, including myocardial ischemia, cardiac hypertrophy secondary to essential hypertension and valvular heart disease, hypertrophic cardiomyopathy, and congestive cardiomyopathy. Grossman and coworkers, in particular, have related this prolongation in isovolumetric relaxation in part to abnormal calcium handling.9-11 The present study supports using τ as a reflection of calcium handling by the myofilaments. As is visually evident in Figure 2, the plot of the ln of LVP versus time was linear for all baseline, preload, and total load beats. This exponential decay of pressure was consistent with mathematic models of calcium release from the myofilaments. Potter et al, for instance, used a numeric computer solution to display the exponential time course of calcium release from troponin and calmodulin.26

There were several limitations to this study. The absence of a change in τ with a decrease in preload may be due to opposite physiologic effects produced by the method chosen to alter load. Inferior vena cava occlusion, by unloading the right ventricle, may change the radius of curvature of the intraventricular septum. Resultant asynchronous relaxation of the left ventricle would prolong τ. 27 A simultaneous decrease in left ventricular preload, however, would be expected to decrease τ according to isolated cardiac muscle studies.2 These two opposite effects might cancel one another and produce no change in τ with alterations in preload, as seen in this study. A second limitation of this study was the inability of inferior vena cava occlusion to produce a statistically significant decrease in systolic LVP before the appearance of a reflex increase in heart rate. It is difficult, therefore, to reach firm conclusions regarding the total load dependence of τ on the basis of this study. Third, although the patients chosen to participate in this study were normal by cardiac catheterization criteria, their baseline LVEDPs were elevated. This finding was an artifact of the computer digitization routine. The computer software was written to locate LVEDP at the peak of the R wave of the electrocardiogram. Reanalysis of LVEDP “by hand” defined by the atrial systolic deflection on the upstroke of LVP gave a mean LVEDP of 14 ± 2 mm Hg. Finally, our results were not in conflict with the known load dependence of relaxation in isolated papillary muscle. It is an intrinsic property of cardiac muscle that the rate of relaxation is load dependent.1-4 Rather, in the intact human heart, when isolated reductions in preload are evaluated, τ is found to be load independent over a relatively narrow physiologic range. Although we produced statistically significant reductions in preload, the magnitude of decrease in LVEDP was only over an approximately 6-9 mm Hg range. Therefore, when isolated reductions in preload are performed in patients, this method of assessment of isovolumetric relaxation as a variable of active muscle relaxation is not affected.

In conclusion, this study has demonstrated that τ is a preload-independent measure of isovolumetric relaxation. This conclusion is strengthened by the method used: altering load with inferior vena cava occlusion before the onset of reflex changes and recording pertinent analog signals on cassette tape for later “on-line” computer digitization. Unlike τ the baseline pressure (Pb) extrapolated from isovolumetric relaxation is load dependent. Because of the frequency of computer digitization used, this study lends support to exponential pressure decay as an appropriate mathematic model for isovolumetric relaxation. Finally, this study supports the use of τ as a reflection of myocardial physiology because of its load independence.

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References


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