Load independence of the rate of isovolumic relaxation in man

MARK R. STARLING, M.D., DANIEL G. MONTGOMERY, B.S., G. B. JOHN MANCINI, M.D., AND RICHARD A. WALSH, M.D.

ABSTRACT This investigation was designed to determine whether the rate of isovolumic left ventricular pressure decline is affected by load in man. Fourteen patients were instrumented with micromanometer left ventricular and right atrial pacing catheters to maintain a constant heart rate during control conditions and infusion of methoxamine or nitroprusside. The isovolumic relaxation period was defined as the time from peak (−)dP/dt to 5 mm Hg above left ventricular end-diastolic pressure of the following beat. The rate of isovolumic relaxation was calculated as time constants (τ) from the linear regression of natural log pressure vs time (Tln) and instantaneous (−)dP/dt vs pressure (TDP), which includes a variable asymptote (P0). The mean heart rates and average (+)dP/dt values normalized at 40 mm Hg development pressure (DP40) did not differ significantly, despite 33% and 43% increases in left ventricular peak and end-diastolic pressures during the infusion of methoxamine (p < .001 and p < .01, respectively) and 24% and 29% decreases during the infusion of nitroprusside (p < .001 and p < .01, respectively). The average Tln and TDP values were not significantly affected by these alterations in load. In two patients, an inverse linear relationship was demonstrated between decreases in Tau and increases in contractile state produced by an infusion of dobutamine, as shown by correlation of Tln and TDP with (+)dP/dt/DP40 (τ = −.88 and −.83, respectively). We conclude that the time constants of left ventricular isovolumic relaxation are unaffected by modest alterations in loading conditions in man when heart rate is maintained constant. In the absence of nonuniformity, therefore, the time constant of relaxation probably represents an estimate of energy-dependent inactivation of contractile proteins under these conditions.

relaxation in patients with normal left ventricles is affected by modest alterations in loading conditions.

Methods

Patients. The patient population consisted of 14 subjects (nine men and five women; ages 32 to 60 years [mean 48 ± 8]) who were being evaluated for chest pain. All patients had a normal physical examination, electrocardiogram, chest roentgenogram, and M mode echocardiographic study. Before cardiac catheterization, written informed consent for this investigation, as approved by the Human Studies Committee of the University of Michigan and VA Medical Centers, Ann Arbor, Michigan, or the University of Texas Health Science Center, San Antonio, Texas, was obtained. All medications were discontinued 24 to 48 hr before cardiac catheterization. All patients had normal intracardiac pressures, cardiac outputs, coronary arteriograms, biplane left ventriculograms, and negative ergonovine stimulation tests.

Protocol. After completion of the routine cardiac catheterization, a precalibrated, high-fidelity micromanometer catheter (VPC-780C or VPC-784D; Millar Instruments, Houston) was placed in the left ventricle. In addition, a bipolar pacing catheter was placed in the right atrium to maintain a constant heart rate throughout the protocol. Two electrocardiographic leads, high-fidelity micromanometer left ventricular pressures, and the first derivative of left ventricular pressure (dp/dt) obtained by continuous electronic differentiation of the left ventricular pressure signal were recorded with an Electronics for Medicine VR-16 or VR-12 physiologic recorder at 100 mm/sec paper speed. These hemodynamic recordings were obtained for 20 beats at three different times separated by approximately 3 min to establish hemodynamic steady state during control and during an infusion of each pharmacologic agent.

Pharmacologic interventions. After the control hemodynamic recordings were obtained, each patient received an infusion of methoxamine adjusted to increase left ventricular pressure by approximately 40 mm Hg compared with control. The steady-state infusion rate ranged from 200 to 1000 µg/min. This was followed by an infusion of nitroprusside to reduce left ventricular pressure by approximately 30 mm Hg compared with control. The steady-state infusion rate for nitroprusside ranged from 35 to 90 µg/min. Finally, in three patients, an infusion of dobutamine was begun at 5 µg/kg/min after left ventricular pressures had returned to the control values. In two of these three patients, hemodynamic recordings were made frequently to obtain a range of values as contractile function progressively increased during the infusion of dobutamine until steady state was reached, whereas in one patient hemodynamic recordings were made only at steady state. Hemodynamic steady state was defined for each pharmacologic intervention as less than a 10 mm Hg variation in left ventricular peak pressure.

Computer analysis. The left ventricular pressure signals during control and steady-state infusion of each pharmacologic agent were hand digitized with a Calcomp 9100 inductance tablet interfaced to an IBM PC computer, and the results were averaged over a full respiratory cycle. The program developed in our laboratory provides instantaneous left ventricular pressure and the first derivative of left ventricular pressure, dp/dt, by differentiating the digitized left ventricular pressure signal at a variable sampling frequency after a three-point running smooth of the raw data. For this investigation, the sampling frequency was 200 Hz. The isovolumic relaxation period was then defined as the period from peak (−dp/dt) to 5 mm Hg. Other investigators have suggested that the isovolumic relaxation period should end 10 mm Hg above left ventricular end-diastolic pressure of the following beat. Other investigators have suggested that the isovolumic relaxation period should end 10 mm Hg above left ventricular end-diastolic pressure of the following beat to ensure that mitral valve opening has not occurred and that the fall in left ventricular pressure relative to time permits the use of a monoeponential model. Thus we also evaluated the isovolumic relaxation period ending 10 mm Hg above left ventricular end-diastolic pressure of the following beat.

Calculation of the time constants. We calculated the time constant of isovolumic relaxation (τ) in several ways, as demonstrated in a representative patient in figure 1. First, we used the method originally described by Weiss et al. This approach assumes that left ventricular pressure falls monoexponentially during the isovolumic relaxation period to zero pressure, then:

\[ P(t) = P_0 \cdot e^{-t/\tau} \]

where \( P(t) \) is the left ventricular pressure at any time \( t \), \( P_0 \) is the initial left ventricular pressure during isovolumic relaxation, and \( e \) is the base of the natural logarithm. The natural logarithmic transformation of both sides of this equation yields:

\[ \ln P = -\frac{1}{\tau} t + \ln P_0 \]

Log pressure, therefore, is a linear function of time (t) with a slope equivalent to \(-1/\tau\). The time constant, denoted in this construct as \( T_\infty \) (figure 1, left), is the negative reciprocal of the slope \((-1/\tau\)). It has been suggested by others that this relationship may not be monoexponential. They observed that the relationship between log pressure vs time during early isovolumic relaxation (0 to 40 msec) was slower than during late isovolumic relaxation (40 to 80 msec). Consequently, we also calculated the time constant as the linear relationship between log pressure vs time during the first 40 msec \( (T_\infty) \). These methods are all, however, potentially sensitive to errors in the absolute value of pressure because of pleural and pericardial pressure changes and pressure measurement errors. Thus it has been suggested that the time constant should be calculated with a variable asymptote. Consequently, we also used the method proposed by Raff and Glantz, who demonstrated that dp/dt was a linear function of P with a variable asymptote:

\[ \frac{dp}{dt} = -\frac{1}{\tau} (P - P_B) \]

The time constant, denoted in this construct as \( T_D \) (figure 1, right), is the negative reciprocal of the slope \((-1/T)\) of \((−dp/dt)\) vs pressure with a pressure-axis intercept of \( P_B \). Although \( P_B \) may represent the extrapolated baseline pressure to which left ventricular pressure would fall if force dissipated infinitely, the exact physiologic meaning of this measure is uncertain. The correlation coefficients for all Tau calculations obtained from the linear regression of log pressure vs time ranged from \(-.984\) to \(-1.000\) and those of \((−dp/dt)\) vs pressure ranged from \(-.942\) to \(-.998\).

We also assessed the rate of isovolumic relaxation as peak \((−dp/dt)\) \([−dp/dt] \) in addition, since \((−dp/dt)\) \([mp/min]\) is a function of instantaneous pressure (P), the use of \((−dp/dt)\) \([mp/min/P]\) has been proposed by Karliner et al. as a measure of the rate of isovolumic left ventricular pressure decline, which offers the advantage of being easily obtained. This simplified measure of the rate of isovolumic relaxation at one instant in time was also calculated.

Statistical analysis. All data are presented as the mean ± 1 SD. The hemodynamic and relaxation data during control conditions and infusion of methoxamine or nitroprusside were compared...
pared by an analysis of variance. If a significant $F$ statistic was obtained, paired $t$ tests with a Bonferroni correction were used to identify where differences occurred. For the log pressure vs time and $(-)dP/dt$ vs pressure calculations, the average beat during control was processed nine times and 9 sequential beats during control were also processed to determine the variability of the time constant calculations over a full respiratory cycle. Then the coefficients of variation were calculated to establish normal limits to the intrinsic variability of these calculations using this approach. Least-squares linear regression analysis was also performed on data from the two patients who had progressive increases in contractile function induced by dobutamine, between the time constants and several hemodynamic variables, including $(+dP/dt)/DP40$, left ventricular peak pressure (LVP), left ventricular end-diastolic pressure (LVEDP), and heart rate (HR). Then a multiple regression analysis was performed to establish the major determinants of $T_{ln}$ and $T_d$ (MIDAS, University of Michigan, Ann Arbor, 1976). In all statistical analyses, a probability value of .05 or less was required to establish significance.

**Results**

**Hemodynamics.** The mean hemodynamic data for the control, methoxamine, and nitroprusside conditions are shown in table 1. The mean heart rates during the three loading conditions were similar because of right atrial pacing. In contrast, both the mean left ventricular peak and end-diastolic pressures increased by 33% and 43% during the infusion of methoxamine ($p < .001$ and $p < .01$, respectively) and decreased by 24% and 29% during the infusion of nitroprusside ($p < .001$ and $p < .01$, respectively) compared with control. The mean peak $(+)dP/dt [(+dP/dt)_{max}]$ increased during the infusion of methoxamine ($p < .01$) but was unchanged during the infusion of nitroprusside compared with control. In contrast, the mean $(+dP/dt)/DP40$ values were not significantly affected by these permutations in loading conditions.

The mean time from the onset of the QRS complex to peak $(−)dP/dt$, a measure of the duration of electromechanical systole, was prolonged during the infusion of methoxamine ($p < .001$) and was shortened during the infusion of nitroprusside ($p < .001$) compared with control. The mean $(−dP/dt)_{min}$ increased during the infusion of methoxamine ($p < .05$) and decreased during the nitroprusside infusion ($p < .01$) compared with control. In contrast, the average $(−dP/dt)_{min}/P$ values were similar during the three loading conditions.

**Table 1**

<table>
<thead>
<tr>
<th>Hemodynamic data (n = 14)</th>
<th>HR (beat/min)</th>
<th>LVP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>$(+dP/dt)_{max}$ (mm Hg/sec)</th>
<th>$(+dP/dt)/DP40$ (sec)</th>
<th>$(−dP/dt)_{min}$ (mm Hg/sec)</th>
<th>$(−dP/dt)_{min}/P$ (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>80 ± 8 (SD)</td>
<td>131 ± 18</td>
<td>14 ± 3</td>
<td>1145 ± 189</td>
<td>365 ± 31</td>
<td>−1613 ± 388</td>
<td>−18.3 ± 5.4</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>79 ± 10</td>
<td>174 ± 22</td>
<td>20 ± 5</td>
<td>1311 ± 153</td>
<td>392 ± 38</td>
<td>−1786 ± 282</td>
<td>−17.2 ± 4.4</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>82 ± 10</td>
<td>100 ± 16</td>
<td>10 ± 4</td>
<td>1149 ± 237</td>
<td>342 ± 39</td>
<td>−1243 ± 467</td>
<td>−19.4 ± 5.1</td>
</tr>
</tbody>
</table>

HR = heart rate; LVP = left ventricular pressure; LVEDP = left ventricular end-diastolic pressure.

$^a p < .05; ^b p < .01; ^c p < .001$ vs control.
TABLE 2
Effects of altered load on the time constant (n = 14)

<table>
<thead>
<tr>
<th></th>
<th>IVRP (msec)</th>
<th>T_{in} (msec)</th>
<th>T_{in*} (msec)</th>
<th>T_{40} (msec)</th>
<th>T_{D} (msec)</th>
<th>P_B (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>68 ± 14</td>
<td>46 ± 8</td>
<td>47 ± 9</td>
<td>50 ± 9</td>
<td>63 ± 15</td>
<td>-14 ± 8</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>72 ± 16</td>
<td>48 ± 9</td>
<td>49 ± 10</td>
<td>53 ± 14</td>
<td>73 ± 26</td>
<td>-24 ± 21^</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>66 ± 13</td>
<td>45 ± 9</td>
<td>46 ± 8</td>
<td>49 ± 8</td>
<td>62 ± 9</td>
<td>-10 ± 9</td>
</tr>
</tbody>
</table>

IVRP = isovolumic relaxation period; T_{in} = Tau calculated with the isovolumic relaxation period ending at 10 mm Hg above LVEDP of the following beat.

^p < .05 vs control.

Effects of load on the time constants. The mean durations and rates of isovolumic relaxation for the control, methoxamine, and nitroprusside conditions are shown in table 2. The mean durations of isovolumic relaxation did not differ significantly between the three loading conditions. The average time constant values also demonstrated no significant difference between the three loading conditions. The mean T_{in} and T_{in*} values did not differ significantly from each other. Moreover, the T_{40} values were similar to the T_{in} values. Despite no significant difference in the mean T_{D} values, the asymptote, P_B, did demonstrate a difference. The averaged P_B during control conditions was -14 ± 8 mm Hg and decreased during the infusion of methoxamine to -24 ± 21 mm Hg (p < .05). There was no significant difference, however, between the average P_B values during the infusion of nitroprusside and control conditions.

Variability of the time constants. The variability of the time constants, calculated by the present methods, was also evaluated. When the average beat was repeatedly digitized, T_{in} ranged from 43.3 to 45.7 msec (mean 44 ± 1), and T_{D} ranged from 61.6 to 74.2 msec (mean 67 ± 4). The coefficients of variation were 2.0% and 6.1%, respectively. When consecutive control beats over a full respiratory cycle were digitized, T_{in} ranged from 43.5 to 47.4 msec (mean 45.4 ± 1.4), and T_{D} ranged from 65.6 to 86.6 msec (mean 76.3 ± 5.9). The coefficients of variation were 3.1% and 7.7%, respectively. The coefficients of variations for T_{in} were less than those for T_{D} (p < .05 for both).

Effects of positive inotropic stimulation on the time constants. The effects of a steady-state infusion of dobutamine on T_{in}, T_{D}, P_B, and hemodynamic variables are shown in table 3. Of the three patients who were given dobutamine to alter inotropic state, one showed no change in mean heart rate, whereas two demonstrated a significant increase in their mean heart rates with the infusion of dobutamine (p < .001 and p < .01). The mean left ventricular peak pressures increased in all three patients during the infusion of dobutamine compared with control (p < .001), whereas the mean left ventricular end-diastolic pressures did not differ significantly. The mean (+)dP/dt/DP40 values were increased by the infusion of dobutamine in all three patients compared with control (p < .01 to p < .001). The mean T_{in} and T_{D} values were shortened by the infusion of dobutamine (p < .05 to p < .001), whereas

TABLE 3
Effects of positive inotropic stimulation on the time constant

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>LVP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>(+)dP/dt/DP40 (mm Hg/sec)</th>
<th>(-)dP/dt/min/P (sec^{-1})</th>
<th>T_{in} (msec)</th>
<th>T_{D} (msec)</th>
<th>P_B (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Control</td>
<td>87 ± 2</td>
<td>101 ± 4</td>
<td>7 ± 2</td>
<td>1010 ± 130</td>
<td>-24 ± 4</td>
<td>38 ± 4</td>
<td>43 ± 10</td>
</tr>
<tr>
<td></td>
<td>Dobutamine</td>
<td>99 ± 8^a</td>
<td>130 ± 9^c</td>
<td>6 ± 2</td>
<td>1715 ± 154^c</td>
<td>-32 ± 4^b</td>
<td>29 ± 2^c</td>
<td>30 ± 5^b</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Control</td>
<td>79 ± 1</td>
<td>123 ± 2</td>
<td>16 ± 1</td>
<td>1004 ± 31</td>
<td>-23 ± 2</td>
<td>43 ± 2</td>
<td>45 ± 4</td>
</tr>
<tr>
<td></td>
<td>Dobutamine</td>
<td>104 ± 2^c</td>
<td>187 ± 19^e</td>
<td>16 ± 4</td>
<td>2294 ± 207^c</td>
<td>-49 ± 7^c</td>
<td>20 ± 3^c</td>
<td>20 ± 3^c</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Control</td>
<td>79 ± 1</td>
<td>172 ± 2</td>
<td>18 ± 1</td>
<td>1049 ± 39</td>
<td>-19 ± 1</td>
<td>43 ± 2</td>
<td>68 ± 10</td>
</tr>
<tr>
<td></td>
<td>Dobutamine</td>
<td>79 ± 3</td>
<td>201 ± 4^c</td>
<td>21 ± 5</td>
<td>1540 ± 168^b</td>
<td>-28 ± 26^b</td>
<td>32 ± 5^c</td>
<td>44 ± 12^b</td>
</tr>
</tbody>
</table>

^a p < .05; ^b p < .01; ^c p < .001 vs control.
the mean $P_B$ values were not significantly affected. Notably, the mean $(-)dP/dt_{min}/P$ values were also significantly affected by dobutamine, but they moved directionally opposite the time constants.

In the two patients who had graded increases in contractile state produced by the infusion of dobutamine, a progressive shortening of both $T_{in}$ and $T_D$ was inversely correlated with a progressive increase in contractile state as measured by $(+)(dP/dt)/(dP/40)$ ($r = - .83$ to $- .90$). The correlations between $T_{in}$ and $T_D$ and heart rate ($r = .03$ to $- .65$), left ventricular peak pressure ($r = - .52$ to $- .80$), and left ventricular end-diastolic pressure ($r = .41$ to $- .39$) were less apparent. A multiple regression analysis demonstrated that the only independent determinant of $T_{in}$ and $T_D$ was contractile state, as measured by $(+)(dP/dt)/(dP/40)$ ($r = .88$ and $.90$).

**Discussion**

The data from this investigation indicate that the time constants of isovolumic relaxation are not significantly affected by modest changes in loading conditions in patients with normal left ventricular size and performance when heart rate is maintained constant by right atrial pacing. As shown in figure 2, the infusion of methoxamine produced a parallel, rightward shift in the isovolumic natural log pressure vs time relations, $T_{in}$, whereas infusion of nitroprusside produced a parallel, leftward shift in $T_{in}$ compared with control. As shown in figure 3, the isovolumic $(−)(dP/dt)$ vs pressure relations, $T_D$, for each of the three hemodynamic conditions were essentially superimposable, but the extrapolated pressure-axis intercept was significantly reduced by methoxamine. In contrast, an infusion of dobutamine, which increased contractile state, shortened the duration and rate of isovolumic relaxation. These changes in the time constants were inversely correlated with changes in inotropic state, which was identified as the only independent determinant of $T_{in}$ and $T_D$ by multiple regression analysis in these patients.

Our data in man are consistent with the observations reported by Weiss et al. and Frederiksen et al. from an isolated canine left ventricular preparation, but they differ from the data reported by other investigators from intact canine preparations. In a conscious animal preparation, Karliner et al. also reported that the rate of isovolumic left ventricular pressure decline was prolonged when load was substantially increased by both volume and phenylephrine. Our findings in man, which contrast with these data in intact animals, can probably be explained considering that our observations were made in conscious subjects and that we used only modest increases in load. Thus the specific preparation, the conditions under which the study is performed, and the magnitude of the changes in left ventricular load may influence the reported findings on the load dependency of the time constants.

Our investigation does not exclude the possibility that a greater increase in load may have prolonged the rate of isovolumic left ventricular pressure decline. It suggests, however, that a family of parallel shifting $T_{in}$ curves may exist below some threshold value of load, where no change in $T_{in}$ is detectable (figure 2) or superimposable $T_D$ curves are evident (figure 3). A tendency for the mean $T_D$ to be prolonged with the infusion of methoxamine was detected only by a paired t test ($p < .01$ vs control) but not by an appropriate analysis of variance. The more negative $P_B$ values observed during the infusions of methoxamine suggest the possibility that a more negative asymptote may precede an alteration in $T_D$ as a manifestation of the load dependence of Tau. Nevertheless, our data do not suggest that modest alteration in loading conditions cause a significant, systematic prolongation in the time.
constants in a patient with a normal left ventricle and no ischemic heart disease.

Our data must also be considered with respect to the complex interplay between contraction and relaxation loading. This concept suggests that a shift from late to early ejection loading (contraction loading) will prolong left ventricular relaxation, whereas a shift from early to late loading (relaxation loading) will accelerate the rate of isovolumic left ventricular pressure decline. Hori et al. have demonstrated in isolated canine hearts that early ejection pressure loading will prolong both $T_m$ and $T_D$, whereas late ejection pressure loading will have the opposite effect. Ariel et al. reported similar observations using volume steps in an intact canine preparation. Thus the loading sequence has important effects on isovolumic relaxation velocity. These shifts in load may be affected by neurohumoral or pharmacologic alterations in arterial impedance. The prolonged infusions of methoxamine and nitroprusside used in our subjects may have produced equal effects on contraction and relaxation loading and therefore resulted in no significant alteration in isovolumic relaxation rate as measured by the time constants. If we had increased load more extensively, a shift to greater contraction loading may have occurred at some threshold level of load and produced a prolongation of isovolumic relaxation that would have been detected by the time constants.

Few data have been reported on the load dependence of $\tau$ in man. Ludbrook et al. reported that an increase in systemic arterial pressure prolonged the rate of isovolumic relaxation, whereas nitroglycerin accelerated the rate of isovolumic relaxation, in patients with coronary artery disease. Our data from subjects with normal left ventricles and no evident cardiac disease did not confirm these findings. The difference between our observations and those of Ludbrook et al. may be related to changes in relaxation mediated by an imbalance between myocardial oxygen supply and demand produced by altered loading conditions and the effects of nonuniformity of relaxation on the time constants in patients with coronary artery disease. In contrast to previous studies, the potential confounding effects of reflex neurohumoral changes in heart rate on isovolumic left ventricular pressure decline were also eliminated by right atrial pacing in our subjects.

Several investigators have demonstrated in animals and man that increases in heart rate accelerate the rate of isovolumic relaxation. Similarly, a positive inotropic agent will accelerate the rate of isovolumic relaxation, whereas a negative inotropic agent will produce opposite results. We noted in our subjects that infusion of dobutamine significantly shortened the duration and accelerated the rate of isovolumic relaxation. Despite significant concomitant changes in mean left ventricular peak and end-diastolic pressures and heart rate, the progressive shortening in the time constants was principally related to increases in inotropic state. These observations may be explained by the effects of catecholamines on myocardial calcium kinetics. Katz has proposed that catecholamines facilitate dissociation of Ca$^{2+}$ from troponin and sequestration of Ca$^{2+}$ in the sarcoplasmic reticulum. Both of these processes would accelerate relaxation. Thus the present results suggest that the time constants of isovolumic relaxation are

![Isovolumic Relaxation](http://circ.ahajournals.org/)

**FIGURE 3.** Isovolumic relaxation period characterized by $T_m$ for all 14 patients. Note the superimposition of the mean $\tau$ for the control (solid circles), methoxamine (solid squares), and nitroprusside (solid triangles) conditions.
probably determined by the recycling of internal calcium stores and are not significantly altered by modest changes in left ventricular load produced by the present methods when heart rate is maintained constant in man.

The optimal approach to modeling the isovolumic relaxation period has been debated.\(^2\)\(^,\)\(^3\)\(^,\)\(^{16-23}\) Weiss et al.\(^2\) characterized the rate of isovolumic relaxation as a linear relationship between log pressure vs time, \(T_{\ln}\), Rousseau et al.\(^19\) then suggested that the \(T_{\ln}\) calculation may not be a monoexponential function. Consequently, Raff et al.\(^5\) proposed using the linear relationship between instantaneous \((-\frac{dP}{dt})\) and left ventricular pressure, \(T_P\), to characterize the isovolumic relaxation period. In the present investigation, we calculated \(\tau\) from the linear regression of log pressure vs time, \(T_{\ln}\), and of instantaneous \((-\frac{dP}{dt})\) vs \(P, T_P\). All definitions of \(\tau\) were highly linear, which supports the monoexponential nature of each approach, and they all showed no significant alteration in their slope values with changes in load ranging from +43% to −29% from control. These data therefore suggest that either approach to calculating the rate of isovolumic left ventricular pressure decline may be appropriate in man.

Several studies in man have demonstrated that the rate of isovolumic relaxation is altered in patients with ischemic heart disease,\(^19\)\(^,\)\(^20\)\(^,\)\(^{26-28}\) hypertrophy,\(^29\) and hypertrophic obstructive cardiomyopathy\(^26\)\(^,\)\(^{30}\)\(^,\)\(^{31}\) and by pharmacologic interventions in patients with these disease processes.\(^19\)\(^,\)\(^{27}\)\(^,\)\(^{28}\)\(^,\)\(^{30}\)\(^,\)\(^{31}\) The effects of these disease processes and pharmacologic interventions on the rate constants could be due to their alterations of load, the cardiac inactivation process, nonuniformity of relaxation, or a complicated interaction of these factors. In the present investigation, the rate of isovolumic relaxation was shown in patients with normal left ventricles and no evident cardiac disease to be unaffected by modest changes in loading conditions but strongly influenced by inotropic state. This suggests that the effects of these disease processes and the results of pharmacologic interventions on isovolumic relaxation may be due to their effects on the intrinsic, active cardiac relaxation process and not to alterations in load when heart rate and inotropic state remain constant. Alterations in nonuniformity of relaxation cannot, however, be totally excluded, particularly in patients with ischemic heart disease.

We conclude that modest alterations in left ventricular loading conditions in patients with normal left ventricles and no identifiable cardiac disease do not significantly affect the duration or rate of isovolumic relaxation when heart rate is maintained constant by right atrial pacing. Moreover, this observation is evident regardless of the method of calculating the time constant. Thus these calculations appear to be very useful for determining changes in the rate of isovolumic relaxation as a reflection of the intrinsic active cardiac relaxation process.

We express our appreciation to Ms. Diane Bauer for preparation of the manuscript.

References

15. Walsh RA, O’Rourke RA: Direct and indirect effects of calcium entry blocking agents on isovolumic left ventricular relaxation in conscious dogs. J Clin Invest 75: 1426, 1985
20. Thompson DS, Waldron CB, Juul SM, Nqvi N, Swanton RH, Coltart DJ, Jenkins BS, Webb-Peploe MM: Analysis of left ven...
tricular pressure during isovolumic relaxation in coronary artery disease. Circulation 54: 690, 1982
Load independence of the rate of isovolumic relaxation in man.
M R Starling, D G Montgomery, G B Mancini and R A Walsh

Circulation. 1987;76:1274-1281
doi: 10.1161/01.CIR.76.6.1274

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/76/6/1274