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Role of impaired myocardial relaxation in the production of elevated left ventricular filling pressure

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Hay, Ilan, Jonathan Rich, Paul Ferber, Daniel Burkhoff, and Mathew S. Maurer. Role of impaired myocardial relaxation in the production of elevated left ventricular filling pressure. Am J Physiol Heart Circ Physiol 288: H1203–H1208, 2005.—Although present in many patients with heart failure and a normal ejection fraction, the role of isolated impairments in active myocardial relaxation in the genesis of elevated filling pressures is not well characterized. Because of difficulties in determining the effect of prolonged myocardial relaxation in vivo, we used a cardiovascular simulated computer model. The effect of myocardial relaxation, as assessed by $\tau$ (exponential time constant of relaxation), on pulmonary vein pressure (PVP) and left ventricular end-diastolic pressure (LVEDP) was investigated over a wide range of $\tau$ values (20–100 ms) and heart rate (60–140 beats/min) while keeping end-diastolic volume constant. Cardiac output was recorded over a wide range of $\tau$ and heart rate while keeping PVP constant. The effect of systolic intervals was investigated by changing time to end systole at the same heart rate. At a heart rate of 60 beats/min, increases in $\tau$ from a baseline to extreme value of 100 ms cause only a minor increase in PVP of 3 mmHg. In contrast, at 120 beats/min, the same increase in $\tau$ increases PVP by 23 mmHg. An increase in filling pressures at high heart rates was attributable to incomplete relaxation. The PVP-LVEDP gradient was not constant and increased with increasing $\tau$ and heart rate. Prolonged systolic intervals augmented the effects of $\tau$ on PVP. Impaired myocardial relaxation is an important determinant of PVP and cardiac output only during rapid heart rate and especially when combined with prolonged systolic intervals. These findings clarify the role of myocardial relaxation in the pathogenesis of elevated filling pressures characteristic of heart failure.

heart failure; diastolic dysfunction; heart failure with normal ejection fraction; computer simulation

Patients with heart failure in the setting of a normal ejection fraction (HFNEF) are predominately older individuals who typically have several comorbid conditions (17). Abnormalities in the active (early) phase of diastole have been implicated in the genesis of the elevated filling pressures that are characteristic of this syndrome (32, 33). The high resting filling pressure contributes to dyspnea, effort intolerance, and, in extreme cases, pulmonary edema (8, 16). Although prolongation of myocardial relaxation is commonly found in patients with HFNEF (32, 34) and these patients have comorbidities that are associated with impaired relaxation (7), these abnormalities are also common in various states in which atrial pressure is normal and no signs of heart failure exist, such as in normal aging (18), hypertensive ventricular hypertrophy (10), and ischemic heart disease (11). Additionally, recent data suggest that, although $\tau$ (exponential time constant of relaxation) is longer in patients with HFNEF vs. healthy controls (32), such differences were no longer present after controlling for age and blood pressure (14). Thus the precise role of impaired active myocardial relaxation in the genesis of elevated filling pressures remains unclear (5).

Testing the net influence of impaired myocardial relaxation on end-diastolic ventricular filling pressure in vivo is difficult. The rate of myocardial relaxation is influenced by preload (25), afterload (4), catecholamines levels (13), and ischemia (22). Each of these factors also has a major influence on other hemodynamic parameters. Furthermore, it is not possible to experimentally alter $\tau$ independent of all other hemodynamic factors. Accordingly, the purpose of the present study was to elucidate the mechanisms by which abnormalities in early relaxation could result in pulmonary venous congestion using a previously validated model of the cardiovascular system (6, 26).

Methods

Computer simulation of the cardiovascular system. The cardiovascular system was modeled as shown in Fig. 1. The details of this model have been described previously (6, 26), and only a brief description is given here. The pumping characteristics of each of the four cardiac chambers are represented by modifications of the time-varying elastance model of contraction, which relates instantaneous ventricular pressure to instantaneous volume as follows:

$$P_e(V) = E(V - V_0)$$

$$P_{ad}(V) = A[\exp(B(V_{ad} - V_0)) - 1]$$

$$e(t) = \frac{1}{2}[\sin(\pi t/T_{es} - \pi/2) + 1]$$

$$e(t) = 0.5 \exp\left[(t - \frac{1}{2}T_{es})/T_{es}\right]$$

So that:

$$P(V, t) = P_{ad}(V) + e(t)[P_e(V) - P_{ad}(V)]$$

In this system of equations, $P$ is pressure, $P_{es}$ and $P_{ad}$ are end-systolic and end-diastolic pressures, respectively, $E(V)$ is maximal chamber elastance, $V$ is volume, $V_0$ is the volume at which end-systolic pressure is equal to 0 mmHg, $V_{ad}$ is end-diastolic volume, $A$ and $B$ are constants that describe the end-diastolic pressure-volume relationship (EDPVR), $t$ is time, and $T_{es}$ is the time to end systole.

The systemic and pulmonary circuits are each modeled by lumped venous and arterial capacitances ($C_v$ and $C_a$, respectively), a proximal characteristics resistance ($R_s$, also commonly called characteristic impedance) that relates to the stiffness of the proximal aorta or pulmonary artery, a lumped arterial resistance ($R_a$), and a resistance to return of blood from the venous capacitance to the heart $[R_c$, which is similar, although not identical, to Guyton et al.’s (9) resistance to

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venous return). The heart valves permit flow in only one direction through the circuit.

The value of each parameter of the model was set to an appropriate normal value for a 70- to 75-kg man (body surface area 1.9 m²). These values, adapted from values in the literature, are listed in Table 1. Baseline cardiovascular performance indexes obtained from the simulation using these normal parameter values are shown in Table 2.

Addition of the right and left atria represents new model improvements. To confirm the basic validity of these new features, we determined the effect of an alteration in these parameters. To confirm the basic validity of these new features, we determined the effect of an alteration in these parameters.

Simulations. Simulations were performed to address the following three primary questions: 1) What is the influence of the rate of myocardial relaxation as indexed by $\tau$ on pulmonary venous pressure (PVP) and cardiac output? 2) How does altering heart rate affect the impact of myocardial relaxation ($\tau$) on PVP? 3) What is the interaction between the duration of systole ($T_{es}$) and myocardial relaxation ($\tau$) on PVP?

To address the first two questions, heart rate was initially set at 60 beats/min and the mean PVP was recorded at $\tau$ values of 20, 30, 60, 90, and 100 ms while maintaining end-diastolic volume (EDV) constant at 100 ml by adjusting the total systemic blood volume. This entire simulation was repeated at increases in heart rate of 20 beats/min, with increments ranging from 60 to 140 beats/min. Because $T_{es}$ varies with the heart rate (31) and $T_{es}$ may be a cofactor influencing left ventricular (LV) filling pressure, at each heart rate, $T_{es}$ was adjusted based on the regression equations of Weissler et al. (31). The values of $T_{es}$ used were 300, 280, 250, 200, and 175 ms corresponding to heart rates of 60, 80, 100, 120, and 140 beats/min, respectively. Left ventricular end-diastolic pressure (LVEDP) was also recorded at each heart rate, $T_{es}$ was adjusted based on the regression equations of Weissler et al. (31). The values of $T_{es}$ used were 300, 280, 250, 200, and 175 ms corresponding to heart rates of 60, 80, 100, 120, and 140 beats/min, respectively. Left ventricular end-diastolic pressure (LVEDP) was also recorded at each heart rate for individual chambers. The value of each parameter of the model was set to an appropriate normal value for a 70- to 75-kg man (body surface area 1.9 m²). These values, adapted from values in the literature, are listed in Table 1. Baseline cardiovascular performance indexes obtained from the simulation using these normal parameter values are shown in Table 2.

Table 1. Baseline parameter values chosen to be appropriate for 75-kg man

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RV</th>
<th>LV</th>
<th>Atria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{es}$, mmHg/ml</td>
<td>0.6</td>
<td>3</td>
<td>0.39</td>
</tr>
<tr>
<td>$V_{es}$, ml</td>
<td>10</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Time to end systole, ms</td>
<td>300</td>
<td>300</td>
<td>125</td>
</tr>
<tr>
<td>Time constant of relaxation, ms</td>
<td>20</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Scaling factor for EDPVR, mmHg</td>
<td>0.35</td>
<td>0.33</td>
<td>0.44</td>
</tr>
<tr>
<td>Exponent for EDPVR, ml$^{-1}$</td>
<td>0.023</td>
<td>0.037</td>
<td>0.049</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Circulation parameters</th>
<th>Pulmonic</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial resistance, mmHg$\cdot$ml$^{-1}$</td>
<td>0.03</td>
<td>1.5</td>
</tr>
<tr>
<td>Characteristic resistance, mmHg$\cdot$ml$^{-1}$</td>
<td>0.03</td>
<td>0.6</td>
</tr>
<tr>
<td>Venous resistance, mmHg$\cdot$ml$^{-1}$</td>
<td>0.025</td>
<td>0.025</td>
</tr>
<tr>
<td>Arterial capacitance, ml/mmHg</td>
<td>13</td>
<td>1.5</td>
</tr>
<tr>
<td>Venous capacitance, ml/mmHg</td>
<td>8</td>
<td>70</td>
</tr>
</tbody>
</table>

Values adapted from the literature. $V_{es}$ volume at which end-systolic pressure = 0 mmHg; RV and LV, right and left ventricles, respectively, EDPVR, end-diastolic pressure-volume relation.

Table 2. Cardiovascular performance indexes derived from model with normal parameter values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{PVP}$, mmHg</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>$V_{es}$, ml</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>SV, ml</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>EF, %</td>
<td>67</td>
<td>67</td>
</tr>
</tbody>
</table>

PVP, pulmonary vein pressure; EDP, end-diastolic pressure; P, ventricular pressure; $V_{es}$, end-diastolic volume; SV, stroke volume; EF, ejection fraction; CVP, central venous pressure; Numbers in parentheses indicate mean.

Fig. 1. Model of the cardiovascular system. See text for details. $R_a$, arterial resistance; $R_c$, characteristic resistance; $R_f$, fractional resistance; $R_v$, resistance of return of blood from the venous capacitance to the heart; $C_v$, venous capacitance; $C_a$, arterial capacitance; RV, right ventricular; RA, right arterial; LA, left arterial; LV, left ventricular; P, pulmonary; S, systemic.

Fig. 2. Mitral inflow pattern at a heart rate of 60 beats/min. Top: time constant of relaxation ($\tau$) = 20 ms; middle: $\tau$ = 60 ms; bottom: $\tau$ = 60 ms and increased central volume (see text for details).
cardiac output was evaluated by altering heart rate from 60 to 140 beats/min at \( \tau \) values of 20, 30, 60, 90, and 100 ms while maintaining PVP constant at 20 mmHg through alteration in total systemic blood volume.

**RESULTS**

*Mitral inflow patterns: influence of \( \tau \) and left atrial pressure.*

Upon increasing \( \tau \) from the normal value of 30–60 ms, changes in mitral inflow pattern compatible with grade 1 diastolic dysfunction (impaired relaxation) were observed (Fig. 2, middle). The change was characterized by a decrease in the E wave and increase in the A wave amplitude so that the E/A ratio was \(<1\). This was accompanied by an only minimal change in left atrial pressure. With further increases in \( \tau \) to as high as 100 ms, the general flow pattern remained essentially the same, and the E/A ratio remained \(<1\). Specifically, there was no E/A reversal that is characteristic of grade 2 diastolic dysfunction. However, grade 2 diastolic dysfunction was generated when atrial pressure was increased by increasing blood volume so that end-diastolic pressure (EDP) increased, in which case the LV filling occurs in a steeper portion of the EDPVR (Fig. 2, bottom). These aspects of model behavior are consistent with previous clinical echo-Doppler studies (3, 15, 24).

*Effects of prolonged \( \tau \) on LV filling pressure and cardiac output.*

Effects of prolonged \( \tau \) on EDP and PVP were dependent on heart rate (Fig. 3, A and B). At a heart rate of 60 beats/min, \( \tau \) was increased from 20 to 100 ms. In response to this dramatic change, EDV was maintained constant with only 3-mmHg increases in PVP and EDP from their respective baseline values. In contrast, repeating the same simulation at a heart rate of 120 beats/min, an increase in PVP of 23 mmHg was required to maintain the same EDV.

The PVP increase was the result of increases in both LVEDP and increases in the pulmonary vein-LVEDP gradient. As can be seen from the simulated pressure-volume (PV) loops obtained at different values of \( \tau \) and at different heart rates (Fig. 4), at slow heart rates increases in \( \tau \) from 20 to 80 ms did not significantly change the PV loop (Fig. 4A), whereas at faster heart rates the diastolic filling phase of the PV loop shifted upward relative to the baseline condition (Fig. 4B). Without changing the constants of the EDPVR curve, this upward shift in the diastolic phase of the loop at high heart rates and prolonged \( \tau \) is explained by incomplete relaxation (see Discussion). As a result, LV pressure was elevated compared with baseline, not only in the rapid early filling period but throughout diastole. The second factor that contributed to the elevation of PVP was the increase in the PVP-LVEDP gradient (Fig. 3C) that was attributable to increases in the transmitral pressure gradient and not to any change in the pressure gradient between the left atrium and pulmonary vein. To maintain constant LV EDV at increasingly shortened diastolic filling periods, the flow, and hence pressure gradient across the mitral valve, must increase. Our analysis demonstrates that this pressure gradient is influenced by \( \tau \) and heart rate (Fig. 3C). At slow heart rates, increases in \( \tau \) caused only small increases in the gradient. However, at higher heart rates, increases in \( \tau \) caused a large increase in the PVP-EDP gradient, and in extreme circumstances (e.g., at a rate of 120 beats/min and \( \tau \) value of 60 ms) the difference between PVP and EDP can be as much as 10 mmHg.

Similar to the effects on filling pressure, the influence of impaired relaxation on cardiac output was also dependent on heart rate. With a \( \tau \) of 20 ms, cardiac filling was maintained and cardiac output increased as a result of increases in heart rate. At values of 60 ms or more, cardiac filling was impaired, and, despite the elevation in heart rate, the net result was a decrease in cardiac output (Fig. 3D). Thus \( \tau \) prolongation can result in elevated filling pressure and low cardiac output at high heart rates.

*Interaction between systolic timing and myocardial relaxation on PVP.*

Shortened diastole at increased heart rates in combination with prolonged \( \tau \) had dramatic effects on both systolic timing and myocardial relaxation on PVP. Shortened diastole at increased heart rates in combination with prolonged \( \tau \) had dramatic effects on both PVP and LVEDP.
PVP and cardiac output. A similar effect on PVP was seen with increasing $T_{es}$. At a heart rate of 60 beats/min, increases in $T_{es}$ had minor effects on PVP needed to maintain filling, regardless of the $\tau$ value (at $\tau$ of 90 ms increase in $T_{es}$ from 150 to 350 ms increases PVP by only 4 mmHg; Fig. 5A). However, as shown in Fig. 5B, at a heart rate of 100 beats/min, the effect of prolongation of $T_{es}$ on PVP was present at even low values of $\tau$. Thus the influence of $\tau$ on PVP is strongly augmented by the synergistic interaction of systolic timing and heart rate.

DISCUSSION

The influence of impaired relaxation (indexed by increased $\tau$) on ventricular filling dynamics and filling pressure required to maintain a constant filling volume over a broad range of conditions that would be encountered in patients with heart failure were studied using a previously validated model of the cardiovascular system (6, 26). We sought to determine the mean PVP needed to maintain a constant filling volume (EDV) with incremental increases in $\tau$ over a range of heart rates to elucidate the mechanisms by which abnormalities in early relaxation could result in pulmonary venous congestion. Our analysis indicates that elevations of filling pressures are not a simple consequence of isolated impairments in relaxation but rather occur when prolonged relaxation is combined with rapid heart rates and/or prolonged systolic intervals.

We demonstrated that, at slow heart rates, marked prolongation of $\tau$ even to extreme values had little effect on PVP. LV pressure curves measured in subjects with HFNEF support these findings (32). Among 47 subjects with a resting heart rate of $\approx$70 beats/min, $\tau$ was prolonged compared with controls ($59 \pm 14$ vs. $35 \pm 10$ ms). The authors corrected LV pressure to account for incomplete myocardial relaxation and were able to show that prolonged $\tau$ accounts for $7 \pm 1$ mmHg elevation of minimum diastolic pressure in the heart failure group compared with control. However, the effect of prolonged $\tau$ on EDP was minimal (convergence of the measured and corrected pressure tracing at the end-diastolic time point; see Fig. 1 in Ref. 32). The long diastolic period at a heart rate of 70 beats/min allowed full relaxation to occur by end diastole, even in the presence of prolonged $\tau$. Thus increased $\tau$, alone, cannot
explain high resting filling pressures seen in patients with heart failure and a normal ejection fraction (34) but could explain why LVEDP and PVP increases are necessary during exertion and tachycardias to maintain filling volume and cardiac output (29).

We observed upward shifts of the diastolic filling phase of the PV loop at high heart rates and prolonged $\tau$ (Fig. 4D) that occurred without changing the constants ($\alpha$ and $\beta$) of the EDPVR curve. This was the result of incomplete relaxation that shifts the diastolic filling phase of the PV loop upward and affects filling rate during the entire period of diastole (21, 30). Recent data suggest that incomplete relaxation may be a mechanism by which increased filling pressures are required to maintain normal filling volume. Invasive measurements during either isometric hand grip or bicycle exercise demonstrated that $\tau$ prolongation to an average value of 85.7 $\pm$ 23.1 ms in hypertensive subjects with HFNEF was associated with an upward shift in the diastolic portion of the PV loop and elevated LVEDP of 32.3 $\pm$ 8.6 mmHg (14). In some of these subjects, the increase in EDP was accompanied by increases in EDV along the patients’ normal EDPVR, suggesting that abnormalities in the passive properties of the ventricle were not the cause of the rise in filling pressures. An alternate explanation for the upward-shifted PV loop is that study is the incomplete relaxation that occurs at increased heart rates. Incomplete relaxation has previously been cited as a mechanism for diastolic dysfunction (21). Mitchell et al. (23) suggested that abbreviation of diastole at high heart rates may leave inadequate time for ventricular relaxation, and Weisfeldt et al. (30) demonstrated that incomplete myocardial relaxation can occur if the time after maximal negative dP/dt to the next beat is shorter than 3.5 times the value of $\tau$.

These results may enhance understanding of the pathogenesis of heart failure with a normal ejection fraction, especially for older individuals. Several aspects of the modeling employed emphasize cardiovascular changes with normal aging and parallel the cardiovascular response to exercise seen in old age. Because the augmentation in myocardial contractility during exhaustive, dynamic exercise decreases with age, due in large measure to a postsynaptic reduction in the efficacy of $\beta$-adrenergic stimulation (27, 28), we did not vary contractility with changes in heart rate to simulate this age-related change. Additionally, both aging (19) and other comorbid conditions associated with HFNEF (1) are characterized not only by prolonged relaxation (increased $\tau$) but also prolonged contraction (i.e., longer time to end systole). Prolonged contraction delays myocardial relaxation, thereby shortening the duration of diastole at a given heart rate. By adjusting for changes in $T_{es}$ with heart rate by the regressions of Weissler et al. (31), we were able to isolate the effects of heart rate from prolonged contraction, revealing that the latter was an equally important determinant of the increase in filling pressures required to maintain a normal filling volume and cardiac output.

In the clinical setting, diagnosis of heart failure is based on the documentation of elevated filling pressures during cardiac catheterization. Although pulmonary capillary wedge pressure, left atrial pressure, and LVEDP are assumed to be equivalent (12, 20), our findings indicate that this assumption is not likely to be generally valid. We demonstrate that $\tau$ prolongation influences the PVP-LVEDP gradient and leads to an overestimation of LVEDP from mean pulmonary venous pressure and that this difference is even greater at higher heart rates. Previous data that demonstrated significant increases in pulmonary capillary wedge pressure with exercise in subjects with heart failure and a normal ejection fraction (16) may therefore have overestimated the rise in LVEDP, and data that demonstrate changes in LVEDP with significant increases in $\tau$ may have underestimated the increase in pulmonary venous pressure (14). Thus measurement of LVEDP, as is commonly performed as part of a diagnostic evaluation in these patients, may not be an accurate reflection of mean pulmonary venous pressure, especially during exertion. Clinicians may therefore erroneously conclude the patient’s symptoms of dyspnea are not attributable to a cardiovascular cause, when in fact there may be significant elevations in mean pulmonary venous pressure not reflected in the measurement of resting LVEDP.

In the present study, a relatively simple model of the cardiovascular system has been analyzed. Such models of the cardiovascular system have proven to be useful in answering hemodynamic questions in circumstances when it is difficult or impossible to perform a definitive experiment (6, 26). The results of the model conform very well to many observations that have been emphasized in clinical practice, including the importance of heart rate control (2), the absence of symptoms at rest in a majority of patients with HFNEF (17), and the predicted changes in mitral inflow pattern after changes in $\tau$ (3). Thus the model behaved in a manner consistent with clinical and experimental observations. Nevertheless, the results and conclusions should be viewed as theoretical.

In summary, our analysis suggests that the effect of impaired relaxation (indexed by increased $\tau$) on LV filling is determined by the length of diastole, which in turn is determined by both heart rate and the length of systole ($T_{es}$). These findings identify an important role of myocardial relaxation in the need for elevated filling pressures to maintain normal filling volumes that are characteristic of heart failure in the setting of a normal ejection fraction.

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