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Chest, July 1, 2007; 132 (1): 11-17.
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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. First published October 21, 2004; doi:10.1152/ajpheart.00681.2004.—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 τ (exponential time constant of relaxation), on pulmonary vein pressure (PVP) and left ventricular end-diastolic pressure (LVEDP) was investigated over a wide range of τ 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 τ 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 τ 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 τ 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 τ and heart rate. Prolonged systolic intervals augmented the effects of τ 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 predominantly 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 τ (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 τ 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:

$$P_{es}(V) = E_{es}(V - V_0)$$

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

$$e(t) = \frac{1}{2}\left[\sin(\pi t/T_{es} - \pi/2) + 1\right] \text{ for } t < \frac{3}{2}T_{es}$$

$$e(t) = 0.5 \exp\left[(t - \frac{3}{2}T_{es})/\tau\right] \text{ for } t \geq \frac{3}{2}T_{es}$$

So that:

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

In this system of equations, P is pressure, P_{es} and P_{ed} are end-systolic and end-diastolic pressures, respectively, E_{es} is maximal chamber elastance, V is volume, V_o is the volume at which end-systolic pressure is equal to 0 mmHg, V_{ed} 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 characteristic resistance (R_c, 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_v, which is similar, although not identical, to Guyton et al.'s (9) resistance to
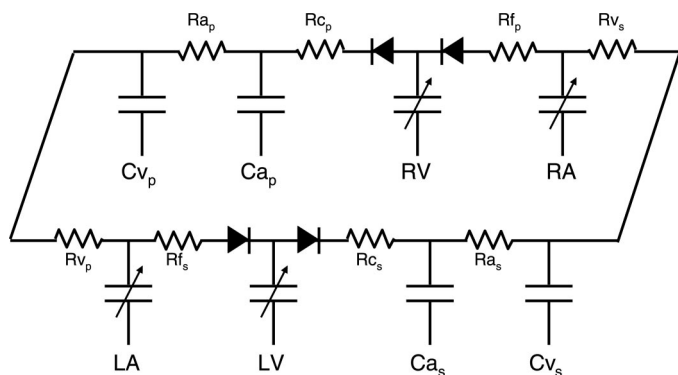
Fig. 1. Model of the cardiovascular system. See text for details. R_a, arterial resistance; R_c, characteristic resistance; R_f, fractional resistance; R_v, resistance of return of blood from the venous capacitance to the heart; C_v, venous capacitance; C_a, arterial capacitance; RV, right ventricular; RA, right arterial; LA, left arterial; LV, left ventricular; P, pulmonary; S, systemic.

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 τ and left atrial pressure on the mitral valve inflow pattern by calculating instantaneous flow through the mitral valve as a function of time (Fig. 2 and discussed below).

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 τ on pulmonary venous pressure (PVP) and cardiac output? *2*) How does altering heart rate affect the impact of myocardial relaxation (τ) on PVP? *3*) What is the interaction between the duration of systole (T_{es}) and myocardial relaxation (τ) on PVP?

To address the first two questions, heart rate was initially set at 60 beats/min and the mean PVP was recorded at τ 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}

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

Heart parameters	RV	LV	Atria
End-systolic elastance, mmHg/ml	0.6	3	0.39
V_o for individual chambers	10	0	10
Time to end systole, ms	300	300	125
Time constant of relaxation, ms	20	20	30
Scaling factor for EDPVR, mmHg	0.35	0.33	0.44
Exponent for EDPVR, ml^{-1}	0.023	0.037	0.049

Circulation parameters	Pulmonic	Systemic
Arterial resistance, mmHg·m^{-1}·s	0.03	1.5
Characteristic resistance, mmHg·m^{-1}·s	0.03	0.6
Venous resistance, mmHg·m^{-1}·s	0.025	0.025
Arterial capacitance, ml/mmHg	13	1.5
Venous capacitance, ml/mmHg	8	70

Values adapted from the literature. V_0, 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*

Heart rate, beats/min		60
Aortic pressure, mmHg		124/81 (101)
Pulmonary pressure, mmHg		22/10 (13)
Cardiac output, l/min		3.9
PVP, mmHg		9
CVP, mmHg		3

	Left Ventricular	Right Ventricular
EDP, mmHg	12	2
V_{ed}, ml	97	97
SV, ml	65	65
EF, %	67	67

	Left Atria	Right Atria
P, mmHg	12/4(7)	3/1(2)
Volume, ml	64	37

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

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 of the aforementioned simulations and was used to calculate the mean PVP-LVEDP gradient.

The second simulation evaluated the effect of T_{es} on PVP. At a heart rate of 60 and 100 beats/min and EDV of 100 ml, PVP was recorded at T_{es} values of 150, 200, 250, 300, and 350 ms at τ values of 30, 60, and 90 ms. Finally, the effect of myocardial relaxation on
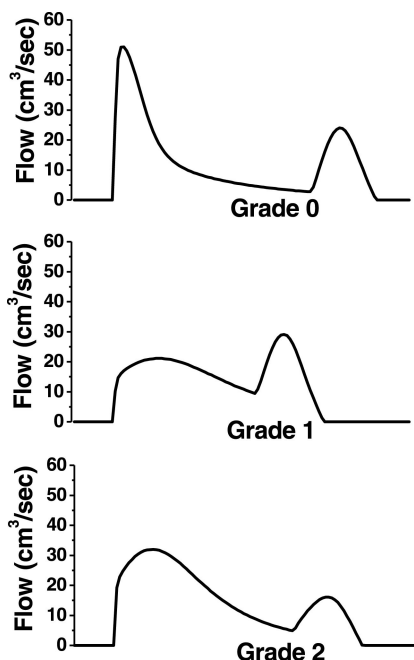

Fig. 2. Mitral inflow pattern at a heart rate of 60 beats/min. *Top*: time constant of relaxation (τ) = 20 ms; *middle*: τ = 60 ms; *bottom*: τ = 60 ms and increased central volume (see text for details).

cardiac output was evaluated by altering heart rate from 60 to 140 beats/min at τ 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 τ and left atrial pressure. Upon increasing τ 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 τ 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 τ on LV filling pressure and cardiac output. Effects of prolonged τ on EDP and PVP were dependent on heart rate (Fig. 3, *A* and *B*). At a heart rate of 60 beats/min, τ 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 τ and at different heart rates (Fig.

4), at slow heart rates increases in τ from 20 to 80 ms did not significantly change the PV loop (Fig. 4*A*), whereas at faster heart rates the diastolic filling phase of the PV loop shifted upward relative to the baseline condition (Fig. 4*B*). Without changing the constants of the EDPVR curve, this upward shift in the diastolic phase of the loop at high heart rates and prolonged τ 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. 3*C*) 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 τ and heart rate (Fig. 3*C*). At slow heart rates, increases in τ caused only small increases in the gradient. However, at higher heart rates, increases in τ caused a large increase in the PVP-EDP gradient, and in extreme circumstances (e.g., at a rate of 120 beats/min and τ 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 τ 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. 3*D*). Thus τ 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 τ had dramatic effects on both
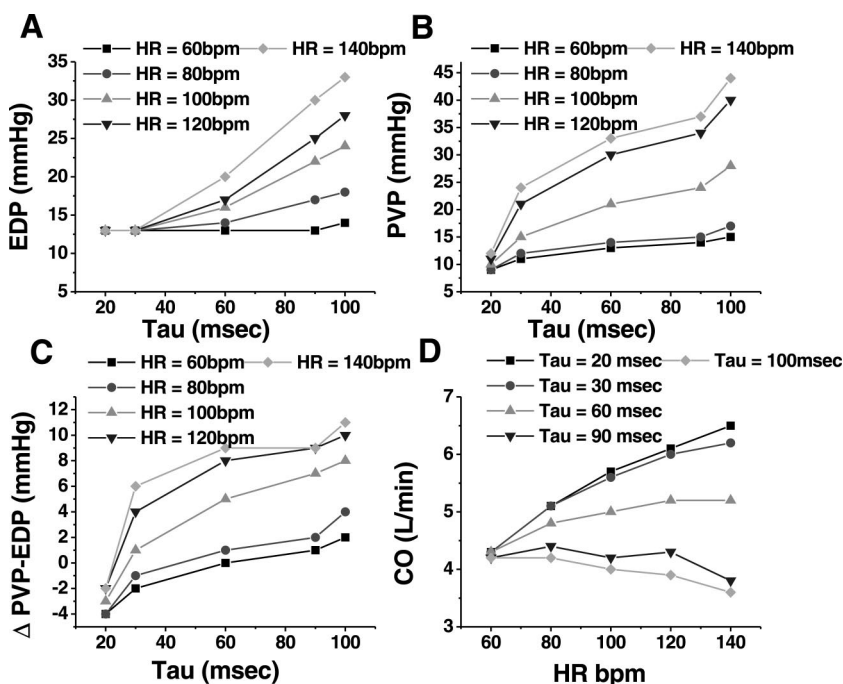
Fig. 3. Relationship between τ and heart rate (HR) on end-diastolic pressure (EDP; *A*), pulmonary vein pressure (PVP; *B*), PVP-EDP gradient (*C*), and cardiac output (CO; *D*). bpm, Beats/min.
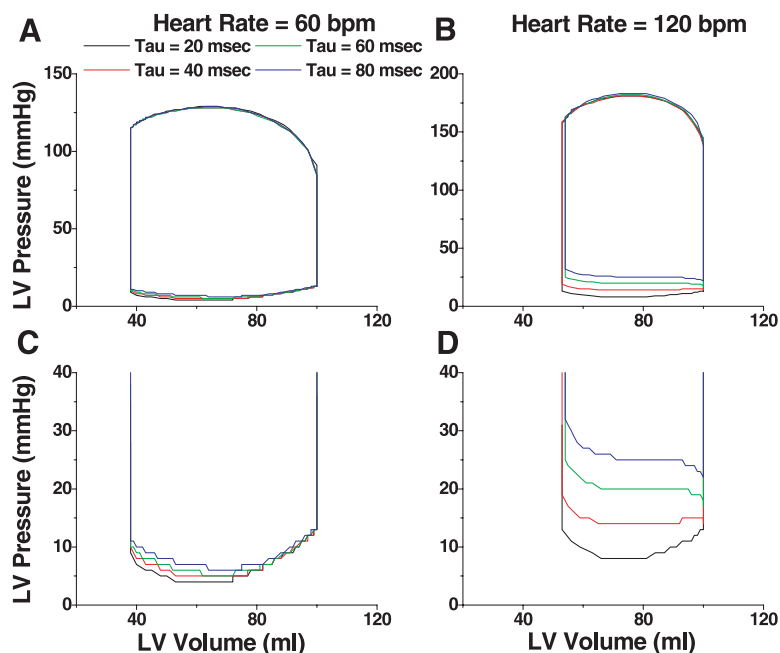
Fig. 4. Pressure-volume loops at heart rate of 60 beats/min (*A* and *C*). Increases in τ values from 20 to 80 ms cause little change in the mitral valve opening time and on EDP. At heart rate of 120 beats/min (*B* and *D*), increases in τ values cause increases in mitral valve opening pressure and in EDP. There is increasing shift of the end-diastolic pressure-volume relationship, simulating incomplete relaxation of the left ventricle (see text for details).

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 τ value (at τ of 90 ms increase in T_{es} from 150 to 350 ms increases PVP by only 4 mmHg; Fig. 5*A*). However, as shown in Fig. 5*B*, at a heart rate of 100 beats/min, the effect of prolongation of T_{es} on PVP was present at even low values of τ. Thus the influence of τ on PVP is strongly augmented by the synergistic interaction of systolic timing and heart rate.

DISCUSSION

The influence of impaired relaxation (indexed by increased τ) 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 τ 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 τ 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 ~70 beats/min, τ was prolonged compared with controls (59 ± 14 vs. 35 ± 10 ms). The authors corrected LV pressure to account for incomplete myocardial relaxation and were able to show that prolonged τ accounts for 7 ± 1 mmHg elevation of minimum diastolic pressure in the heart failure group compared with control. However, the effect of prolonged τ 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 τ. Thus increased τ, alone, cannot
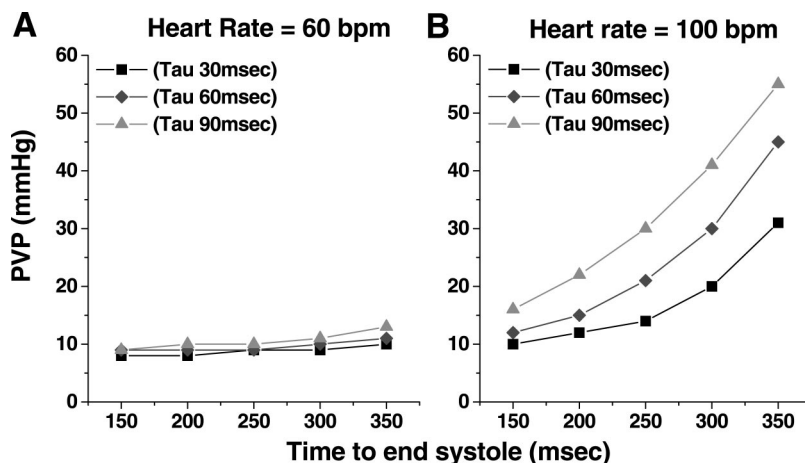
Fig. 5. Effect of prolonged systolic contraction on PVP in combination with impaired relaxation at heart rates of 60 (*A*) and 100 (*B*) beats/min. Increased time to end systole resulted in increases in PVP. This effect was increased at higher values of τ.

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 τ (Fig. 4D) that occurred without changing the constants (α and β) 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 τ prolongation to an average value of 85.7 ± 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 ± 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 in 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 τ.

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 β-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 τ) 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 τ 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. Previ-

ous 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 τ 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 τ (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 τ) 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.

REFERENCES

1. **Andersen NH, Poulsen SH, Helleberg K, Ivarsen P, Knudsen ST, and Mogensen CE.** Impact of essential hypertension and diabetes mellitus on left ventricular systolic and diastolic performance. *Eur J Echocardiogr* 4: 306–312, 2003.
2. **Angeja BG and Grossman W.** Evaluation and management of diastolic heart failure. *Circulation* 107: 659–663, 2003.
3. **Appleton CP, Hatle LK, and Popp RL.** Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 12: 426–440, 1988.
4. **Brutsaert DL, Rademakers FE, and Sys SU.** Triple control of relaxation: implications in cardiac disease. *Circulation* 69: 190–196, 1984.
5. **Burkhoff D, Maurer MS, and Packer M.** Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? *Circulation* 107: 656–658, 2003.
6. **Burkhoff D and Tyberg JV.** Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis. *Am J Physiol Heart Circ Physiol* 265: H1819–H1828, 1993.
7. **Chen HH, Lainchbury JG, Senni M, Bailey KR, and Redfield MM.** Diastolic heart failure in the community: clinical profile, natural history, therapy, and impact of proposed diagnostic criteria. *J Card Fail* 8: 279–287, 2002.
8. **Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, and Little WC.** The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 344: 17–22, 2001.
9. **Guyton AC, Lindsey AW, Abernathy B, and Richardson T.** Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol* 189: 609–615, 1957.

10. **Haber HL, Powers ER, Gimple LW, Wu CC, Subbiah K, Johnson WH, and Feldman MD.** Intracoronary angiotensin-converting enzyme inhibition improves diastolic function in patients with hypertensive left ventricular hypertrophy. *Circulation* 89: 2616–2625, 1994.

11. **Hirota Y.** A clinical study of left ventricular relaxation. *Circulation* 62: 756–763, 1980.

12. **Humphrey CB, Gibbons JA, Folkerth TL, Shapiro AR, and Fosburg RG.** An analysis of direct and indirect measurements of left atrial filling pressure. *J Thorac Cardiovasc Surg* 71: 643–647, 1976.

13. **Karliner JS, LeWinter MM, Mahler F, Engler R, and O'Rourke RA.** Pharmacologic and hemodynamic influences on the rate of isovolumic left ventricular relaxation in the normal conscious dog. *J Clin Invest* 60: 511–521, 1977.

14. **Kawaguchi M, Hay I, Fetics B, and Kass DA.** Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 107: 714–720, 2003.

15. **Kitabatake A, Inoue M, Asao M, Tanouchi J, Masuyama T, Abe H, Morita H, Senda S, and Matsuo H.** Transmitral blood flow reflecting diastolic behavior of the left ventricle in health and disease: a study by pulsed Doppler technique. *Jpn Circ J* 46: 92–102, 1982.

16. **Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, and Sullivan MJ.** Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 17: 1065–1072, 1991.

17. **Klapholz M, Maurer M, Lowe AM, Messineo F, Meisner JS, Mitchell J, Kalman J, Phillips RA, Steingart R, Brown EJ Jr, Berkowitz R, Moskowitz R, Soni A, Mancini D, Bijou R, Sehhat K, Varshneya N, Kukin M, Katz SD, Sleeper LA, and Le Jemtel TH.** Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. *J Am Coll Cardiol* 43: 1432–1438, 2004.

18. **Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Bailey KR, and Seward JB.** Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. *Mayo Clin Proc* 69: 212–224, 1994.

19. **Lakatta EG, Gerstenblith G, Angell CS, Shock NW, and Weisfeldt ML.** Prolonged contraction duration in aged myocardium. *J Clin Invest* 55: 61–68, 1975.

20. **Lappas D, Lell WA, Gabel JC, Civetta JM, and Lowenstein E.** Indirect measurement of left-atrial pressure in surgical patients: pulmonary-capillary wedge and pulmonary-artery diastolic pressures compared with left-atrial pressure. *Anesthesiology* 38: 394–397, 1973.

21. **Litwin SE and Grossman W.** Diastolic dysfunction as a cause of heart failure. *J Am Coll Cardiol* 22: 49A–55A, 1993.

22. **Mann T, Goldberg S, Mudge GH Jr, and Grossman W.** Factors contributing to altered left ventricular diastolic properties during angina pectoris. *Circulation* 59: 14–20, 1979.

23. **Mitchell JH, Linden RJ, and Sarnoff SJ.** Influence of cardiac sympathetic and vagal nerve stimulation on the relation between left ventricular diastolic pressure and myocardial segment length. *Circ Res* 8: 1100–1107, 1960.

24. **Ohno M, Cheng CP, and Little WC.** Mechanism of altered patterns of left ventricular filling during the development of congestive heart failure. *Circulation* 89: 2241–2250, 1994.

25. **Raff GL and Glantz SA.** Volume loading slows left ventricular isovolumic relaxation rate. Evidence of load-dependent relaxation in the intact dog heart. *Circ Res* 48: 813–824, 1981.

26. **Santamore WP and Burkhoff D.** Hemodynamic consequences of ventricular interaction as assessed by model analysis. *Am J Physiol Heart Circ Physiol* 260: H146–H157, 1991.

27. **Stratton JR, Cerqueira MD, Schwartz RS, Levy WC, Veith RC, Kahn SE, and Abrass IB.** Differences in cardiovascular responses to isoproterenol in relation to age and exercise training in healthy men. *Circulation* 86: 504–512, 1992.

28. **Stratton JR, Levy WC, Cerqueira MD, Schwartz RS, and Abrass IB.** Cardiovascular responses to exercise. Effects of aging and exercise training in healthy men. *Circulation* 89: 1648–1655, 1994.

29. **Tabata T, Grimm RA, Asada J, Popovic ZB, Yamada H, Greenberg NL, Wallick DW, Zhang Y, Zhuang S, Mowrey KA, Thomas JD, and Mazgalev TN.** Determinants of LV diastolic function during atrial fibrillation: beat-to-beat analysis in acute dog experiments. *Am J Physiol Heart Circ Physiol* 286: H145–H152, 2004.

30. **Weisfeldt ML, Weiss JL, Frederiksen JT, and Yin FC.** Quantification of incomplete left ventricular relaxation: relationship to the time constant for isovolumic pressure fall. *Eur Heart J Suppl A*: 119–129, 1980.

31. **Weissler AM, Harris WS, and Schoenfeld CD.** Systolic time intervals in heart failure in man. *Circulation* 37: 149–159, 1968.

32. **Zile MR, Baicu CF, and Gaasch WH.** Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 350: 1953–1959, 2004.

33. **Zile MR and Brutsaert DL.** New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. *Circulation* 105: 1503–1508, 2002.

34. **Zile MR, Gaasch WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL, Ghali JK, and Liebson PR.** Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? *Circulation* 104: 779–782, 2001.