Editorial Comment

Enhanced Load Dependence of Relaxation in Heart Failure
Clinical Implications

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The pump performance of the left ventricle (LV) depends on its ability to cycle between two states: 1) a compliant chamber in diastole that allows the LV to fill from a low left atrial pressure and 2) a stiff chamber in systole that ejects the stroke volume at arterial pressure. The transitions from diastole to systole (contraction) and from systole to diastole (relaxation) are essential for the LV to function effectively as a pump.

The signal for contraction is the marked increase in cytosolic Ca\(^{2+}\) that occurs after depolarization. This results from Ca\(^{2+}\) entry into the myocardial cells through voltage-sensitive Ca\(^{2+}\) channels and from the release of Ca\(^{2+}\) from the sarcoplasmic reticulum. The Ca\(^{2+}\) binds to the troponin complex, allowing the interaction between actin and myosin that generates systolic wall tension. Within 100 msec of the increase of cytosolic Ca\(^{2+}\) that triggers contraction, the Ca\(^{2+}\) level rapidly falls as Ca\(^{2+}\) is actively sequestered by the sarcoplasmic reticulum and is pumped out of the cell. As the cytosolic Ca\(^{2+}\) falls, Ca\(^{2+}\) dissociates from the troponin complex, decreasing the interaction between actin and myosin, therefore lessening the force generation, and relaxation begins. The resulting drop in left ventricular pressure stops ejection, and the aortic valve closes as left ventricular pressure falls below aortic pressure. As the force generated by the contractile elements falls, elastic elements compressed during the previous ejection recoil, and the ventricle untwists.\(^1,2\)

As relaxation continues, left ventricular pressure falls below left atrial pressure, and the mitral valve opens. Left ventricular pressure continues to fall, producing a pressure gradient that accelerates blood from the left atrium to the LV.\(^3\) Although the process of left ventricular relaxation is usually completed well before the end of diastole, most left ventricular filling actually occurs early in diastole while the LV is relaxing. In fact, about one fourth of the stroke volume enters the LV while left ventricular pressure is falling.\(^4\) Furthermore, approximately three fourths of the stroke volume enters the LV in the first third of diastole. Therefore, the process of relaxation and elastic recoil are important in producing the explosive filling of the LV early in diastole. Exercise may enhance this process.\(^5\) When left ventricular relaxation is reduced, the filling of the LV is dependent on a vigorous atrial contraction.\(^6,7\) If this left atrial contraction is absent or inadequate, left ventricular filling will require an elevated mean left atrial pressure. It is important to recognize that it is an elevation of mean left atrial pressure (not left ventricular end-diastolic pressure per se) that produces pulmonary congestion,\(^8\) and therefore, changes in the rate of relaxation may have a clinically important influence on overall left ventricular diastolic performance.\(^7\)

In this issue of Circulation, Eichhorn et al\(^9\) report observations of the relation of left ventricular relaxation to systolic performance in a group of patients. They quantified the rate of left ventricular relaxation using the exponential time constant (\(\tau\)) of the fall of left ventricular pressure during isovolumic relaxation. This measure of relaxation is fraught with many potential technical problems and theoretical limitations.\(^10\) However, it does provide an index of the rate of left ventricular relaxation that is adequate to document the large variations in the rates of isovolumic pressure fall observed in the patients in this study. Eichhorn et al observed that the patients with the worst systolic function, quantified by left ventricular ejection fraction or the slope (\(E_{es}\)) of the end-systolic pressure (\(P_{es}\))--volume (\(V_{es}\)) relation, had slower rates of left ventricular relaxation.\(^9\)

The rate of left ventricular relaxation depends on the systolic load.\(^10,11\) Not only is the magnitude of the systolic load important, but so are when it is applied and its uniformity. In simplest terms, in the intact circulation, increases in systolic left ventricular pressure tend to slow the rate of left ventricular relaxation.\(^10\) Eichhorn et al analyzed the dependence of relaxation on systolic load in each of their patients by relating \(\tau\) to \(P_{es}\) during the infusion of nitroprusside: \(\tau = R \cdot (P_{es} + T_0)\). The slope of this relation (\(R\)) represents the dependence of relaxation on the systolic load. In patients with ejection fractions greater than 35%, \(R\) was close to zero. Thus, there was no substantial dependence on \(\tau\) on the 20-mm-Hg change in systolic pressure produced by infusing nitroprusside in these patients. However, as the ejection fraction of patients fell below 35% or \(E_{es}\) decreased below 1 mm Hg/ml, \(R\) markedly increased. Therefore, patients with the most impaired systolic
performance had not only the slowest rate of relaxation but also the most load-dependent relaxation.

Eichhorn et al observed a generally linear relation between \( \tau \) and the left ventricular end-systolic pressure \( (P_{es}) \) (i.e., \( \tau = R \cdot P_{es} + T_0 \)). By combining this relation with the left ventricular end-systolic \( (P_{es}) \)–volume \( (V_{es}) \) relation [i.e., \( P_{es} = E_{es} \cdot (V_{es} - V_0) \)], they predicted that \( E_{es} \) and \( R \) should show a hyperbolic relation [i.e., \( E_{es} \cdot R = (\tau - T_0)/(V_{es} - V_0) \)]. However, there are several limitations of this analysis. First, there is scatter in the relation between \( \tau \) and \( P_{es} \) (Figure 1 of Eichhorn et al). Some of this scatter may be caused by errors inherent in the calculation of \( \tau \). The scatter may also indicate that factors other than \( P_{es} \) have an important influence on \( \tau \). One such factor could be the timing of the systolic load. Second, \( E_{es} \) depends on chamber size. For example, the left ventricular \( E_{es} \) of a normal rat is an order of magnitude greater than that of a normal human. In contrast, the normal systolic pressure and \( \tau \) of the rat and humans are similar. Thus, \( R \) and \( E_{es} \) cannot be simply related in ventricles of widely varying sizes. A third limitation concerns the LV end-systolic pressure–volume relation. This relation is only relatively load independent, as changes in the arterial system can shift the relation.\(^{12}\) Therefore, the use of nitroprusside to generate the end-systolic pressure–volume relation almost certainly altered it, at least somewhat. Finally, consideration of the \( P_{es} - V_{es} \) and \( \tau - P_{es} \) relations predicts a hyperbolic relation between \( R \) and \( E_{es} \) only if \( (\tau - T_0)/(V_{es} - V_0) \) is a constant. This cannot be completely correct because all four parameters are variables, although they may change in an offsetting manner. Despite these theoretical limitations, consistent with their prediction, Eichhorn et al observed a hyperbolic relation between the \( R \) and \( E_{es} \) of the patients they studied.

Are contraction and relaxation coupled as Eichhorn et al suggest? Both contraction and relaxation are energy requiring. Therefore, both processes can be depressed by conditions such as ischemia, which reduce myocardial ATP supplies.\(^6\) Similarly, as observed by Eichhorn et al, patients with congestive cardiomyopathies may have both impaired contractile function and slowed relaxation, perhaps because of a prolonged Ca\(^{2+}\) transient.\(^{13}\) Furthermore, sympathetic stimulation increases both the rates of contraction and relaxation.\(^{14}\) Therefore, under these circumstances, changes in contraction and relaxation appear to be “coupled.” However, contraction and relaxation do not always change together. For example, patients with hypertrophic cardiomyopathy may have supranormal left ventricular systolic function and slowed relaxation.\(^{6,15}\) In addition, digitalis increases the force of contraction without speeding the rate of relaxation in normal myocardium.\(^{14}\)

Why did Eichhorn et al observe that relaxation depends more strongly on systolic pressure in patients with depressed left ventricular systolic performance? A possible explanation is the greater changes in end-systolic volume that occur with changes in end-systolic pressure in these patients. The slope of the left ventricular end-systolic pressure–volume relation, \( E_{es} \), is a measure of left ventricular contractile state, but it also indicates the dependence of LV end-systolic volume (and stroke volume and ejection fraction) on end-systolic pressure. The lower the \( E_{es} \), the greater the change in systolic ejection that will result from an alteration of systolic left ventricular pressure. Systolic muscle length, which is determined by end-systolic volume, is an important determinant of relaxation rate.\(^9,16,17\) In addition, the smaller the end-systolic volume, the greater the amount of energy that is stored during systolic ejection by compressing elastic elements and changing the configuration of the LV.\(^1,2\) One could speculate that release of this stored energy during relaxation may speed the rate of left ventricular pressure fall and significantly contribute to early diastolic filling. In the normal LV \( (E_{es}=7\) mm Hg/ml), a 20-mm Hg fall in end-systolic pressure produces only a small (<3 ml) change in end-systolic volume. Thus, there is little change in the rate of isovolumic pressure fall. In contrast, in a patient with depressed systolic function \( (E_{es}=1\) mm Hg/ml), a similar 20-mm Hg reduction in end-systolic pressure will reduce end-systolic volume by 20 ml, and produce a large change in \( \tau \). Therefore, digitalis may improve relaxation in patients with severe left ventricular dysfunction by allowing a decrease in end-systolic volume even if it does not directly influence relaxation in an LV with normal systolic function.\(^14\)

Recently it has been recognized that diastolic dysfunction may play an important role in producing symptoms and exercise limitation in patients with congestive heart failure.\(^{18}\) Traditionally, the improvement in these parameters in response to afterload reduction in patients with heart failure has been attributed to enhanced systolic performance. As discussed above, a small decrease in arterial pressure, produced by a vasodilator, results in a large increase in stroke volume in a patient with markedly depressed left ventricular systolic function. Observations by Eichhorn et al indicate that the rate of left ventricular relaxation in these patients is also markedly dependent on the systolic pressure. This indicates that patients with reduced ejection fractions (and low \( E_{es} \)) will respond to a fall in systolic pressure by increasing both their systolic left ventricular performance and rate of relaxation. Such an enhancement in the rate of relaxation and a decrease in end-systolic volume would be expected to increase early dia-stolic mitral valve flow, potentially allowing left ventricular filling at a lower mean left atrial pressure.\(^7\) Because the amount of pulmonary congestion is determined by the mean left atrial pressure, this may decrease congestion even if the left ventricular end-diastolic pressure is unchanged.\(^8\) Therefore, the clinical importance of the study of Eichhorn et al is their observation that the dependence of relaxation on systolic left ventricular pressure is enhanced in patients with severe systolic left ventricular dysfunction. In these patients, even a 10–20-mm-Hg decrease in systolic pressure can result in improvement in both systolic left ventricular performance and the rate of relaxation. This observation has potentially important implications for the therapy of diastolic dysfunction in such patients.

References


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