Association of Asynchronous Protodiastolic Segmental Wall Motion with Impaired Left Ventricular Relaxation

PHILIP A. LUDBROOK, M.D., JOSEPH D. BYRNE, C.P.T., AND ALAN J. TIEFENBRUNN, M.D.

with the technical assistance of Frank R. Reed

SUMMARY  To determine if asynchronous segmental relaxation is associated with altered left ventricular (LV) diastolic function, we examined systolic and diastolic wall motion and function indexes in 16 patients without and 16 with asynchronous relaxation (groups 1 and 2, respectively). The segment with asynchronous relaxation was observed most frequently in the free anterior LV wall and was not consistently related geographically to coronary stenosis, nor to systolic asynergy in the same region, but was frequently accompanied by simultaneous segmental inward motion elsewhere in the ventricle.

LV chamber volume stiffness during diastolic filling and at end-diastole was statistically similar in each group. Conversely, both T (58.3 ± 2.3 msec vs 41.0 ± 3.6 msec) and the isovolumic relaxation period (140.9 ± 7.5 msec vs 116 ± 6 msec) were significantly more prolonged, peak negative dP/dt was lower (1314 ± 57 mm Hg/sec vs 1604 ± 114 mm Hg/sec), and the y-axis intercept of the diastolic pressure-volume curve was higher in group 2 patients (7.96 ± 0.98 mm Hg vs 4.88 ± 0.93 mm Hg) (p < 0.05 for each), indicating impaired relaxation and altered diastolic tone.

With improved systolic function and relaxation properties after nitroglycerin, both the asynchronous outward relaxation and the inferior segment of simultaneous inward motion were ameliorated. Conversely, with increased ventricular preload and afterload induced by isometric exercise, both the asynchronous segmental outward motion anteriorly and the inward motion inferiorly were exaggerated.

Asynchronous segmental relaxation may represent a compensatory mechanism in areas of normal contraction that offsets abnormal inward motion elsewhere, tending to maintain isovolumic status of the ventricle.

OUTWARD segmental left ventricular (LV) wall motion during the isovolumic relaxation period of diastole is frequently observed in left ventriculograms of patients who undergo diagnostic cardiac catheterization. Gooch et al.1 initially described this phenomenon in patients with mitral valve prolapse, and attributed it to a functional myocardial dystrophy; however, it has more recently been reported both in normal subjects2 and patients with coronary artery disease.3-5 It has been given several descriptive designations, including diastolic asynergy,1 segmental early relaxation phenomenon,2 and pre-inflow relaxation.6 The relationship between asynchronous early relaxation and alterations of LV performance has received little attention.

Recent evidence indicates that abnormalities of LV diastolic function during early relaxation may be important early indicators of global ventricular systolic or diastolic dysfunction.6,7 In addition, impaired protodiastolic relaxation may be associated with altered distensile properties during the filling phases of diastole.8,9 This study was designed to compare diastolic function evaluated during both the relaxation and filling phases and systolic function in patients with and without coronary artery disease, both in the basal state and under the influence of interventions that augment or impair LV performance.

Methods

Patient Selection
Thirty-two patients (26 males and six females), mean age 53.4 years (range 33–61 years), were selected from the population scheduled for diagnostic cardiac catheterization for evaluation of chest pain. Patients with rheumatic valvular disease, congenital cardiac disorders, significant hypertension (cuff blood pressure greater than 160/100 mm Hg), or evidence of peripheral vascular disease involving the lower extremities were excluded. During catheterization, LV pressure-volume relations were evaluated using micromanometer catheters in all patients, with intervention ventriculography using maneuvers designed either to reduce or augment ventricular preload and afterload in 29. All patients were in normal sinus rhythm. Each patient gave informed consent. No complications attributable to the procedure were encountered.

Catheterization Procedure
Catheterization was performed through the brachial or percutaneous femoral approach, with patients in the fasting state. Patients were premedicated with 50–100 mg of hydroxyzine hydrochloride 1 hour before the procedure. Cardioactive medications except

---

From the Cardiac Catheterization Unit, Department of Medicine, and the Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri. Supported by SCOR in Ischemic Heart Disease grant HL-17646, NHLBI.

Address for correspondence: Philip A. Ludbrook, M.D., Cardiac Catheterization Unit, Cardiovascular Division, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110

Received August 28, 1980; revision accepted March 5, 1981.

Circulation 64, No. 6, 1981.

Downloaded from http://circ.ahajournals.org/ by guest on May 28, 2017
sustained isometric tension level of 20% of each subject’s previously determined maximum voluntary contraction with the use of a calibrated dynamometer (Jamar; Asimow Eng. Co.). During the procedure, special precautions were taken to avoid an inadvertent Valsalva maneuver, particularly during handgrip exercise.12

Data Analysis

LV dimensions and volumes were measured from the first well-opacified sinus beat, excluding premature depolarizations and the subsequent sinus beat. All analyses were performed within the first five beats after contrast injection, when the effects of the contrast on myocardial function are negligible.13,14 LV serial volumes were derived from the occurrence of minimal diastolic to peak a-wave pressures16 from consecutive frames of the cineventriculogram using standard area-length methods.16 Simultaneously recorded high-fidelity LV diastolic pressures were determined serially at 16.7-msec intervals from the high-gain LV pressure recording at intervals synchronized precisely with each ventriculographic frame, and hence with each ventricular volume determination.

Pressure-volume coordinates were analyzed by fitting (least-squares technique) to the monoexponential function16-18

\[ P = be^{\frac{V}{V_{0}}} \]

where \( P \) = left ventricular pressure (mm Hg), \( b \) = data constant, \( e \) = base of the natural log, \( V \) = left ventricular volume (ml), and \( k \) = the rate constant of the exponential pressure-volume relation used as an index of diastolic LV chamber volume stiffness in individual subjects.9, 10, 12, 19

To provide an indicator of the position of each subject’s pressure-volume curve within a graphic pressure-volume coordinate system, exponentially fit pressure-volume curves were extrapolated to the pressure (y) axis at zero volume.9, 10, 12 This extrapolated index is a mathematic expression intended solely to indicate the position of the pressure-volume curve within the conventional coordinate graphic system in each patient under defined hemodynamic conditions, and has no specific physiologic analog.

To assess chamber volume stiffness under the various hemodynamic and ventricular geometric circumstances induced by the interventions, we used the rate constant “\( k_{\text{norm}} \)” of the volume-normalized pressure-volume elasticity relationship.12, 20, 21 Diastolic function was also analyzed specifically at end-diastole in terms of operational end-diastolic chamber stiffness,22 and the asymptotic slope of the log pressure–log volume relationship at end-diastole, which at pressures above 10 mm Hg is relatively insensitive to ventricular geometry and pressure but sensitive predominantly to muscle stiffness.21, 23, 24

LV early diastolic relaxation was analyzed in terms of peak negative \( \frac{dp}{dt} \);25 and “T,” an index of the time course of isovolumic relaxation26 that is independent of aortic systolic pressure and end-systolic LV
volume and fiber length, minimally dependent upon heart rate, and independent of systolic myocardial shortening within the physiologic range of cardiac output;\textsuperscript{26, 27} and the duration of isovolumic relaxation, determined angiographically as the interval between end-systole and the end of isovolumic relaxation, as indicated by the cineventriculographic frame immediately preceding that in which nonopacified blood first appeared in the inflow tract of the left ventricle.\textsuperscript{28} The termination of isovolumic relaxation was clearly identifiable in all cases, and two expert observers agreed consistently.

Systolic wall motion abnormalities and asynchronous segmental early diastolic relaxation were diagnosed by visual inspection of cineventriculograms, and were readily observed by at least two independent observers during routine projection of cineventriculograms.\textsuperscript{2} Segmental early diastolic relaxation was diagnosed when, after end-systole (defined as the last frame showing uniform inward motion of the ventricular walls, or the smallest ventricular cavity area in the presence of significant systolic asynergy), a segment of the LV wall exhibited discrete outward motion before the termination of isovolumic relaxation, and before outward motion was observed in the remainder of the LV wall, occurring in three or more normally conducted consecutive beats.\textsuperscript{2, 3}

Systolic asynergy and asynchronous relaxation were confirmed by manual tracing of serial ventriculographic frames during the respective portions of the cardiac cycle, with superimposition of serial ventricular images throughout the cardiac cycle performed by alignment both of the aortic valve plane and the long axis between the apex and midaortic valve, together with the superimposition of a segment of spine or rib to ensure the absence of movement of the patient or radiographic equipment.\textsuperscript{29}

Quantitative changes in the extent of outward motion of the segment of asynchronous relaxation and inward motion of asynergic inferior wall segments were determined by analysis of chordal dimensions. A longitudinal axis from LV apex to midaortic valve plane was constructed upon the ventriculographic silhouettes traced at end-systole and maximum early relaxation, and chords constructed perpendicular to the long axis, through the asynergic and early relaxing segments.\textsuperscript{29} Percentage changes in the dimensions of these chords were determined before and after the intervention.

Statistical comparisons of the measurements of cardiac function between the groups of patients with and without segmental early diastolic relaxation were performed with the $t$ test for difference between group means. Comparisons between the values of the same measurements between basal and intervention states in individual patients were performed with a paired $t$ test.

**Results**

**Clinical and Angiographic Characteristics**

Sixteen patients showed normal uniform diastolic wall motion; these patients make up group 1. Of these patients, 15 had normal systolic wall motion. Segmental hypokinesis was limited to the inferior wall in the remaining patient. Mitral valve prolapse was the only abnormality in seven of these patients; four had significant coronary artery disease (> 75% diameter) and two congestive cardiomyopathy. No cardiovascular abnormality was detected in the other three patients.

Sixteen patients showed asynchronous segmental diastolic relaxation; these patients make up group 2. Eight had hemodynamically significant coronary artery disease, three had mitral valve prolapse and two had congestive cardiomyopathy. No cardiac abnormality was detected in the remaining three patients. In group 2, 11 patients had systolic asynergy: nine had localized regional hypokinesis involving one or more myocardial segments, and two had diffusely hypokinetic wall motion characteristic of congestive cardiomyopathy. The remaining five patients had normal systolic wall motion.

The segment displaying asynchronous early relaxation was located in the anterobasal or mid anterolateral wall (as defined from the RAO ventriculogram) in each patient in whom the phenomenon was observed (figs. 1 and 2); however, in no patient was significant obstruction present in the subventing coronary artery (left anterior descending in each) proximal to the site

![Figure 1. Selected frames from the left ventriculogram in the right anterior oblique (RAO) projection from a representative patient. (left) End-systole. (right) End-diastole. (center) Maximal early relaxation movement of the anterior wall (arrow) during isovolumic relaxation.](image-url)
of early relaxation. Further, although five patients with early relaxation had segmental systolic hypokinosis involving the LV anterior free wall, in no patient were both systolic asynergy and early diastolic relaxation identified in the same myocardial segment.

Hypokinetic motion of the LV inferior wall was identified in 10 of the patients who had segmental early relaxation (fig. 2). In eight of these patients, the inferior hypokinesis was localized, and was subtended by a significantly obstructed right or circumflex coronary artery. In the remaining two patients, inferior hypokinesis was a manifestation of diffusely hypokinetic wall motion characteristic of congestive cardiomyopathy, and was not associated with obstructive disease within the coronary artery perfusing the specific area. In each of these 10 patients, frame-by-frame analysis indicated asynchronous inward motion of these asynergic inferior segments occurring simultaneously with the early relaxation outward motion in the anterior wall.

Hemodynamics and LV Systolic Function

No statistically significant difference was observed between the groups of patients with and without segmental early diastolic relaxation in regard to systemic arterial systolic, diastolic and mean arterial pressure, or LV systolic, minimal diastolic or end-diastolic pressures (table 1).

Although LV ejection fraction was significantly lower in group 2 than group 1 patients, average ejection fraction was within normal limits in both groups (0.71 ± 0.03 for group 1; 0.61 ± 0.02 for group 2, p < 0.01). Among the patients with segmental early relaxation, ejection fraction was within normal limits (> 50%) in 13 and was below normal in only three patients with more prominent systolic asynergy. LV end-diastolic volume index was significantly greater in group 2, consistent with the higher incidence of systolic asynergy. However, average end-diastolic volumes were within normal limits in each group. Despite the higher incidence of regional systolic asynergy and the associated lower ejection fraction in patients in group 2, mean circumferential fiber shortening rate, mean systolic ejection rate, and ratio of LV peak systolic pressure to end-systolic volume were similar in the two groups.

Left Ventricular Diastolic Function

LV chamber volume stiffness during the filling phases of diastole, as assessed by the rate constant k of the diastolic pressure-volume relation, and the rate constant knorm of the pressure-volume elasticity relation were not significantly different between the groups. Likewise, operational chamber stiffness at end-diastole and the asymptotic slope of the LV log pressure-log volume relationship at end-diastole were similar in both groups, suggesting that altered late diastolic chamber or muscle stiffness is not associated with segmental early relaxation.

Conversely, in group 2, the isovolumic relaxation time and T were significantly more prolonged and peak negative dP/dt was significantly lower than in group

Figure 2. Successive sequential left ventricular silhouettes traced from the projected left ventriculogram (right anterior oblique projection) of a representative patient with early relaxation. The timing of each frame from end-systole (black) till the occurrence of maximal early relaxation (yellow) is indicated in msec: the initial (end-systolic) configuration is depicted in each silhouette by the dotted black line. Progressive outward motion of a segment of the anterolateral wall and simultaneous inward motion of a segment of the inferior wall is apparent. The upper figure (composite) depicts the sequential configurational changes in the segments of outward and inward motion, respectively, superimposed upon the end-systolic (black) silhouette.
chronous early properties relaxation patients, suggesting groups, in reduction in to-end-systolic volume, as decreased pressures in relation sure-volume systolic ejection rate. were diastolic chamber stiffness, of the in our As previous previous after decrease nitroglycerin, value stiffness of the LV systolic pressure-volume relation (exponential fit); T = time constant of isovolumic relaxation. Values are mean ± SEM. Abbreviations: LV = left ventricular; FA = femoral artery; LV P-V relation = left ventricular diastolic pressure-volume relation (exponential fit); T = time constant of isovolumic relaxation.

1 patients, suggesting impaired LV early diastolic relaxation properties in association with asynchronous early relaxation.

Intervention Ventriculography

Nitroglycerin

Ventriculography was repeated after nitroglycerin in eight group 2 and seven group 1 patients. In both groups, LV and femoral arterial systolic and diastolic pressures decreased significantly. In association with this reduction of preload and afterload, LV ejection function, as assessed by ejection fraction, mean circumferential fiber shortening rate, mean normalized systolic ejection rate, and the peak systolic pressure-to-end-systolic volume ratio were significantly enhanced in both groups (table 2).

As in our previous studies,⁶,¹⁰ the LV pressure–volume relation was translated downward after nitroglycerin, as confirmed by a decrease in the extrapolated value of the y-axis intercept of the pressure-volume relation. However k, kₙ₉₉₉, operational end-diastolic chamber stiffness, and the asymptotic slope of the log pressure–log volume relation at end-diastole were insignificantly changed, suggesting the absence of alteration of intrinsic LV chamber or muscle stiffness properties after nitroglycerin.⁶ Conversely, the duration of isovolumic relaxation and T were significantly abbreviated, indicating enhancement of the rate of isovolumic relaxation. Peak negative dP/dt fell significantly after nitroglycerin, but this decrease may be attributed predominantly to concomitant changes in loading conditions, particularly aortic systolic pressure and ventricular end-systolic volume, and thus may not of itself indicate a significant alteration of ventricular relaxation properties. A small, statistically insignificant decrease in the RR interval occurred after nitroglycerin in both groups of patients. Changes in systolic and diastolic measurements after nitroglycerin were directionally concordant and quantitatively similar in groups 1 and 2 (table 2).

Accompanying the enhancement of systolic ejection performance and facilitation of relaxation after nitroglycerin, segmental asynchronous early relaxation disappeared entirely in seven patients and persisted minimally in the eighth (fig. 3). Superimposition of serial ventriculographic frames indicated that asynchronous inward motion of the inferior wall segment was also significantly reduced. Chordal analysis of these frames indicated an average reduction of 78.1% in the extent of outward motion of the segment of early relaxation and reduction of 56.6% in inward motion during isovolumic relaxation of the inferior asynergic segment (p < 0.01 for each).
### TABLE 2. Hemodynamics and Left Ventricular Systolic and Diastolic Function Before and After Nitroglycerin in 15 Patients

<table>
<thead>
<tr>
<th></th>
<th>Patients with early relaxation</th>
<th>Patients without early relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre-NG</td>
<td>post-NG</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>127.8 ± 7.0</td>
<td>108.1 ± 0.51</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>17.8 ± 1.7</td>
<td>12.9 ± 2.6</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml/m²)</td>
<td>74.6 ± 7.8</td>
<td>64.7 ± 2.9</td>
</tr>
<tr>
<td>LV end-systolic volume (ml/m²)</td>
<td>28 ± 4.3</td>
<td>19 ± 2.2</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.62 ± 0.03</td>
<td>0.70 ± 0.03</td>
</tr>
<tr>
<td>LV mean circumferential fiber shortening rate (circ/sec)</td>
<td>1.09 ± 0.16</td>
<td>1.38 ± 0.14</td>
</tr>
<tr>
<td>LV mean normalized systolic ejection rate (sec⁻¹)</td>
<td>1.81 ± 0.21</td>
<td>2.30 ± 0.15</td>
</tr>
<tr>
<td>LV peak positive dP/dt (mm Hg/sec)</td>
<td>1182 ± 38</td>
<td>1320 ± 48</td>
</tr>
<tr>
<td>LV systolic pressure/ end-systolic volume</td>
<td>2.45 ± 0.56</td>
<td>2.88 ± 0.58</td>
</tr>
<tr>
<td>RR interval (msec)</td>
<td>868 ± 82</td>
<td>783 ± 21</td>
</tr>
<tr>
<td>Rate constant k of LV P-V relation (mm Hg/ml)</td>
<td>0.009 ± 0.003</td>
<td>0.011 ± 0.006</td>
</tr>
<tr>
<td>Y-axis intercept of LV P-V relation (mm Hg)</td>
<td>6.12 ± 1.1</td>
<td>4.03 ± 0.9</td>
</tr>
<tr>
<td>Rate constant k₉ₕₐ₉ of LV P-V elasticity relation (mm Hg/unit volume)</td>
<td>2.048 ± 0.72</td>
<td>2.03 ± 0.70</td>
</tr>
<tr>
<td>Operational end-diastolic stiffness</td>
<td>0.146 ± 0.04</td>
<td>0.102 ± 0.03</td>
</tr>
<tr>
<td>End-diastolic stiffness ([V/P][dP/dV])</td>
<td>1.317 ± 0.51</td>
<td>1.55 ± 0.62</td>
</tr>
<tr>
<td>T (msec)</td>
<td>53.8 ± 6.7</td>
<td>40.9 ± 6.3</td>
</tr>
<tr>
<td>Isovolumic relaxation time (msec)</td>
<td>141.1 ± 5</td>
<td>130.6 ± 5</td>
</tr>
<tr>
<td>LV peak negative dP/dt (mm Hg/sec)</td>
<td>1259 ± 85</td>
<td>1108 ± 112</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Abbreviations: pre-NG = before nitroglycerin; post-NG = after nitroglycerin; LV = left ventricular; LV P-V relation = LV diastolic pressure-volume relation (exponential fit); T = time constant of isovolumic relaxation.

### Isometric Handgrip Exercise

Ventriculography was repeated during handgrip in six group 2 and eight group 1 patients. LV systolic and diastolic pressures rose similarly in both groups. LV end-diastolic and end-systolic volumes increased significantly and systolic performance decreased, with significant reduction of ejection fraction, mean circumferential fiber shortening rate, mean systolic ejection rate, and peak systolic pressure/end-systolic volume ratio (table 3).

Although in association with the increased LV preload and afterload diastolic pressure-volume curves were translated upward (as indicated by an increase of the y-axis intercept of the pressure-volume relation), chamber volume stiffness as assessed by k, k₉ₕₐ₉, operational end-diastolic stiffness, and the end-diastolic log pressure–log volume relation was unchanged, in agreement with the results in our previous reports. However LV relaxation was attenuated, as indicated by significant prolongation of the isovolumic relaxation time and T, while the extent of relaxation as assessed by peak negative dP/dt, was significantly reduced. A small and statistically insignificant decrease in RR interval occurred during handgrip exercise in both groups. Again, changes in LV systolic and diastolic function were directionally concordant and quantitatively similar in each group.

Concomitant with the decrease in systolic ejection performance and attenuation of relaxation induced by
isometric exercise, superimposition of serial ventriculographic silhouettes indicated that the extent of asynchronous segmental outward motion increased in all six patients exhibiting this phenomenon in the resting state (fig. 4). Analysis of chordal dimensions indicated an average increase in the extent of outward motion of the segment of early relaxation during handgrip of 23%, and an increase in the extent of inward motion of the asynergic inferior wall segment of 37% (p < 0.01 for each).

**Discussion**

Various forms of temporally and segmentally asynchronous wall motion during LV relaxation have been recognized in experimental animals and in man. An abrupt increase in the base-to-apex dimension with ballooning of the apex has been recognized in canine hearts. However, asymmetric wall motion during the relaxation phase in man received little attention until the description of outward bulging of the LV anterior wall during late systole or early diastole in patients with mitral valve prolapse by Gooch et al., who referred to the finding as diastolic asynergy and attributed it to a functional myocardiopathy. Ruttle et al. described outward motion in various portions of the anterior or apical ventricular walls, designated pre-inflow relaxation, in patients with both normal and abnormal ventricles. Observing that such outward movement occurred predominantly in more compliant wall segments with better contractile function, rather than in less compliant areas displaying systolic asynergy, they suggested that these phenomena are the result rather than the cause of concomitant changes in LV volume. Altieri et al. observed regional outward wall motion, designated segmental early relaxation phenomenon (SERP), in various locations throughout the ventricle in 83% of a consecutive series of patients who underwent diagnostic cardiac catheterization for evaluation of chest pain, 59% of them with and 41% without significant coronary artery disease. In ventricles with systolic asynergy, these authors also noted that SERP occurred predominantly in normally contracting areas, and in view of its presence in a substantial percentage of apparently normal patients, regarded it as a normal variant of LV relaxation. Conversely, Wilson et al. reported a close correlation between SERP of the anteroapical LV wall, and left anterior descending coronary artery stenosis. Similarly, Hamby et al. observed late systolic bulging that became more prominent in early diastole in some patients, attributing the diastolic bulge to early relaxation resulting from the asynchronous contraction.

Our results indicate that the myocardial segment that displays asynchronous early relaxation is not consistently related to stenosis within the subventing coronary artery, nor to systolic asynergy in the same region, but is frequently accompanied by simultaneous inward segmental motion elsewhere, in regions also displaying systolic asynergy, supplied by stenosed coronary arteries. This inward movement might be at-
TABLE 3. Hemodynamics and Left Ventricular Diastolic Function Before and During Handgrip Exercise in 14 Patients

<table>
<thead>
<tr>
<th></th>
<th>Patients with early relaxation</th>
<th>Patients without early relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre-HG</td>
<td>post-HG</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>129.8 ± 11.6</td>
<td>160.8 ± 12.9</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>23.7 ± 3.4</td>
<td>31.9 ± 7.9</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml/m²)</td>
<td>61.1 ± 2.8</td>
<td>65.7 ± 1.4</td>
</tr>
<tr>
<td>LV end-systolic volume (ml/m²)</td>
<td>21.6 ± 3.6</td>
<td>32.3 ± 2.7</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.65 ± 0.05</td>
<td>0.51 ± 0.04</td>
</tr>
<tr>
<td>LV mean circumferential fiber shortening rate (circ/sec)</td>
<td>1.23 ± 0.22</td>
<td>0.85 ± 0.11</td>
</tr>
<tr>
<td>LV mean normalized systolic ejection rate (sec⁻¹)</td>
<td>2.21 ± 0.21</td>
<td>1.64 ± 0.17</td>
</tr>
<tr>
<td>LV peak positive dP/dt (mm Hg/sec)</td>
<td>1055 ± 305</td>
<td>1590 ± 610</td>
</tr>
<tr>
<td>LV systolic pressure/end-systolic volume</td>
<td>3.44 ± 0.4</td>
<td>2.62 ± 0.4</td>
</tr>
<tr>
<td>RR interval (msec)</td>
<td>938 ± 83</td>
<td>899 ± 97</td>
</tr>
<tr>
<td>Rate constant k of LV P-V relation (mm Hg/ml)</td>
<td>0.0077 ± 0.001</td>
<td>0.0065 ± 0.002</td>
</tr>
<tr>
<td>Y-axis intercept of LV P-V relation (mm Hg)</td>
<td>8.41 ± 4.3</td>
<td>9.27 ± 0.26</td>
</tr>
<tr>
<td>Rate constant k₅₀ of LV P-V elasticity relation (mm Hg/unit volume)</td>
<td>2.046 ± 0.19</td>
<td>2.065 ± 0.34</td>
</tr>
<tr>
<td>Operational end-diastolic stiffness</td>
<td>0.206 ± 0.06</td>
<td>0.269 ± 0.09</td>
</tr>
<tr>
<td>End-diastolic stiffness (LV/P)(dP/dV)</td>
<td>1.12 ± 0.03</td>
<td>1.076 ± 0.57</td>
</tr>
<tr>
<td>T (msec)</td>
<td>48.4 ± 3.6</td>
<td>59.6 ± 4.4</td>
</tr>
<tr>
<td>Isovolumic relaxation time (msec)</td>
<td>120.9 ± 10.5</td>
<td>150.2 ± 11.9</td>
</tr>
<tr>
<td>LV peak negative dP/dt (mm Hg/sec)</td>
<td>1203 ± 72</td>
<td>963 ± 110</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Abbreviations: pre-HG = before handgrip exercise; post-HG = after handgrip exercise; LV = left ventricular; LV P-V relation = LV diastolic pressure-volume relation (exponential fit); T = time constant of isovolumic relaxation.

tributable to "sustained" or "delayed" contraction or "incomplete relaxation" in these areas with altered coronary supply. To determine the role of acute ischemia in the genesis of these phenomena, their response to relief of ischemia by nitroglycerin and to accentuation of stress by isometric exercise, a maneuver known to increase LV wall stress and thus myocardial oxygen demands, was examined. The substantial improvement of the segmental asynchronous relaxation, and contraction elsewhere after nitroglycerin, and their exaggeration during handgrip exercise, suggest a causative contribution by acute ischemia in these patients. These responses differ from those observed by Gibson et al., who, using a combination of digitized isochronically displayed M-mode echocardiograms with timing of physiologic events portrayed by simultaneous apexcardiograms, indirectly observed no change in these phenomena during isometric stress and aggravation after nitroglycerin. They attributed the early relaxation phenomenon to irreversible modification of regional function possibly by an ischemic episode in the past rather than to transient ischemia. This disparity may be at least partially attributable to methodologic differences: Ventriculography was used to study the results of the interventions in our patients, whereas Gibson used M-mode echocardiograms and timed physiologic events from simultaneous apexcardiograms; potential error in the analysis of wall motion, and quantification of ventricular dimensions and volumes introduced by the
limited sampling of the LV available using these techniques, especially in patients with dilated or asynergic ventricles, is well appreciated. In particular, depiction of the strictly localized area of segmental asynchronous relaxation by the ice-pick view afforded by the M-mode echocardiogram may be less reliable than the broader perspective of biplane ventriculography.

The present study confirms the functional correlation between segmental early relaxation and obstructive coronary artery disease, although its occurrence in association with mitral valve prolapse and cardiomyopathy, as well as in apparently normal subjects, is also corroborated. All of our patients in whom segmental early relaxation was demonstrated manifested altered global LV relaxation properties, in contrast to patients without early relaxation. Elevated diastolic pressure-volume curves (confirmed in our patients with asynchronous relaxation by higher y-axis intercept of the pressure-volume relationships) has been related to altered “diastolic tone” associated with sustained contraction or incomplete relaxation. Further, while the two groups of patients were not statistically different with regard to the indexes of LV chamber and muscle stiffness properties used, suggesting that abnormal distensible properties per se were not the major cause of asynchronous relaxation, a numerical trend was apparent toward higher LV diastolic pressures and stiffer ventricles in patients with asynchronous relaxation, suggesting some impairment of overall global LV diastolic properties, as might be expected from the higher incidence of systolic asynergy and, thus, myocardial scarring.

The functional relationship of abnormalities of systolic contractile function and diastolic properties of the left ventricle are controversial. Although changes in ventricular distensibility have been reported in association with changes in inotropic state induced by catecholamines, other investigators have detected no change in length-tension relationships in isolated papillary muscle preparations or in the distensibility of the intact heart under such circumstances. However, many investigators have observed a relationship between relaxation abnormalities, and alterations of LV distensible properties. Further evidence suggests a relationship at the cellular metabolic level between myocardial inotropic state, and the state of active relaxation, both of which are fundamentally influenced by cytosolic concentrations of calcium. Thus, under certain circumstances, incomplete or delayed relaxation or sustained contraction may apparently alter ventricular distensibility and pressure-volume relationships during diastolic filling, though by extrapolation from the canine situation, Weisfeldt et al. suggested that such effects are operative during diastole after an interval of 3.5 T. In our patients, an association between asynchronous segmental relaxation and systolic dysfunction is suggested, but is inconstant. Thus, although ejection fraction and peak positive dP/dt were significantly lower, and end-diastolic volume was significantly greater in patients with early relaxation in keeping with the higher incidence of systolic asynergy, mean circumferential fiber shortening rate, normalized systolic ejection rate, and the peak systolic pressure/end systolic volume ratio were similar in the two groups. Further, among the patients displaying early relaxation, ejection fraction was normal (> 50%) in 13 and below normal in only three patients with more severe asynergy. Likewise, although peak positive dP/dt was significantly lower in group 2, in 50% of our group 2 patients it approximated the average value in group 1 patients.

Likewise, some relationship between asynchronous...
segmental relaxation and altered diastolic chamber stiffness is suggested in our patients, although the association is inconsistent and universally statistically significant. Thus, LV diastolic pressures, $k$, $k_{\text{norm}}$, operational end-diastolic stiffness and the end-diastolic log pressure–log volume relation were all appreciably greater in patients with asynchronous relaxation, although the differences between the groups did not reach statistical significance. However, in patients with asynchronous relaxation, pressure-volume curves were positioned significantly higher on the pressure-volume graphic system (as indicated by a greater value of the y-axis intercept of the pressure-volume curves), a finding that has been related to increased "diastolic tone" and attributed to sustained contraction or a failure of relaxation.

Most important, however, asynchronous relaxation was consistently accompanied by impaired LV global relaxation properties. The present study confirms the frequent occurrence of segmental inferior wall motion synchronous with the outward motion of the prematurely relaxing segment located in the anterior ventricular wall. The presence of significant stenosis in the coronary arteries subtending the asynergic inferior wall segment, and the absence of coronary disease proximal to the prematurely relaxing segment in the anterior wall suggests that the inferior wall inward motion may be the primary functional abnormality. The association between abnormal asynchronous wall motion during isovolumic relaxation and alterations of ventricular global diastolic function, ventricular loading conditions and transient acute myocardial ischemia is suggested by the differential responses of the early relaxation phenomenon to nitroglycerin compared with isometric stress. Thus, in patients displaying segmental early relaxation, ventricular end-diastolic volume decreased and systolic function significantly increased after administration of nitroglycerin (table 2). Although diastolic chamber stiffness was unchanged, diastolic pressure-volume curves were significantly translated downward, as manifested by the lower y-axis intercept of the extrapolated pressure-volume relation. $T$ and the duration of the isovolumic relaxation period were both significantly shortened. Since the average RR interval was insignificantly changed after nitroglycerin, these changes were not attributable to increased heart rate. Although peak negative $\Delta P/\Delta t$ decreased, the physiologic significance of this change is questionable in view of the dependence of this variable on loading conditions. Concomitant with improved systolic and diastolic function and facilitation of the relaxation process, abnormal inward wall motion in the inferior wall was reduced and outward early relaxation ameliorated in all but one patient, in whom the phenomenon persisted minimally.

Conversely, when ventricular preload and afterload were increased during isometric exercise, end-diastolic ventricular volume increased and ejection function decreased significantly. Although ventricular diastolic chamber stiffness was unchanged, pressure-volume curves were translated upward and isovolumic relaxation was significantly attenuated, with a decrease in the extent of relaxation as assessed by peak negative $\Delta P/\Delta t$. The average RR interval was unchanged; thus, the prolongation of isovolumic relaxation is not attributable to alteration of heart rate.

Comitant with the impairment of both systolic and diastolic LV functional properties during isometric exercise, the extent both of asynchronous inward motion inferiorly and of outward motion anteriorly were exaggerated in all patients. However, in no patient was early relaxation produced de novo, indicating that the early relaxation phenomenon was not merely a response to augmented ventricular loading conditions.

Acknowledgment

The authors express appreciation to Burton E. Sobel, M.D., for helpful review of the manuscript, and to Therese Whelan for her assistance in preparation of the manuscript.

References

10. Ludbrook PA, Byrne JD, McKnight RC: The influence of right ventricular hemodynamics on left ventricular pressure-volume relations in man. Circulation 59: 21, 1979
12. Ludbrook PA, Byrne JD, Reed FR, McKnight RC: Modification of left ventricular diastolic behavior by isometric handgrip exercise. Circulation 62: 357, 1980
16. Noble MIM, Milne ENC, Goerke RJ, Carson E, Domeonce
24. Laird JD: A simple index of the diastolic elastic wall properties of the left ventricle from angiographic data. (abstr) Am J Cardiol 35: 151, 1975
34. Ludbrook PA, Karliner JS, Peterson K, Leopold G, O'Rourke RA: Comparison of ultrasound and cineangiographic measurements of left ventricular performance in patients with and without wall motion abnormalities. Br Heart J 35: 1026, 1973
Association of asynchronous protodiastolic segmental wall motion with impaired left ventricular relaxation.

P A Ludbrook, J D Byrne and A J Tiefenbrunn

Circulation. 1981;64:1201-1211
doi: 10.1161/01.CIR.64.6.1201

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 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/64/6/1201

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/