Shape and Volume Changes During “Isovolumetric Relaxation” in Normal and Asynergic Ventricles

By Michael S. Ruttley, M.D., Douglass F. Adams, M.D., Peter F. Cohn, M.D., and Herbert L. Abrams, M.D.

SUMMARY
Clinically suspected coronary artery disease was assessed in 52 patients by 16-mm biplane left ventriculography. Outward movement of the left ventricular wall was observed prior to mitral valve opening in normal patients and those with coronary artery disease. In the normal ventriculogram, outward movement was usually visible in the anterior wall and the apex. In the asynergic ventricle, the outward movement almost invariably occurred at the region of optimal contraction. Outward movement of the ventricular wall during protodiastole and isovolumetric relaxation was accompanied by a significant volume increase over the end-systolic volume. The volume increase was greater in the abnormal than in the normally contracting ventricle.

The altered ventricular volume was probably associated with the return to the ventricle of blood contained between the patent aortic leaflets at the end of ventricular ejection. This event occurs during aortic valve closure when ventricular pressure is falling more rapidly than aortic pressure. It accounts for the alteration in volume between end ejection and pre-mitral valve opening.

The stroke volume, which is generally calculated from end-systolic and end-diastolic volumes, may therefore be inaccurate by at least 10% because ventricular volume immediately before mitral valve opening is not utilized in the calculation. Some of the discrepancies between angiocardioangiographic stroke volume and ejection fraction measurements and those obtained by other methods may be explained by failure to use pre-inflow volume (PIV) in the calculations.

Additional Indexing Words:
Pre-inflow relaxation
Coronary artery disease
Isovolumetric diastole
Protodiastole

It is commonly assumed that there is no change in left ventricular volume during the period between termination of left ventricular ejection and mitral valve opening. This phase of the cardiac cycle has traditionally been divided into protodiastole (end-ejection to aortic valve closure) and isovolumetric diastole (aortic valve closure to mitral valve opening). In recent years this division has been abandoned by some physiologists, and the entire period has been designated by the term isovolumetric diastole.1

Observations made in our laboratory have suggested that outward movements of the left ventricular wall (ventricular shape changes) occurring during aortic valve closure and before mitral valve opening have been accompanied by left ventricular volume increments in man.2 We have termed the phenomenon of outward left ventricular wall motion occurring prior to mitral valve opening pre-inflow relaxation (PIR). In order to examine its characteristics in greater detail, a series of ventriculographic and coronary arteriographic studies have been critically analyzed.

Materials and Methods
Fifty-two patients with clinically suspected coronary artery disease were examined. All patients had simultaneous biplane cine-left ventriculography at 100 frames/sec on 16-mm film. Eclere cameras photographed the output phosphors of dual-mode 6–10 inch high-resolution image intensifiers. On the side of each cine frame continuous records of the electrocardiogram and brachial artery pressure traces were included in both planes. The equipment provided pulsed exposures within the range of 1–4 msec. Simultaneous biplane tape recording with immediate playback and review was utilized to assure that the quality of the cineangiograms was satisfactory.

Contrast medium (76% Renografin) was injected into the ventricle at 10–15 ml/sec for 3 sec. One or more cardiac cycles after the completion of contrast injection were chosen for analysis. Premature ventricular contractions and the first postextrasystolic contractions were excluded from consideration.
All cases were initially examined by at least three observers and the frame depicting the smallest ventricular size (end ejection), the frame immediately before the beginning of mitral valve opening (end isovolumetric relaxation), and the frame revealing the largest ventricular size (end diastole) were selected from the right anterior oblique (RAO) projection. The interval between end ejection and mitral valve opening varied between 70 and 110 msec (7-11 frames). These three points in the cine were readily identifiable in almost every case. When specific frames could not be repeatedly selected by any of the observers, several frames were measured so as to include either the smallest or the largest ventricular size. The opening of the mitral valve was clearly identifiable in every case. The identification of mitral valve opening was often aided by detecting the leaflet in the partially open state and running the film in reverse to make it look as though the valve was closing.

The corresponding end-systolic and end-­isovolumetric relaxation frames were then identified on the simultaneously obtained left anterior oblique (LAO) projection. The LAO was carefully examined to assure that there was no inward motion of the ventricular walls seen in that projection during the interval between end ejection and mitral valve opening. In no case was there such an inward motion, and in most the free left ventricular wall was observed to move outward.

It was then clear that the LAO projection mimicked the RAO projection and that wall motion was parallel during the period of interest. It was further reasoned, and checked in a number of instances, that when quantitating very small changes in volume an analysis in a single plane would give satisfactory results. Thus, only the RAO projections were traced for the purpose of volume analysis. These frames were superimposed for a better fit which does not account for absolute movement of the heart in space. Additionally, 15 cases were excluded from the volume analysis because they did not contain the fine detail required for such a rigorous analysis.

Volume analyses were performed by a method previously described on 37 of the 52 patients. This method adapts Dodge’s formulas to the RAO projection and assumes equality of the minor axes in the two planes, 90 degrees from each other, after the manner of Greene. Calibration is performed with a one centimeter grid placed in the same plane as the ventricle and recorded on cine film. No regression equation is used. Stroke volume (SV) and ejection fraction (EF) were calculated in the usual manner from the end-systolic and end-diastolic volumes (ESV, EDV) (i.e., \(SV = EDV - ESV; EF = \frac{SV}{EDV}\)). Similar calculations of left ventricular volume were also made substituting the pre-inflow volume (PIV) obtained immediately before mitral valve opening for the end-systolic volume. The volume increment during the pre-inflow relaxation period was calculated (PIV – ESV); this was also expressed as a percentage of the SV (\(\frac{PIV - ESV \times 100}{SV}\)).

Results

The ventriculographic investigations revealed normally contracting ventricles in 23 and asynergy† in 29 patients. Coronary arteriography demonstrated normal coronary arteries in nine and significant disease (complete occlusion or at least 80% stenosis) in 14 of the patients with normal ventriculograms. In all 29 patients with asynergy, there was at least 80% stenosis of one or more of the major coronary branches.

In all cases, irrespective of whether there was coronary disease or a ventriculographic contraction abnormality, some change in the ventricular silhouette with expansion of the ventricular cavity occurred during closure of the aortic valve and before opening of the mitral valve. A slight movement of the ventricular catheter from the aortic valve toward the ventricular apex was also detectable at this time, and it was usually possible to perceive a simultaneous change in direction of flow of contrast material within the ventricle. The phenomenon of PIR was readily observed during the routine projection of the cineventriculogram in most cases; in some, it was apparent only during frame-by-frame analysis and comparison of tracings.

The patterns of PIR were related to the presence or absence of normal contractions.

I. The Normandy Contracting Ventricle

Type A. Diffuse

In two patients (one with and one without coronary artery disease), the entire ventricular wall participated in the outward movement prior to mitral valve opening. A heightened excursion was observed in the apical region in these two patients.

Type B. Anterior Wall

Four patients (three with and one without coronary artery disease) showed predominant outward movement of the anterior wall (fig. 1).

Type C. Apical

One patient with 75% stenosis of the left anterior descending coronary artery displayed an expansion which was strikingly confined to the apex (fig. 2).

Type D. Apical and Anterior Wall

In 16 patients (seven with normal coronary arteries and nine with coronary artery disease), the outward movement involved the apex and the anterior wall (fig. 3).

†Asynergy (or dysynergy, a synonym) is a term which designates the absence of a coordinated, uniform, normal left ventricular contraction pattern. It includes absence of wall motion, diminished wall motion, systolic ventricular expansion, and an altered temporal sequence of contraction. The term should be reserved for abnormalities of contraction.
II. The Asynergic Ventricle

Type E. The Area of Best Contraction

In 27 of 29 patients with ventricular asynergy, the outward movement of the ventricular wall occurred precisely at the site where systolic contraction had been best, usually at the base of the ventricle (fig. 4). In these cases, asynergy was usually gross with large areas of hypokinesis, akinesis, and often dyskinesis.

Type F. The Site of Asynergy

In two patients the outward wall motion occurred at the segment of ventricular wall which was asynergic. In these patients, the asynergy represented localized hypokinesis and the bulge during PIR was the most striking ventriculographic event (with a greater excursion than in normal subjects).

In 12 patients with normally contracting ventricles and 14 with asynergy, a portion of the ventricle was observed moving inward (synchronous with PIR). This inward motion usually occurred in the inferior border of the ventricle just beneath the mitral valve or in the area of dyskinesis.

Volume Analysis

1. Patients with Normal Coronary Arteries and Ventriculograms

The mean ventricular volume in eight subjects immediately prior to mitral valve opening (PIV) was 11 ml higher than the mean end-systolic volume, an increment of 13% (table 1) (P < 0.001).

2. Patients with Coronary Artery Disease and Normal Ventriculograms

The mean ventricular volume in 12 subjects immediately prior to mitral valve opening (PIV) was 11 ml higher than the mean end-systolic volume, an increment of 13% (table 1) (P < 0.001).

Figure 1

Pre-inflow Relaxation: Anterior Wall. Cine left ventriculogram. This patient had a normal coronary arteriogram and a normal ventriculogram. A) End systole. B) End of isovolumetric relaxation, immediately prior to mitral valve opening. The anterior wall has moved outward (arrow), and the volume of the ventricle increased. C) End-diastolic frame. D) Tracings from cine-ventriculographic prints A, B, and C.
Apical Pre-Inflow Relaxation. Cineventriculogram. This patient had a normal left ventriculogram but significant stenosis of the left anterior descending coronary artery. A) End-systolic frame. B) End-isovolumetric relaxation, immediately prior to mitral valve opening. Note the outward movement of the apex (arrow) in contrast to the appearance in end systole. C) End-diastolic frame. D) Tracings of cine left ventriculogram A, B, and C.

Table 1

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Abbreviations: EDV = end-diastolic volume; ESV = end-systolic volume; EDV - ESV = stroke volume; EDV - ESV/EDV = ejection fraction; PIV = pre-mitral inflow volume; EDV - PIV = true forward stroke volume; EDV - PIV/EDV = corrected ejection fraction; PIV - ESV = difference in LV volume between end systole and pre-mitral valve opening; PIV - ESV × 100/EDV - ESV = percentage difference in corrected stroke volume for original estimate of stroke volume.
Figure 3
Apical and Anterior Wall Pre-Inflow Relaxation, Cine left ventriculogram. A) End systolic frame. B) End isovolumetric relaxation, immediately prior to mitral valve opening. The anterior wall and apex have moved outward. Although a slight inward movement of the posterior wall is also apparent, the volume of the ventricle increased by 11% over the end-systolic volume. C) End-diastolic frame. D) Tracing of cine left ventriculograms A, B, and C.

Table 2
Difference in Stroke Volume and Ejection Fractions Based on End-systolic and Pre-inflow Volume Measurements in Patients with Coronary Artery Disease and Normal Ventriculograms

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See table 1 for explanation of abbreviations.
3. Patients with Coronary Artery Disease and Abnormal Ventriculograms

The mean ventricular volume in 17 subjects immediately prior to mitral valve opening (PIV) was 16 ml higher than the mean end-systolic volume, an increment of 18% (table 3) ($P < 0.001$). The mean difference between ESV and PIV in group 3 (16 ml, abnormal ventriculograms) was significantly different from that in groups 1 and 2 (11 ml, normal ventriculograms) ($P < 0.025$). The data for the three groups are summarized in table 4.

Discussion

The events and mechanics of ventricular systole have properly been the central focus of prolonged physiologic and dynamic morphologic investigation. Similarly, abnormalities of ventricular contraction have been subjected to careful description and analysis within the past few years (with particular emphasis on their relationship to coronary disease and to myocardial performance).5-8

Ventricular diastole, on the other hand, because of its passive role in the action of the heart, has received far less attention. In some texts devoted to cardiovascular dynamics, it is difficult to uncover a systematic description of the nature of ventricular relaxation, its sequence, or the dynamic morphologic changes which accompany it.9 Furthermore, distinctly less attention has been paid to the precise shape and volume changes occurring during protodiastole.

The classical description of the period which immediately follows ventricular ejection includes aortic

Figure 4

Pre-inflow relaxation in the asynergic ventricle. Cine left ventriculogram. Note that the relaxation occurs in the area of best contraction rather than in the asynergic area. A) End-systolic frame. Prominent contractions of the posterior papillary muscle and of the posterior wall were observed. The anterior wall and apex remained fixed and had no significant excursion. B) End-isovolumetric relaxation. Frame immediately prior to mitral valve opening. Significant relaxation has occurred in the area of best contraction (the posterior wall of the ventricle). C) End-diastolic frame. The fixed character of the anterior wall in the apex is apparent. D) Tracing of cine left ventriculograms A, B, and C.
Table 3

**Difference in Stroke Volume and Ejection Fractions Based on End-systolic and Pre-inflow Volume Measurements in Patients with Coronary Artery Disease and Ventricular Asynergy**

<table>
<thead>
<tr>
<th>Patient</th>
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See table 1 for explanation of abbreviations.

valve closure and ends with the opening of the mitral valve\(^1\) as follows:

Tension in the ventricular muscle continues to fall, but no change in ventricular volume occurs until the pressure has fallen below that of the atrium and so has permitted the mitral valve to open.\(^1\)

This description, based on the analysis of cardiac cyclical events by Wiggers,\(^2\) sets the beginning of diastole at a point of uncertain timing shortly before aortic valve closure. This point is denoted by the deepening downward movement of the ventricular pressure curve prior to the aortic incisura; the phase has been labeled "protodiastole." Because of the difficulty encountered in measuring the precise onset and termination of protodiastole, in recent years it has often been coupled with the phase of isovolumetric relaxation.\(^1\) During protodiastole, myocardial fibers begin to lose tension. By the completion of the isovolumetric diastolic phase, the entire ventricular musculature is relaxed and the intraventricular pressure is zero. The termination of isovolumetric relaxation is synchronous with mitral valve opening and with the decline of the atrial pressure curve from the height of the V wave. Wiggers, in one of his early descriptions, emphasized that "since blood neither leaves nor enters the ventricles during these stages, the ventricular volumes do not actually change."\(^1\)

In animal models the measured volume of the left ventricle has been thought to remain unchanged during this phase, which seems quite logical since the

Table 4

**Summary and Comparison of Data Based on End-ejection Measurements and Pre-mitral Valve Opening Measurements**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of subjects</th>
<th>Mean ESV ml</th>
<th>Mean PIV ml</th>
<th>Mean PIV − ESV</th>
<th>Mean percent difference</th>
<th>Mean ejection fraction (ESV)</th>
<th>Mean corrected ejection fraction (PIV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal coronary artery and ventricle</td>
<td>8</td>
<td>45</td>
<td>56</td>
<td>11</td>
<td>13</td>
<td>0.68</td>
<td>0.60</td>
</tr>
<tr>
<td>Normal ventricle, abnormal coronary artery</td>
<td>12</td>
<td>45</td>
<td>56</td>
<td>11</td>
<td>10</td>
<td>0.70</td>
<td>0.63</td>
</tr>
<tr>
<td>Asynergic ventricle, abnormal coronary artery</td>
<td>17</td>
<td>141</td>
<td>158</td>
<td>16</td>
<td>18</td>
<td>0.43</td>
<td>0.37</td>
</tr>
</tbody>
</table>

See table 1 for explanation of abbreviations.
mitral valve is closed and ejection has ceased. The ventricle is "isovolumetric." Furthermore, no systematic description is available of any shape changes occurring during this interval, which also seems logical since the fibers are relaxed but the volume in the ventricle is presumably unaltered.

The observations on PIR that we have described above suggest that these assumptions are no longer tenable for man. It is now apparent that there are distinct shape changes occurring between the end of ventricular ejection and the opening of the mitral valve which can be seen both in the normal and abnormal ventricle. Furthermore, such changes have already been recorded in the literature either without comment or under the designation "diastolic asynergy." The term is clearly inappropriate for two reasons: asynergy has been applied exclusively to contraction phenomena, until now, and to abnormalities of contraction, whereas pre-inflow relaxation is diastolic in time and a normal event of the heart cycle. In a more recent study, the relative frequency of "early relaxation" was noted, and it was considered a normal variation of left ventricular relaxation without reference to volume changes and with no explanation for its occurrence.

If the outward motion so commonly observed in the apex and the anterior wall of the ventricle during protodiastole were invariably associated with an equal, concurrent, inward movement of another segment of the ventricular wall, it might be dismissed as rotational in origin or as a normal variant in the sequence of relaxation. The assumption would be reasonable that relaxation need not occur simultaneously for all fibers in all segments of the ventricle. It now seems far less likely that the outward movement of the ventricular wall is a primary event. Instead, the apparent shape change is almost certainly a response to a volume increment.

How is it possible that the volume of the left ventricle can change when the mitral valve is closed — precluding an increase in volume from left atrial blood — and when ventricular ejection of blood has ceased completely?

Conceivably, blood flow through the Thebesian veins into the ventricular cavity might account for a slight increase in ventricular volume. In fact, the increase is observed when the intraventricular pressure remains significantly higher than coronary venous pressure, and there is no good evidence that Thebesian vein emptying occurs except during that part of ventricular diastole when the intraventricular pressure is zero.

Another possibility is that as the left atrium reaches maximal distension prior to ventricular diastole, the mitral valve leaflets bulge into the left ventricle, thereby producing an apparent increase in intraventricular volume. To the extent that the position of the leaflets can be defined on sequential ventriculographic tracings, no significant forward bulging of the mitral valve has been confirmed in our experience.

Still a third possibility is that the shape change is real — an integral but variable aspect of the relaxing muscle wall — but that the volume change reflects a ventricle with a different configuration than at end ejection with a consequent difference in the accuracy of the volume measurement. This seems unlikely because the shape changes are frequently localized yet are still accompanied by increases in all dimensions.

A more credible hypothesis is that blood is returned to the left ventricular cavity from the aortic root during closure of the aortic valve. The fact that the catheter and sometimes the contrast agent can be seen moving toward the ventricular apex at the time of the volume increase lends some support to this explanation. In 1961, Hawthorne demonstrated a sudden increase in the base to apex length of a dog's left ventricle at the end of systolic ejection. An increase in length immediately after aortic valve closure with ballooning of the apex in some cases was also found in canine hearts by Lynch and Bove. Neither Hawthorne nor Lynch and Bove detected any concurrent decrease in any other measured intraventricular distance; therefore, it is difficult to escape the conclusion that an increment in ventricular volume occurred in their animal model investigations.

With the broadened interest in ventricular volume measurements during this past decade, the detection of an increase in left ventricular volume during PIR should certainly have been recorded in the literature if it in fact exists. Review of some articles fails to indicate any awareness of such a volume change.

On the other hand, careful scrutiny of certain articles is revealing. In the paper by Rackley et al., figure 3 demonstrates four sequential beats with the volume curves for each. Immediately before diastolic filling there appears to be a slight increase in left ventricular volume in each beat. In figure 4 a slight increase above end-systolic volume is clearly demonstrated prior to mitral valve opening in a patient without valvular disease. In the classic paper by Chapman et al., ventricular pressure and ventricular volume in a normal dog are illustrated (figure 8 in their paper). Prior to the onset of ventricular filling from the left atrium, the intraventricular volume appears to rise from 33 ml to approximately 35.5 ml, an increment of 2.5 ml; this is associated with a stroke volume of 21 ml, giving a percentage increment of 12% (very close to that which we have observed in man). No such change was recorded in the humans...
studied by Chapman and his coworkers. It is of interest that the limitations of the equipment permitted only 15 frames/sec in man, too few to be certain that all the nuances of the ventricular volume could be accurately depicted.

Greene et al. have demonstrated a volume increment of about 5 ml prior to mitral valve opening and a stroke volume of approximately 70 ml in a patient with mild mitral stenosis (their figure 9).

There are too few points on the curve to be certain of the exact timing of this increment, but it apparently coincides with the volume increments which we have described in our studies above. Similarly, in their analysis of instantaneous pressure volume ratios in the canine left ventricle, Suga et al. demonstrated unequivocally in their figure 4 that the volume curve of the left ventricle begins to rise prior to the point at which intraventricular pressure is zero and the mitral valve is open. Even the standard physiology texts depict without comment a volume increment occurring prior to mitral valve opening (figs. 5, 6).

It is equally important to seek corroboration of the ventricular volume changes in aortic flow phenomena. Spencer and Greiss have demonstrated that at or about the time of aortic valve closure, blood flow reverses in the aorta. In their figure 9, the calculated backflow volume represents a little more than 3% of the stroke output (fig. 7). Although this percentage differs from the data we have presented in man, the evidence of reflux through the aortic valve, contained in their article, is compelling. Similarly, inspection of aortic flow curves in the articles of Suga et al. and Noble et al. demonstrate a downward deflection approximately at the time of protodiastole (fig. 8). It seems reasonable to suppose that at the time of aortic valve closure this may be accounted for by the return to the ventricle of blood contained in the area between the patent leaflets at the end of ventricular ejection. Furthermore, Fabian and Abrams demonstrated the presence of such a minimal aortic "reflux" following the termination of ventricular ejection in dogs with normal aortic valves under varying conditions of intrathoracic pressure and varying volumes of contrast injection.

Because volume analyses indicate that a significant

![Figure 5](image1.png)

*Figure 5*

Diagram of the electrical, pressure, and volume events of the heart cycle. An increase in ventricular volume has occurred during isovolumetric relaxation, beginning at the end of ejection and visible during protodiastole (arrow). (Reprinted with permission from Best and Taylor, page 735.)

![Figure 6](image2.png)

*Figure 6*

Pressure volume events of the heart cycle. A definite upward movement of the volume curve of the left ventricle is visible beginning immediately at the end of ventricular ejection during protodiastole and extending through isovolumetric relaxation (arrow). (Reprinted with permission from Wiggers, page 597.)
percentage of the ventriculographic stroke volume is returned to the ventricle prior to mitral valve opening, current figures on stroke volume do not represent true forward stroke output in the systemic circulation. This may well be a factor in the discrepancies between cardiac output calculated from the ventriculogram as compared to figures derived from other methods. A more accurate estimate of true forward cardiac output from the ventriculogram would employ the silhouette immediately prior to mitral valve opening rather than the end-systolic silhouette.

The ventricular shape changes are presumably the result of the volume changes rather than the cause. If the volume of the ventricular cavity increases after ejection, there must be changes in ventricular shape to accommodate the augmented volume. The changes in the normally contracting ventricle were apparent in the apex and the anterior wall in the large majority of patients. Although this was not the only pattern, it was certainly the commonest pattern of pre-inflow relaxation in the normal ventricle.

In the asynergic ventricle, however, in which volume increase during PIR was significantly greater than in the normal ventricle, the outward movement of the ventricular wall occurred almost invariably at the location of optimal systolic contraction. Altieri et al. also observed that PIR in patients with contraction abnormalities usually occurred in the normally contracting areas.\(^{16}\)

The explanation for the different patterns in normal and asynergic ventricles may lie in local alterations of muscle compliance. Decreased compliance of hypoxic heart muscle has been demonstrated in the isolated papillary muscle,\(^{31}\) in experimental myocardial ischemia,\(^{32, 33}\) and in man with coronary artery disease.\(^{34}\) The relationship of left ventricular asynergy to myocardial ischemia or fibrosis is well documented.\(^{5, 7, 35, 36}\) In the majority of asynergic ventricles the outward wall excursion of PIR occurred in the relatively compliant area (that of best systolic contraction) rather than in the stiffer, asynergic area with locally decreased compliance. In two of the 29 patients, however, PIR occurred at the site of asynergy and was markedly exaggerated, in each case the most striking ventriculographic event. This also suggests a local alteration in compliance but an increase in this instance. Although Forrester et al. have reported an early increase in left ventricular compliance following myocardial infarction in dogs,\(^{37}\) the two patients in question had no signs of recent infarction. The explanation for the increased compliance in the involved areas is not apparent.

Finally, it is by no means clear why the increase in mean PIV over the end-systolic volume was somewhat greater in patients with asynergic ventricles than in those with normal ventricles. This difference might be related to the end-systolic volumes, which were approximately twice as great in the asynergic ventricles. There is some experimental evidence that the rate of ventricular relaxation is augmented in the presence of higher end-systolic volumes.\(^{38}\) Clearly, this is a matter which requires further documentation and investigation. Perhaps more importantly, the relative constancy of the directional change in value for PIV − ESV despite marked differences in EDV and different sites of pre-inflow relaxation supports the validity of the observation.

The ejection fraction of the asynergic ventricle, calculated on the basis of pre-inflow volume rather than end-systolic volume, was reduced by a factor of 14% from 0.43 to 0.37 (table 3). This is particularly

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**Figure 7**

Contours and time relationships to aortic pressure (AP), left ventricular pressure (LVP), and the ascending aortic flow. The aortic flow curve drops below zero precisely at the moment of protodiastole with return of blood into the ventricle probably accounting for the observed shape and volume changes. (Reprinted with permission from Spencer and Greiss.\(^{27}\))

**Figure 8**

Aortic pressure, left ventricular pressure, and aortic flow curves. A negative deflection of the aortic flow curve occurs in protodiastole synchronous with the observed shape and volume change. (Reprinted with permission from Noble.\(^{36}\))
important when one considers that the mean ejection fraction of the asynergic ventricle — at least in this series — was only 62% of that of the normal ventricle.

References

12. Wiggers CJ: Studies of the consecutive phases of the cardiac cycle, 1) the duration of the consecutive phases of the cardiac cycle and the criteria for their precise determination. Am J Physiol 56: 415, 1921
Shape and Volume Changes During "Isovolumetric Relaxation" in Normal and Asynergic Ventricles
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