Comparison of Early Systolic and Holosystolic Ejection Phase Indexes by Contrast Ventriculography in Patients with Coronary Artery Disease

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SUMMARY To compare the discriminant ability of early systolic and holosystolic ejection phase indexes to detect abnormalities of left ventricular performance, the contrast ventriculograms of 20 control patients and 55 patients with coronary artery disease (at least 70% stenosis of one or more major coronary arteries) were analyzed. All subjects were studied to evaluate chest pain, and none was taking propranolol or antihypertensive drugs. Several ejection phase indexes were evaluated, using holosystole, the first third of systole and the first half of systole. In the patients with coronary disease, 14 (25%) had one-vessel disease, 13 (24%) had two-vessel disease and 28 (51%) had three-vessel disease. In general, the ejection fraction was more useful than indexes based on velocity of ejection. Ejection fraction was lower in the coronary patients than in normal subjects for holosystole (0.62 ± 0.14 vs 0.70 ± 0.08, p < 0.01), for the first third of systole (0.30 ± 0.06 vs 0.36 ± 0.04, p < 0.01), and for the first half of systole (0.24 ± 0.09 vs 0.53 ± 0.07, p < 0.001). Fourteen patients with coronary artery disease (25%) had a depressed holosystolic ejection fraction, 36 (65%) had a depressed first-half ejection fraction and 52 (94%) had a depressed first-third ejection fraction. We conclude that early ejection phase indexes, particularly the first-third ejection fraction, are more useful than holosystolic indexes in identifying resting abnormalities of left ventricular function.

EJECTION PHASE INDEXES of left ventricular performance are often more useful in discriminating normal from abnormal function than indexes derived from the isovolumic phase of contraction.1,2 In patients with coronary heart disease, wall motion abnormalities may be present at midsystole without being apparent at the end of systole,3 observations that were extended in a study by Johnson et al.4 to include an assessment of the volume of blood ejected during the first third of systole. These studies suggested that a variety of measures of the early ejection phase often are abnormal, even when all of the holosystolic indexes are normal. To further compare the relative power of early systolic and holosystolic indexes to detect ventricular dysfunction, and to elucidate which period during systole is most useful, we analyzed the contrast ventriculograms in 20 control subjects and 55 patients with coronary heart disease.


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Received April 26, 1979; revision accepted November 30, 1979.
Circulation 61, No. 6, 1980.
Methods

Patient Population

Group 1 consisted of 20 subjects who underwent cardiac catheterization with left ventriculograms and coronary angiograms for the diagnosis of atypical chest pain. Their mean age was 50.9 ± 6.6 (SD) years (range 39–73 years). Each control subject fulfilled the following criteria: 1) no evidence of any coronary disease; 2) left ventricular end-diastolic volume index ≤ 90 ml/m²/BSA; 3) left ventricular end-diastolic pressure ≤ 12 mm Hg; 4) an increase in left ventricular end-diastolic pressure after angiography of < 4 mm Hg; 5) no evidence of intracardiac shunts by a standard radionuclide method or valvular heart disease; 6) no evidence of hypertension or diabetes; 7) not taking medications; 8) normal resting and stress treadmill ECGs; and 9) no evidence of coronary spasm or mitral valve prolapse syndrome. No patient underwent ergonovine stress; however, no patient had rest pain in association with ST-segment elevation. Additionally, no subject had coronary spasm with catheter placement during coronary angiography.

Group 2 consisted of 55 patients who underwent diagnostic cardiac catheterization for evaluation of chest pain and were found to have at least one stenosis (diameter reduction of at least 70% confirmed by two experienced readers) of a major coronary artery. No patient had a history of recently increased chest pain, recent myocardial infarction, or other change in clinical status. No patient had a history of a definite myocardial infarction, although 23 patients had significant Q waves on their resting ECGs. Twenty-three patients were in New York Heart Association functional class II, 24 were in functional class III, and three were in functional class IV. The classification was based on complaints of chest pain with activity; no patient had complaints compatible with occult congestive heart failure. The patients met the following criteria in order to be included in the study: 1) no evidence of valvular heart disease or intracardiac shunts; 2) no recent use (within 1 week) of quinidine, procainamide or propranolol; 3) no history of hypertension or diabetes mellitus; and 4) no intraventricular conduction abnormalities on the resting ECG, as evidenced by a QRS duration of > 0.10 second. This group included 18 women and 37 men who had a mean age of 51.9 ± 8 years (range 36–78 years).

Data Collection and Processing

All patients were studied in the postabsorptive state under mild sedation (sodium pentobarbital, 100 mg i.m.) and local anesthesia (1% lidocaine). Catheters were inserted through the femoral artery or, less commonly, through the brachial artery, and left ventricular pressure was measured by means of either a Statham SF1 or Millar Instruments #8F or #7F catheter-tip micromanometer with a zero reference level 10 cm above the table top. The high-fidelity left ventricular pressure tracing was calibrated by matching a signal with a simultaneous pressure obtained through the lumen or by a predetermined electronic calibration constant. Left ventriculograms were performed using a pigtail (#7F or #8F) or a Lehman ventriculography catheter. A special effort was made to position the side holes directly in front of the mitral valve to minimize stimulation of premature ventricular contractions. Left ventricular volumes were measured using the area-length method. The cineangiograms were recorded at 58 frames/sec on 35-mm film and contrast injection into the left ventricle was performed in mid-inspiration by injecting 50–70 ml of Renographin-75 over 2–3 seconds. Biplane cineangiograms were performed in the anteroposterior and lateral projections in 10 of 20 normal subjects and 35 of 55 patients. Single-plane cineangiograms were performed in the 30° right anterior oblique position in 10 of 20 normal subjects and 20 of the 55 patients. During the cineangiograms the brachial artery pressure, ECG and cine pulse time marker corresponding to each cineframe were recorded at a paper speed of 200 mm/sec.

For calculation of ventricular volumes, end-diastole was identified by selecting the frame before the visualization of ejection of contrast material into the aorta (61 of 75 cases). In these cases, the mean time from the peak of the QRS to the end-diastolic frame was 0.044 ± 0.003 second (mean ± SD). When this could not be done with confidence, the frame closest to 0.04 second after the peak of the QRS complex of the ECG was chosen. Each frame was 0.018 second in duration (58 frames/sec) so that either the second or third frame after the peak of the QRS was chosen, depending upon when inward motion of the ventricular silhouette was noted (14 of 75 cases). In these 14 cases, the mean time from the peak of the R wave to the end-diastolic frame was 0.042 ± 0.003 second, not significantly different from the previous method (unpaired t test). End-ejection was defined as the maximal inward excursion determined by visual inspection of the cineangiogram. When the time around end-systole was located, four or five silhouettes were planimetered and the one with the smallest volume was chosen. The number of the frames between the two points was then used to calculate the left ventricular ejection time. To find the left ventricular volume at the first third of systole, the total number of frames was divided by three and the corresponding frame was chosen. When the division was not even, the first and second thirds were made equal and the last third made either one frame shorter or longer in duration, as previously described by Johnson et al. To find the left ventricular volume at the first half of systole, the total number of frames was divided by two and the corresponding frame was chosen. When the division was not even, the extra frame was always added to the first half of ejection. In either the right anterior oblique or anterior projection, the long axis of the ventricle was drawn between the midpoint of the aortic valve to the apex. The internal diameter of the minor axis was then drawn and measured at a point perpendicular to and at the midpoint of the long axis. At no time was an extrasystolic or postextrasystolic beat used. All beats...
selected were within four beats from the time of contrast injection and only five beats were used that were not within three beats after injection. The following calculations were performed:

1) Ejection fraction (EF) = end-diastolic volume - end-systolic volume/end-diastolic volume.

2) Mean velocity of circumferential fiber shortening (mVcf = end-diastolic circumference - end-systolic circumference/(end-diastolic circumference/ejection time).

3) Mean normalized systolic ejection rate (mNSER) = end-diastolic volume - end-systolic volume/(end-diastolic volume/ejection time).

4) First-third ejection fraction (1/3 EF).

5) First-third mean velocity of circumferential fiber shortening (1/3 mVcf).

6) First-third mean normalized systolic ejection rate (1/3 mNSER).

7) First-half ejection fraction (½ EF).

8) First-half mean velocity of circumferential fiber shortening (½ mVcf).

9) First-half mean normalized systolic ejection rate (½ mNSER).

The last six measures were identical to calculations 1–3, except that the volume or circumference at the end of the first third or first half of systole was used instead of the end-systolic volume.

The right anterior oblique image of the single-plane ventriculograms and the anterior view of the biplane contrast ventriculograms underwent chordal analysis in a manner similar to that described by Herman et al. and Helfant and Banka. A longitudinal axis was drawn from midaortic valve plane to the apex. This line was then divided by four perpendicular transverse hemiaxes. Each hemiasix was measured and recorded as the percentage change from end-diastole to end-systole. The same coordinates were used in the frontal view of the biplane studies. In addition, in the lateral view the ventricular silhouette was quadrisectioned by drawing the longest axis from the midpoint of the aortic valve plane to the apex and drawing a perpendicular at the midpoint of that axis. By this approach, 545 segments in patients with coronary disease and 190 segments in normal subjects were analyzed. A segment was defined as showing an abnormal contraction pattern if chordal shortening was not within 2 standard deviations of shortening seen in that region in the normal subjects. Similar analyses were performed using the ventricular silhouette tracing at the first third of systole and compared with the end-diastolic silhouette.

Data were analyzed using the t test for unpaired data, and when appropriate an analysis of variance was used.

**Results**

The age range and standard hemodynamic and angiographic data in all subjects are presented in Table 1.

The mean of the systolic blood pressures for the control group was 127.4 ± 17 mm Hg (mean ± sd) and was not significantly different from that in the coronary patients (125.8 ± 19.7 mm Hg). Control subjects had a mean diastolic pressure of 76.1 ± 10.8 mm Hg and a heart rate of 78.7 ± 11.4 beats/min, which did not differ significantly from the corresponding values in the patients with coronary artery disease (76.1 ± 10.8 mm Hg and 78.7 ± 11.4 beats/min, respectively). The left ventricular end-diastolic pressure was significantly greater in coronary disease patients (15.6 ± 8.6 mm Hg) than in control subjects (8.1 ± 2.4 mm Hg, < 0.0003); however, there was no significant difference in the end-diastolic volume index between the two groups.

**Ejection Phase Indexes**

All abnormal indexes were defined as being below the lowest result in the control group.

**Holosystolic Indexes**

Patients with coronary artery disease had a significantly lower mean ejection fraction than control subjects (0.62 ± 0.14 [mean ± sd] vs 0.70 ± 0.08, < 0.01), but only 14 of the 55 patients (25%) had a reduced ejection fraction (< 0.56) (fig. 1). Patients with coronary heart disease had a significantly lower mean Vcf than controls (1.26 ± 0.49 vs 1.84 ± 0.51 diam/sec, < 0.001), and 19 of 55 patients (35%) had an abnormal mean Vcf (< 1.06 diam/sec) (fig. 2).

The patients with coronary disease had a lower mean NSER than controls (2.48 ± 0.97 vs 3.57 ± 0.67 vol/sec, < 0.001), and 27 of the 55 patients (49%) had a depressed mean NSER (< 2.3 units) (fig. 3).

**First-half Ejection Phase Indexes**

The coronary patients had a significantly lower first-half ejection fraction than the control subjects (0.34 ± 0.09 vs 0.53 ± 0.10, < 0.001). Of the 55 coronary patients, 36 (65%) had a reduced first-half ejection fraction (fig. 1).

Patients with coronary heart disease also had a significantly lower first-half mean Vcf than controls (1.19 ± 0.46 vs 1.71 ± 0.28 circ/sec, < 0.001), and 28 of 55 patients (51%) had a reduced first-half mean Vcf (< 1.17 circ/sec) (fig. 2). Similarly, 25 of 55 patients (45%) had a reduced mean first-half NSER compared with controls (< 2.38 vol/sec), and the group as a whole had a significantly lower NSER than the control subjects (2.47 ± 0.77 vs 3.56 ± 0.72 vol/sec, < 0.001) (fig. 3).

**First-third Ejection Phase Indexes**

The coronary patients had a significantly lower first-third ejection fraction than controls: 52 of 55 coronary patients (95%) had a reduced first-third ejection fraction (fig. 1), significantly lower than in the control subjects (0.20 ± 0.06 vs 0.36 ± 0.06, < 0.001). The patients with coronary artery disease also had a significantly lower first-third mean Vcf than the control subjects (1.12 ± 0.53 vs 1.56 ± 0.3 circ/sec, < 0.001); 26 of the 55 patients (47%) had a
TABLE 1. Hemodynamic Results

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| Normals (n = 20) | Age (years) | HR (beats/min) | SBP (mm Hg) | DBP (mm Hg) | LVEDP (mm Hg) | LVEDVI (mm Hg) | Holosystole 
|                  | 50.9  | 78.7  | 127.4 | 76.1 | 8.1 | 57 | EF |
| Mean             |       |       |       |       |     |    |    |
| ART              | 6.6   | 11.4  | 17.1  | 10.8 | 2.4 | 15 |    |
| Range            | 37–60 | 92–95 | 4–12  | 35–90 |    | 0.003 |    |
| Coronary patients (n = 55) | Mean | SD | Range | p Value compared with normals | NS | NS | NS | 0.003 | NS | 0.01 |
| Mean             | 51.9  | 72.8  | 125.8 | 71.7 | 15.6 | 61.4 | 0.62 |
| ART              | 8     | 9.7   | 19.7  | 9.6  | 8.6  | 22.5 | 0.14 |
| Range            | 37–55 | 85–98 | 4–98  | 30–151 |    | 0.003 |    |
| p value compared with normals | NS | NS | NS | 0.003 | NS | 0.01 |

Abbreviations: HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; LVEDP = left ventricular end-diastolic pressure; LVEDVI = left ventricular end-diastolic volume index; EF = ejection fraction; mVcf = mean velocity of circumferential fiber shortening; mNSER = mean normalized systolic ejection rated; LVET = left ventricular ejection time.

Depressed first-third mean Vcf (fig. 2), and 36 patients (66%) had a reduced first-third mean NSER (fig. 3).

Ejection Times

The patients with coronary disease had a significantly shorter left ventricular ejection time (LVET) than the control subjects (0.276 ± 0.04 vs 0.298 ± 0.04 second [mean ± sd], p < 0.04). Patients taking digoxin (n = 13) had a shorter LVET than patients not on digoxin (0.267 ± 0.04 vs 0.28 ± 0.04 second, p > 0.05). Additionally, the patients on digoxin, as a group, had more marked left ventricular dysfunction than the patients not taking this drug (mean ejection fraction 0.43 ± 0.11 vs 0.67 ± 0.08, p < 0.001).

To explain the reduced sensitivity of the early ejection indexes of velocity compared to the first-third ejection fraction, differences in ejection times between coronary patients with normal and decreased first-

Figure 1. The ejection fractions (EF) during the first half of systole, the first third of systole and holosystole. While the mean EF and EF, during the first half and first third of systole are lower in coronary patients than in normal subjects, the overlap between normal subjects and patients decreases as earlier ejection periods are evaluated.

Figure 2. The results of the mean velocity of circumferential fiber shortening (mVcf) are displayed here. The holosystolic mVcf, first-half mVcf and first-third mVcf are plotted for the normal subjects and the coronary patients. The mean values between the groups are significantly lower for the coronary heart disease patients, but the first systolic indexes are not more discriminating than holosystolic indexes in discerning normal subjects from patients with coronary heart disease.
third mean Vcf and first-third mean NSER were also examined. Patients with a normal first-third mean Vcf had an average LVET of 0.257 ± 0.04 vs 0.299 ± 0.03 second for patients with a reduced first-third Vcf (p < 0.001). The percent of circumferential shortening during the first third of systole was a more sensitive index than the first-third mean Vcf alone, and 34 of 55 patients with coronary disease (62%) showed a reduced value when compared with the normal subjects, although only 26 of 55 (47%) had a depressed first-third mean Vcf. Patients with an abnormal first-third mean NSER had a significantly shorter LVET than the patients with a normal first-third mean NSER (0.26 ± 0.04 vs 0.287 ± 0.04 vol/sec, respectively, p < 0.04). Thus, of 41 patients with a normal holosystolic ejection fraction, 38 had one or more abnormal measures of the first third of systole, but all 38 were also identified by the first-third ejection fraction alone.

Ejection Phase Indexes and Coronary Artery Lesions

In patients with one-vessel coronary disease, the mean first-third ejection fraction in patients with a normal holosystolic ejection fraction was 0.20 ± 0.05 (n = 15). In patients with two-vessel coronary artery disease and normal holosystolic ejection fraction, the mean first-third ejection fraction was 0.22 ± 0.07, and in patients with three-vessel disease (n = 7), the first ejection fraction averaged 0.22 ± 0.05. These three values for the first-third ejection fraction were not significantly different.

The patients with a reduced holosystolic ejection fraction (n = 14) had a lower mean first-third ejection fraction than the patients with a normal (n = 4) holosystolic ejection fraction (0.15 ± 0.06 vs 0.22 ± 0.04, p < 0.05). In the group with coronary disease and a depressed first-third ejection fraction, one patient had one-vessel coronary disease and a first-third ejection fraction of 0.25; five patients had two-vessel disease with a mean first-third ejection fraction of 0.17 ± 0.06; and eight patients had three-vessel coronary disease with a mean first-third ejection fraction of 0.13 ± 0.07.

Ejection Phase Indexes and Left Ventricular Wall Motion

Of 545 segments analyzed in the coronary patients, 160 (29%) were abnormal (percent shortening not within 2 standard deviations of normal shortening). Of these 160 abnormal segments, 87 were in patients with a reduced resting holosystolic ejection fraction. The abnormal segments in these patients were, in general, associated with pathologic Q waves and with severe contraction abnormalities (17 hypokinetic, 48
akinetically contracting and 22 dyskinetic). The remaining 73 abnormal segments were in patients with a normal resting ejection fraction and were mainly hypokinetic (only three akinetic and none dyskinetic).

The correlation between the ejection fraction and the number of abnormally contracting segments was good ($r = -0.84$) (fig. 4); however, the correlation with any early systolic index was poor ($r = -0.42$) (fig. 5). In the 41 patients with a normal ejection fraction, only 18% of the analyzed segments contracted abnormally (73 of 410), yet 38 patients had a reduced first-third ejection fraction, suggesting that analysis of the early phase better disclosed contraction abnormalities. These 38 patients had early abnormally contracting segments, but only 12 had abnormal shortening at the end of systole.

Of the 545 segments analyzed at the end of the first-third of systole, 265 showed reduced excursion compared with normal segments. Thus, there were more abnormal segments at the end of the first-third of systole than at the end of systole (265 vs 160, $p < 0.001$). The correlation between the first-third ejection fraction and the mean percent of chordal shortening at the first third of systole was $-0.88$, and with the number of abnormally contracting segments $-0.71$ (fig. 6).

Reproducibility

Fifteen studies were selected at random. Intraobserver variation was assessed by repeating the calculations 2 months after the original analysis. For the first-third ejection fraction, the variation between studies was $0.02 \pm 0.02$ (ejection fraction units, $\pm$ SD, range 0.00–0.06) and the correlation between the two studies was excellent ($r = 0.96$). Interobserver variation was assessed by having a second investigator unaware of the results of the first observer calculate the data for these 15 patients. The variation for the first-third ejection fraction was $0.03 \pm 0.03$ (ejection fraction units $\pm$ SD, range 0.01–0.07) when the first and second observers’ results were compared ($r = 0.93$) (table 2).
dxes and to determine the most useful time to study during each ejection, we examined a large group of patients with coronary artery disease and compared them with subjects who had no angiographic or clinical evidence of myocardial disease. Our data indicate that indexes calculated early during ejection are more sensitive than those calculated from the full period of wall shortening. The first-third ejection fraction appears to be more useful than the first-half ejection fraction or other measures of early ejection, because it was depressed in 95% of all patients studied with coronary heart disease. One reason for the first-third ejection fraction measurement being more useful than the time-dependent indexes of velocity is the well-known shortening of the ejection time in patients with left ventricular dysfunction, which tends to maintain the velocity indexes closer to normal. In addition, because the first-third mean Vcf is calculated at the minor equator, localized wall motion abnormalities may not be detected.

Possible explanations for the high incidence of abnormal early ejection phase indexes in the coronary patients are complex, partly because patients with coronary atherosclerosis may also have atherosclerosis of the aorta. Thus, they could have abnormal aortic compliance leading to increased impedance to ejection, a well-described mechanism for producing acute effects on cardiac ejection. However, the ages in the normal and coronary patients were similar, and it may be argued that any such impedance effect should be gradual in onset and chronic in nature, thus allowing time for left ventricular compensation. Another hypothesis that could account for the wall motion disturbances characterized by Leighton et al. is a relationship between wall motion abnormalities and left ventricular fibrosis. Certain sections of the left ventricle may contain fewer viable muscle fibers, and thus fail to generate sufficient force to contract against the high wall stress present in early systole. Ideker et al. demonstrated a relationship between the severity of wall motion abnormalities and the degree of myocardial fibrosis, although this has not been confirmed by all investigators. It is possible that because peak tension is usually reached relatively early in systole, this phase can most sensitively reflect the contractile ability of partially scarred regions. When wall motion was also analyzed by assessment of chordal shortening in multiple regions, there were more abnormally contracting segments early in systole than at the end of systole, and the presence of early systolic wall motion abnormalities correlated with abnormal early systolic indexes. These abnormal indexes also occurred in the absence of akinetic or dyskinetic segments and historical or electrocardiographic evidence of myocardial scar. Additional phenomena that might contribute to abnormal early contraction patterns include local conduction abnormalities and subtle coronary blood flow disturbances not well visualized by standard contrast or radionuclide angiograms.

Whatever the pathophysiology of this abnormality in early left ventricular ejection, the early ejection phase indexes of ventricular performance, in par-
ticular first-third ejection fraction, should prove useful in detecting abnormal left ventricular function in patients with coronary artery disease, particularly when noninvasive approaches are used in screening patients for possible coronary heart disease.

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Comparison of early systolic and holosystolic ejection phase indexes by contrast ventriculography in patients with coronary artery disease.
R Slutsky, J S Karliner, A Battler, K Peterson and J Ross, Jr

Circulation. 1980;61:1083-1090
doi: 10.1161/01.CIR.61.6.1083

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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