Value of partial ejection fraction, volume increment, and regional wall motion in identifying patients with clinically significant coronary artery disease

Florence H. Sheehan, M.D., Harold T. Dodge, M.D., Edward L. Bolson, M.S., Woo Hok-Wai, B.S., Gary R. Caputo, M.D., and Douglas K. Stewart, M.D.

ABSTRACT  Recent studies suggest that the partial ejection fraction (EF) in early systole is a more sensitive index of left ventricular (LV) dysfunction than the holosystolic EF. We examined LV volume, partial EF, and volume increment at each of 12 time points in systole to determine which parameter best distinguishes normal subjects from patients with coronary artery disease (CAD). Contrast ventriculograms, obtained either in the right anterior oblique projection (60 frames/sec) or in the biplane projection (30 frames/sec), of 58 normal subjects and 68 patients with CAD were studied. The endocardial contour in each frame of a sinus beat was traced to derive a volume curve. At each twelfth of systole, LV volume was extrapolated from the curve and the partial EF was calculated. The increment in volume between successive time points was also calculated. Both partial EF and LV volume in patients with CAD became progressively more abnormal with time; peak abnormality occurred at end-systole. In a subgroup of patients with CAD who had normal holosystolic EF, both partial EF and volume were normal throughout systole. The increment in volume with each twelfth of systole in patients with CAD deviated less than 1 SD from normal throughout systole. Thus, maximum abnormality in partial EF and volume occurs at end-systole. Of the parameters of global LV function tested, holosystolic EF best distinguishes patients with CAD from normal subjects. However, regional wall motion measured in the area of interest is more sensitive to localized abnormality, the severity of which may be overestimated or underestimated by the EF due to hyperkinesis or hypokinesis in other regions of the left ventricle.

Circulation 68, No. 4, 756-762, 1983.
them into two groups, depending on the criteria fulfilled. The first group was classified as normal subjects and the second group as patients with coronary artery disease (CAD).

The group with normal left ventricles (normal subjects) was selected by use of the records at the hospital from 1974 to 1980 from all patients who underwent diagnostic cardiac catheterization for chest pain. There were 36 men and 22 women who fulfilled the following criteria for selection: no significant coronary artery disease, no other cardiac disease or history of thoracotomy, and a ventriculogram of adequate quality for frame-by-frame analysis. The group with normal left ventricles had normal electrocardiograms (ECGs), LV end-diastolic pressure less than 15 mm Hg, and end-diastolic volume less than 110 ml/m². The data measured in this group were used to define the values for the normal mean and standard deviation for LV volume and EF. For 36 subjects, ventriculograms were obtained from the right anterior oblique (RAO) projection; for 22 subjects, ventriculograms were obtained from the biplane projection. In this group of subjects with normal ventriculograms, 31 were taking propranolol at the time of study, 24 were not, and in three information on medication was unavailable.

Patients with coronary artery disease (CAD) were selected by querying the data base of cardiac catheterization patient data for patients with significant stenosis (defined as ≥ 50% narrowing of coronary artery diameter as assessed by visual inspection of coronary angiograms) in at least one major coronary artery, presence of a normal sinus beat not following a premature ventricular contraction, and optimal technical quality of the ventriculogram. The technical quality of each ventriculogram analyzed in our laboratory is routinely graded on a 10-point scale on the basis of contrast and visibility of all borders of the endocardial contour at end-diastole and end-systole. Inadequate quality of a ventriculogram or lack of a normal sinus beat were the most common reasons for exclusion; patients were also excluded if they had congenital or valvular heart disease. The medical records of acceptable patients were then examined, and patients were excluded from the group with CAD if they had a conduction defect present on the ECG other than first-degree block or if they had a prior thoracotomy. The study was arbitrarily closed after 68 patients with CAD (34 with single-vessel disease and 34 with multivessel disease) were selected from 1359 patients with CAD who underwent cardiac catheterization between 1976 and 1980. There were 55 men and 13 women. The presence or absence of regional wall motion abnormality was not a consideration in the acceptance or rejection of patients. Of the patients with CAD, 46 were taking propranolol at the time of study, 17 were not, and information on medication was unavailable in five patients. RAO ventriculograms were obtained for all. None of the patients had significant left main coronary artery stenosis. In all but one patient, coronary stenosis exceeded 70% and in all but five patients, stenosis exceeded 85% in at least one coronary artery. For one normal subject and two patients with CAD, a calibration grid used to correct for magnification could not be obtained; in these people only the partial and holosystolic EF were calculated.

To undergo cardiac catheterization, both groups were premedicated with either 50 mg of meperidine (Demerol) and 25 mg of promethazine (Phenergan) parenterally or 10 mg of oral diazepam. Selective coronary angiography was performed by use of either the Judkins or Sones technique. For ventriculography, 40 to 60 ml of radioopaque medium (Renovist II) was delivered over 2 to 3 sec through a No. 8F catheter positioned in the left ventricle. RAO ventriculograms were recorded on 35 mm film at 60 frames/sec and biplane ventriculograms at 30 frames/sec.

**Volume and EF.** Left ventriculograms were projected and the endocardial contour was traced by hand from each frame in one cardiac cycle of a sinus beat not following a premature ventricular contraction. The frames were numbered with a timing strip to correlate them with the ECG. The LV contours were entered into a PDP-11 computer with an x-y digitizer (Autotrol). A grid pattern of known dimension filmed at the time of cardiac catheterization was also digitized to correct for magnification. Subsequent calculations were performed directly through the computer with specially written programs. End-diastole was defined as 0.04 sec after the peak of the R wave on the ECG, and end-systole was defined as the frame at which the LV chamber volume reached a minimum. For each frame in systole, the volume of the left ventricle was computed by the area-length method. A volume-time curve (figure 1) was constructed by the computer. Systole was divided into twelfths, and the LV volume at each of the 12 time points was read from the volume-time curve. Whenever the time point failed to coincide with an angiographic frame, the volume for that time point was linearly interpolated from the volumes measured in the two adjacent frames.

All volumes were normalized for body surface area. Partial EF was computed as (EDV - V(t))/EDV, in which EDV = end-diastolic volume per m² and V(t) = LV volume at time point t in systole. The volume increment or change in volume between successive time points was calculated as V(t + 1) - V(t).

**Regional wall motion analysis.** Regional wall motion was measured with the centerline method (figure 2) at 100 chords constructed perpendicular to and evenly spaced along a centerline drawn midway between the end-diastolic and end-systolic endocardial contours. Motion at each chord, represented by the chord length, was normalized for heart size by dividing by the perimeter of the end-diastolic contour. To compare different chords, which requires that their motion be expressed in compa-
was measured in the LAD or RCA region according to the dominant system. In patients with multivessel disease, the overlap region was arbitrarily halved and the LAD and RCA territories were assigned chords 10 to 58 and 59 to 80, respectively. The magnitude of regional abnormality was measured by averaging the motion of chords in the most hypokinetic segment of the artery territory. The length of this most abnormal segment was restricted to 50% of the artery territory, since this yields a better distinction between subjects with normal arteries from patients with stenosed coronary arteries than the motion of chords averaged over longer or shorter segments of the artery territory. In patients with single-vessel CAD, regional hypokinesis was measured in the territory of the stenosed artery. In patients with multivessel disease, the more hypokinetic measurement of the two territories was selected for comparison with the EF.

When regional wall motion was compared with the EF, the EF was expressed in units of standard deviations from the mean of the 64 normal subjects. This was done to clarify the comparison by use of similar units, since wall motion was expressed in standard deviations from the mean of these 64 normal subjects.

Statistical analysis was performed with one-way analysis of variance and chi-square. To determine which of the 36 parameters (volume, volume increment, or partial EF at each twelfth of systole) best distinguished normal subjects from patients with CAD, discriminant analysis was performed. Discriminant analysis selects the variable that maximizes the multivariate F ratio for difference between groups.

Results

Partial EF. The partial EF in the 68 patients with CAD differed significantly from that of normal subjects at each twelfth of systole. The abnormality in partial EF in the patients with CAD was least severe in early systole but became progressively worse with time, so that the EF was most depressed at end-systole (figure 3). In a subgroup of patients with holosystolic EF equal to or greater than 57.6%, i.e., not less than 2 SD below the normal group mean, the depression in partial EF was significant from 7/12 systole to end-systole, when it was most abnormal (figure 3).

Partial EF was also tested in the following subgroups: patients with (n = 45) and without (n = 23) myocardial infarction and patients with single-, double-, or triple-vessel disease. In all subgroups the partial EF displayed the same pattern of progressive abnormality with time and peak abnormality at end-systole.

The time in systole at which partial EF was most depressed was individually determined for each of the 68 patients with CAD (table 1). In one patient, partial EF was most depressed at 7/12 systole. In six patients, partial EF was most depressed at the onset of systole (7/12 systole). Peak abnormality in partial EF occurred most frequently (34/68 patients) at end-systole. Of the five patients with coronary artery stenosis less than 85%, peak abnormality in partial EF occurred at 7/12 systole in two and at 7/12, 7/12, and end-systole in the
other three. In the subgroup of patients with CAD with holosystolic EF equal to or greater than 57.6%, the peak abnormality in partial EF occurred more frequently at end-systole than at other times.

When the effect of propranolol was examined, we found that the partial and holosystolic EF of normal subjects who were taking propranolol at the time of study were almost identical to that of normal subjects not on propranolol. In patients with CAD who had an EF equal to or greater than 57.6%, both on and off propranolol, partial EF did not differ significantly from normal throughout systole. In patients with an end-systolic EF less than 57.6%, both on and off proprano-

**TABLE 1**

<table>
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<th>Time in systole (twelfths)</th>
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<td>34</td>
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EF = holosystolic ejection fraction.

A57.6% is 2 SD below the mean EF in the group with normal ventriculograms.

**FIGURE 3.** Abnormality in partial EF in all patients with CAD and in a subgroup with end-systolic EF ≥ 57.6%. Results are expressed as the difference, in units of standard deviations, between the values for partial EF in the normal group (zero line) and that of patients with CAD. Significant difference between the patient group and normal group is indicated by the symbols on the curves.

In patients with CAD who had an EF equal to or greater than 57.6%, the partial EF varied no more than 0.6 SD from normal throughout systole. The partial EF in patients with CAD who had an EF less than or equal to 57.6% became progressively subnormal with time in both groups.

**Volume.** LV volume expressed in terms of standard deviations from the normal mean was significantly larger in patients with CAD than in normal subjects throughout systole, with maximum difference occurring at end-systole (figure 4).

The increment in volume between successive twelfths of systole, again expressed as standard deviations from the normal mean, was near normal throughout systole, differing significantly only at 1/12th systole (figure 5).

**Discriminant analysis.** Of the 36 parameters tested (volume, partial EF, and volume increment at each twelfth of systole), the holosystolic EF best distinguished normal subjects from those with CAD (figure 6). The holosystolic EF also best separated the subgroup of patients with CAD who had a normal holosystolic EF (≥ 57.6%) from normal subjects.

**Regional wall motion analysis.** If the threshold for sig-
significant abnormality is defined as $-2$ SD, then regional hypokinesis was significant in 41 of the 68 patients with CAD, 32 of 45 with myocardial infarction, and nine of 23 without prior infarction, whereas the end-systolic EF was abnormal in only 29 of 68 patients with CAD, 25 of 45 with infarction, and four of 23 without infarction. Although mean regional hypokinesis, $-2.13 \pm 1.14$ SD/chord, was similar to mean EF, $-2.29 \pm 1.93$ SD, correlation between them was poor with a coefficient of $r = .57$. To determine the reason for this poor correlation, the influence on the EF of motion on the wall opposite the most hypokinetic region was examined. We found that in patients with normal or hyperkinetic motion on the opposite wall, the EF was significantly less depressed than wall motion in the hypokinetic region ($-0.77 \pm 1.00$ SD vs $-1.30 \pm 1.00$ SD/chord, $n = 24$, $p = .030$). In patients who had hypokinesis on both walls, the EF was more depressed than regional motion in the more hypokinetic of the two walls ($-3.12 \pm 1.18$ SD vs $-2.59 \pm 0.84$ SD/chord, $n = 44$, $p = .040$). Thus the EF not only was less sensitive in detecting significant (more depressed than $\leq -2$ SD) abnormalities in patients with CAD, but also overestimated or underestimated the severity of hypokinesis in the most abnormally contracting region due to the influence of hypokinesis or hyperkinesis on the opposite wall of the left ventricle.

**Discussion**

A number of studies have been performed that examine the effect of coronary artery stenosis on the

**FIGURE 4.** Systolic volumes for patients with CAD compared with that of the normal subjects in terms of standard deviations. See legend to figure 3.

**FIGURE 5.** Increments in volume between successive twelfths in systole, compared with those observed in normal subjects and shown in units of standard deviations from the normal mean. See legend to figure 3.
volume of EF or partial EF at multiple times in systole. In this study we found that the partial EF was near normal throughout systole in patients with normal EF at end-systole. In patients with depressed function, the partial EF became progressively subnormal with time and reached peak abnormality at or near end-systole.

Our data confirm the findings of Leighton et al.,

which demonstrate the poor sensitivity of the partial EF, measured at $\frac{1}{4}$ and $\frac{1}{2}$ systole, in distinguishing normal subjects from patients with CAD who have normal holosystolic EF and wall motion. Jones, Kemper, Denenberg, and their colleagues also reported the EF at $\frac{1}{3}$ systole to be a poor discriminator of patients with CAD without prior myocardial infarction.

Our results, however, differ from the data in three other reports. Johnson et al. measured the rate of volume change at each third of systole in patients with isolated LAD stenosis, no prior infarction, and normal EF at end-systole. They found this index to be significantly depressed at $\frac{1}{3}$ systole although function was normal at end-systole. Slutsky et al. and Holman et al. also found significant depression of the partial EF at $\frac{1}{3}$ systole in patients with CAD who have a normal holosystolic EF.

The discrepancy between these and our results may be due to the different methods used. For example, Slutsky et al. defined the onset of systole as either the frame preceding the appearance of angiographic dye in the aorta if clearly visualized or else the frame nearest to 0.04 sec after the R wave on the ECG; Leighton et al. determined the onset of ejection from the volume-time curve with a computer method and two observers. Our study analyzed many time points, however. Thus, if there is a time in early systole at which LV function is depressed, we would have observed it. Furthermore, the partial EF was more accurately determined in our study. We interpolated from LV volume curves derived from frame-by-frame measurements, rather than merely using the volume from the angiographic frame closest to the desired time. We were also careful to exclude factors that might affect wall motion or timing such as ventricular conduction defects and a history of prior thoracotomy.

Factors that were not excluded, history of hypertension and of medication with propranolol, were analyzed separately. The partial EF in normal subjects who were and were not taking propranolol, or who were normotensive or hypertensive, were very similar. Furthermore, when patients with CAD were grouped according to these factors, the partial EF demonstrated the same pattern of abnormality as that seen in other subgroups; that is, patients with a normal holosystolic EF had a normal partial EF throughout systole. In patients with a low holosystolic EF, the abnormality in partial EF worsened with time through systole and was most severe at end-systole. Our results are consistent with other reports in that oral propranolol in dosages usually used clinically causes no significant change in global function or regional wall motion in patients at rest.

Thus propranolol administration or hypertension in our subjects was not the basis for the difference between our results and those previously reported.
A third possibility is that there may be a subpopulation of patients in whom early systolic hypokinesis predominates. Only one of our 68 patients had a more subnormal EF at 1/3 systole than later in systole, however. When the partial EF was calculated in several subgroups of patients with CAD, function was consistently most abnormal at end-systole.

In addition to reports of early systolic depression in global left ventricular function, there have been reports of early systolic depression of regional function in underperfused regions of the left ventricle. However, even if an early systolic regional abnormality existed, there are several factors why global EF would still not reach peak abnormality until end-systole. First, regional hyperkinesis in the nonischemic region may compensate, resulting in normal global function. Indeed, we found that the global EF measured at end-systole reflected the combined abnormalities of both the anterior and inferior walls of the left ventricle and thus correlated poorly with the motion measured only in the more abnormal of the two regions. Second, the severity of hypokinesis or the size of the region with depressed function may be inadequate to significantly reduce global function. For these reasons, regional abnormalities in the timing of contraction may not be reflected by measurements of global function.

In summary, our study of volume, volume increment, and partial EF at each twelfth of systole indicates that the holosystolic EF is the most sensitive indicator of global LV dysfunction in patients with CAD. Since the EF measures global function, however, it is less sensitive to localized abnormality than measurement of regional wall motion in the area of interest, because hyperkinesis or hypokinesis in other regions of the left ventricle may cause the EF to underestimate or overestimate the severity of abnormality in the area of interest.

We appreciate the assistance of Suzanne Mitten.

References
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*Circulation*. 1983;68:756-762
doi: 10.1161/01.CIR.68.4.756

*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

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