The Interval Ejection Fraction: A Cineangiographic and Radionuclide Study

ANDREW J. KEMPER, M.D., JESUS A. BIANCO, M.D., ROBERT M. SHULMAN, M.D.,
EDWARD D. FOLLAND, M.D., ALFRED F. PARISI, M.D., AND DONALD E. TOW, M.D.

SUMMARY To evaluate the clinical usefulness of the first-third ejection fraction (1/3 EF) for detecting patients with coronary artery disease (CAD), resting contrast ventriculography and first-pass radionuclide angiography with a high-count-rate, multicrystal camera system were performed in 47 subjects: 22 normal controls (group 1) and 25 patients with clinically stable angina pectoris and severe CAD (mean 2.3 vessels) without (group 2, n = 12) and with (group 3, n = 13) resting wall motion abnormalities. By contrast angiography, only group 3 had depressed global EF or 1/3 EF compared with control (global EF: group 1, 0.71 \pm 0.09; group 2, 0.67 \pm 0.09 [NS]; group 3, 0.49 \pm 0.05 [p < 0.01 vs groups 1 and 2]; 1/3 EF: group 1, 0.29 \pm 0.06; group 2, 0.28 \pm 0.05 [NS]; group 3, 0.22 \pm 0.05 [p < 0.01 vs groups 1 and 2]). Whereas 11 of 25 CAD patients had global EF outside the normal range, only two of 25 had depressed 1/3 EF. Both had left ventricular asynergy and a depressed global EF. Studies performed using first-pass radionuclide angiography revealed similar results, i.e., only four of 25 CAD patients, all with left ventricular asynergy and depressed global EF, had depressed 1/3 EF values.

A wide range of 1/3 EF values was found in normal subjects by both techniques. Thus, the ejection fraction during the first third of systole at rest is of limited value for detecting patients with CAD.

LEFT VENTRICULAR ejection fraction (EF) is usually normal in patients without prior myocardial infarction even in the presence of severe coronary artery disease (CAD). The early phases of left ventricular ejection have been investigated in hopes of detecting left ventricular dysfunction as a clue to the presence of underlying CAD. However, significant controversy exists as to the presence and prevalence of an early contraction abnormality in ischemic heart disease, particularly in the absence of end-systolic wall motion abnormalities.

In an angiographic study, Hammermeister et al.\(^1\) noted no significant alteration in the configuration of the systolic ejection curve or peak ejection rate in patients with CAD, even in the presence of significant left ventricular dysfunction. Herman et al.\(^2\) found an abnormality in the sequence of regional cardiac contraction, which they termed asynchrony, in only 10 of 41 CAD patients studied angiographically.\(^3\) Most of the patients in this study had regional asynergy, as well as depressed global ventricular function.

Other studies have shown a significant alteration of the time course of ejection by ischemia. Noble et al.\(^4\) using a conscious dog model, showed that temporary coronary occlusion results in a greater depression of maximal acceleration of flow than a peak flow or stroke volume. Johnson et al.\(^5\) found a similar phenomenon in humans studied angiographically. Eight patients with isolated stenosis of the left anterior descending coronary artery and normal end-systolic function showed a depression in left ventricular ejection during the first third of systole compared with a control population. Slutsky et al.\(^6\) presented both angiographic\(^4\) and single-crystal, first-pass radionuclide data\(^7\) suggesting that this phenomenon is a generalized disorder of contraction that is detectable in most patients with coronary stenosis even in the absence of end-systolic wall motion abnormality. This abnormality, they postulate, may be a sensitive marker for the presence of ischemic heart disease.

The clinical utility of the determination of global first-third EF (1/3 EF) has not been confirmed. Neither Hoshino et al.\(^8\) nor Jones et al.\(^8\) separated CAD patients from normal subjects using the angiographic early systolic ejection fraction. In addition, Sonnemaker et al.\(^9\) failed to detect this abnormality when a scintillation probe with high temporal resolution was used to monitor the first transit of a radiotracer. The present investigation was designed to further evaluate the value of global interval EF in detecting CAD. CAD patients with and without wall motion abnormalities were studied using both contrast angiography and a high-count-rate, multicrystal-camera, first-pass radionuclide technique.

Methods

Patient Population

The study sample involved 47 subjects. The radionuclide control group (group 1A) consisted of 14 subjects, mean age 42 years (range 24–56 years). There were 10 volunteers (seven males and three females) and four male subjects with no angiographic abnormalities. The volunteers had no history of cardiac disease, diabetes mellitus, hypertension, hyperlipidemia or smoking. All had normal physical examination, ECG and chest x-ray. Each had normal ventricular function at rest as evidenced by normal radionuclide EF and regional left ventricular wall motion.

The contrast angiographic control group (group 1B) consisted of 12 male patients, mean age 46 years (range 34–58 years), who underwent catheterization to rule out CAD. All patients had normal left ventricular function (EF > 0.55), normal regional systolic wall motion as judged by three observers, a left ventricular
end-diastolic pressure less than 10 mm Hg, and no evidence of narrowing > 25% of a major coronary artery or its branches.

The patients consisted of 25 consecutive males who underwent catheterization for the evaluation of stable angina pectoris and had both contrast angiographic and radionuclide studies technically adequate for examination. All had angiographically documented CAD, defined as greater than 70% luminal narrowing of one or more of the major coronary arteries or its branches.

Group 2 consisted of 12 patients, mean age 58 years (range 38–70 years), who had normal regional ventricular contraction as defined by the area contraction method. Group 3 consisted of 13 males, mean age 54 years (range 40–64 years), who had angiographically demonstrable left ventricular asynergy. There was no significant difference in the number of vessels with 70% stenosis in groups 2 and 3 (2.2 ± 0.8 vs 2.3 ± 0.8).

Quantitative Ventriculography

Ventriculography was performed using a 9-inch cineangiographic single-plane system at 50 frames/sec in a 30° right anterior oblique view after injection of 40–50 ml of Renografin-76 over 3 seconds. To determine the presence of asynergy, ventriculograms were traced with the largest area related to aortic valve opening and the smallest related to closing, designated as end-diastole and end-systole, respectively. Premature and first postextrasystolic beats were excluded. Ventriculograms were analyzed using an Electronics for Medicine CLC cardiac computer with model VVF automated ventriculography feature, which was programmed to quantify the percent area reduction in systole using a method reported from this laboratory. Briefly, the ventricle was divided according to a modified Herman-Gorlin axis system, which included anterobasal, anterolateral, apical, diaphragmatic and posterobasal left ventricular regions. Patients were defined as having asynergy when contraction of an area was more than 2 standard deviations below the normal reference value previously determined in 10 subjects without angiographic CAD.

Ventricular ejection during the first third of systole was determined angiographically using the method of Johnson et al. and Slutsky et al. For each contraction, end-diastole was defined as the frame occurring immediately before the appearance of contrast material above the aortic valve and end-systole as the frame showing minimal planimetered area. Frames from end-diastole to end-systole were counted and divided by 3. Any inequality in number of frames was assigned to the final third of systole. Ventricular silhouettes traced at end-diastole, the frame corresponding to the end of 1/3 EF, and end-systole were planimetered and ventricular volumes determined according to the method of Sandler and Dodge. EF was calculated as (end-diastolic volume — end-systolic volume)/end-diastolic volume. One-third EF was calculated as (end-diastolic volume — volume at end 1/3 systole)/end-diastolic volume. First and second postextrasystolic beats were not analyzed. All beats analyzed occurred before the fourth beat after the injection of contrast. Angiographic and radionuclide studies were performed within 1 month on all patients. No patient had an intervening change in clinical status.

Radionuclide Ventriculography

Left ventricular function was evaluated by the first-pass technique using a multicrystal scintillation camera computer system (Baird Atomic System 77) that has been described in detail elsewhere. Briefly, with the camera positioned in the modified left anterior oblique projection, counts emanating from the first transit of a 20-mCi bolus of technetium-99m were collected at 25-msec intervals in frame mode and stored on computer disc. After temporal smoothing, studies were played back and a preliminary left ventricular region of interest was determined by the operator during the levophase of bolus transit. End-diastolic and end-systolic frames for each beat were selected by computer on the basis of maximal and minimal counts in the region of interest. Sequential background frames equal to the number of selected cardiac cycles were identified from the time-activity curve in the region of interest just before the inflection of the left ventricular phase. After repeated iterations, a final region of interest was determined by computer. EF was defined as (end-diastolic counts — end-systolic counts)/(end-diastolic counts — background). After calculation of the left ventricular EF, a representative cardiac cycle was constructed by synchronously summing successive background-corrected frames from end-diastole to end-diastole in all previously selected beats with the additional constraint that the emptying and filling times of the selected beats be at least half that of the longest selected beat. Representative cycles generally consisted of four to eight superimposed beats with an average of 4600 counts in the background-corrected summed end-diastolic frame decreasing to an average of 2200 counts in the summed end-systolic frame. All data were calculated from the derived background-corrected representative cycles framed at 25-msec time intervals.

The 1/3 EF was defined as (end-diastolic counts — counts in 1/3 systolic frame)/(end-diastolic counts — background) (fig. 1). When the number of frames was not divisible by three, a linear interpolation was made between counts in the two adjacent frames to obtain counts at the end of one-third systole.

Global and interval EF studies repeated in seven of the normal volunteers at 1 week were reproducible. The mean variability was 0.03 ± 0.03 for global EF and 0.03 ± 0.01 for 1/3 EF.

Statistical Analysis

All data are expressed as mean ± SD. The three groups were compared by unpaired t test. The clinical value of global and interval data in identifying patients with CAD was assessed as suggested by Glantz, with values up to 2 standard deviations below the mean of the control population defined as normal.
FIGURE 1. Determination of one-third ejection fraction and global ejection fraction by radionuclide ventriculography from a representative (REP) cycle. LV ROI = left ventricular region of interest; LVTAC = LV time-activity curve.

Results

Angiographic Data

Global left ventricular EF was not significantly different between the control group and the CAD patients without left ventricular asynergy (group I A, 0.71 ± 0.09 vs group II, 0.67 ± 0.09, NS). The patients with asynergy had a significantly depressed global EF compared with the other two groups (group III, 0.49 ± 0.05, p < 0.01 vs groups I and II). Nine of 13 patients with left ventricular asynergy had abnormal global EF, whereas none of the patients without left ventricular asynergy had an abnormal global EF (fig. 2A).

The 1/3 EF values were similar for the control group and the patients with CAD and no asynergy (group I A, 0.29 ± 0.06 vs group II, 0.28 ± 0.05, NS). Both values were significantly higher than values in patients with left ventricular asynergy (group III, 0.22 ± 0.05, p < 0.01 vs groups I and II). Only four patients, all of whom had left ventricular asynergy, had 1/3 EF values outside the normal range. These patients had a depressed global EF (fig. 2B).

Radionuclide Studies

The correlation between angiographic global EF and radionuclide-derived global EF found in multiple series performed in this laboratory over the last 5 years ranges from 0.78-0.90. The correlation for all patients who underwent both studies in this series was 0.88 (EF by catheterization = 1.16 EF by radionuclide ventriculography + 3.68).

Values for left ventricular EF in the control group and the group without left ventricular asynergy were similar (group I, 0.54 ± 0.05 vs group II, 0.53 ± 0.05, NS). The patients with CAD and left ventricular asynergy had a depressed left ventricular EF (group III, 0.40 ± 0.07, p < 0.01 vs groups I and II). Ten of 13 patients with left ventricular asynergy had abnormal global EF values, whereas no patient with normal left ventricular wall motion had a depressed global EF (fig. 3A). The 1/3 EF values in the control subjects were slightly higher than those in the CAD patients without asynergy (group I, 0.16 ± 0.04 vs group II, 0.14 ± 0.03, p = 0.05). Values in the patients with asynergy were significantly depressed compared with the other two groups (group III, 0.11 ± 0.03, p < 0.01 vs group I, p < 0.05 vs group II). Despite the statistical differences between these populations, only four patients, all of whom had asynergy, had 1/3 EF values outside the normal range (fig. 3B). All of these patients also had depressed global EF.

Discussion

This study was designed to investigate the usefulness of interval subdivision of left ventricular EF for detecting patients with CAD. Significant differences in global EF and in 1/3 EF determined angiographically emerged between patients with and without asynergy. Dividing systole into intervals did not improve the detection of patients with CAD. Similar results were found in the same patient sub-
A depressed global groups if only 1/3 EF were used to detect CAD, a significant proportion of the patients with asynergy would not have been detected.

The data in this investigation are consistent with the angiographic data of Hoshino et al. and with the data obtained by Sonnemaker et al. using a nuclear probe first-pass technique. The differences between our results and those found by Johnson et al. and Slutsky et al. might be explained by differences in technique or in the populations studied.

For the angiographic portion of the study, we used the methods used by Johnson et al. and Slutsky et al. to identify the onset and end of systole and to divide systole into thirds.

The multicrystal camera system used for our radionuclide studies allowed more rapid framing (25 vs 40 msec) and higher count rates per frame in the raw data (mean left ventricular counts/end-diastolic frame approximately 1000 vs 75-100) than the single-crystal camera system used by Slutsky et al. We have found that use of the right anterior oblique projection, which was used by Slutsky et al., contaminates the prelevophase background determination because of counts emanating from the right ventricle in approximately 20% of studies (unpublished data). Therefore, we used a modified left anterior oblique projection with 30° cranial angulation. The close proximity of left ventricle to the camera in this position, the spatial resolution possible using a multicrystal camera with repeated iterations to determine region of interest, and atrioventricular separation achieved with cranial angulation probably allow more accurate definition of the left ventricular blood pool than the single-crystal, first-pass method.

The most impressive difference is in values for the normal population determined angiographically by different investigators. Hammermeister et al. found that the configuration of systolic ejection was tively unaltered from normal in patients with CAD. In addition, the peak ejection rate and peak ejection rate normalized for end-diastolic volume were not significantly different between the control and CAD groups, even though many of the CAD patients had a decreased EF. These data suggest that the percentage of stroke volume ejected early in systole should be the same for groups with and without CAD. The angiographic data reported by Jones et al., Hoshino et al., Slutsky et al., Johnson et al. and the data from the present investigation are presented in table 1, with all data expressed in terms of percentage of stroke volume ejected during the first third of systole by dividing 1/3 EF by total EF for each group.

\[
\frac{1/3 \text{ EF}}{\text{EF}} = \left( \frac{\text{SV at 1/3 systole}}{\text{EDV}} \right) / \frac{\text{SV}}{\text{EDV}} = \frac{\text{SV at 1/3 systole}}{\text{SV}} = \% \text{SV at 1/3 systole}
\]

where SV = stroke volume and EDV = end-diastolic volume.

The fraction of stroke volume ejected at one-third of systole reported in the control population is remarkably similar for Jones et al., Hoshino et al., Johnson et al. and in the present study (40-44%).

**TABLE 1. Reported Values for Stroke Volume at One-third Systole**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CAD</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al.</td>
<td>0.44</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Hoshino et al.</td>
<td>0.40</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Jones et al.</td>
<td>0.43</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>0.41</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Slutsky et al.</td>
<td>0.51</td>
<td></td>
<td>0.31*</td>
</tr>
</tbody>
</table>

*Contains patients from both groups.

Angiographic values reported for percent stroke volume ejected at one-third systole. Percent stroke volume at one-third systole = (1/3 EF)/EF.

Abbreviations: CAD = coronary patients with normal end-systolic wall motion; MI = coronary patients with depressed resting ejection fraction or wall motion abnormalities.
while the value found by Slutsky et al. is significantly higher (51%). In addition, whereas the percentage of stroke volume ejected during the first third of systole is remarkably similar for controls and coronary patients with or without asynergy in the study reported by Jones et al. and in the present investigation, the value reported by Slutsky et al. is lower for CAD patients than for controls. The data from the present study and those of Jones et al. are consistent with data reported by Hammermeister et al., whereas those of Slutsky et al. are divergent. Thus, the population reported by Slutsky et al. appears to differ from the others studied and may be less representative of the range of ventricular function found in a broader normal population.

Our angiographic control population consisted of patients without evidence of CAD or left ventricular dysfunction by accepted methods of determination. Our radionuclide control population consisted of healthy volunteers, mean age 42 years, who had no risk factors for CAD and were normal by standard clinical tests. The likelihood of CAD in this radionuclide control population as determined by Diamond and Forrester is less than 2%. Even if 25% had CAD, the results would not be appreciably changed.

The concept of a relative depression of early systolic ejection in CAD rests in large part on the studies of Noble et al., who found a disproportional decrease in the maximal acceleration of ejection during acute coronary ligation in a conscious dog model. Within a few heart beats after coronary ligation in the dog, regional paradoxical bulging appears in areas supplied by occluded vessels. A few weeks after infarction, this paradoxical bulging is replaced by akinesis. In man, areas that showed systolic paradox during the acute phase of infarction did not show this phenomenon in most patients after recovery. Our patient population had chronic angina pectoris and severe CAD. No patient had recently suffered myocardial infarction or was clinically unstable when the studies were performed. The global contraction abnormality described by Noble et al. might be more easily demonstrable during ongoing ischemia, either during acute infarction or induced by exercise. The regional analysis of left ventricular contraction in patients with CAD might also show localized areas of tardokinesis that are obscured when ventricular contraction is looked at as a whole. Early reports suggest that such an approach may prove fruitful.

In conclusion, although depressed global left ventricular ejection during early systole may be present in some patients with CAD, the subtlety of this abnormality in many patients as well as the wide variation in normal left ventricular function limits the value of the resting determination of 1/3 EF in detecting patients with CAD.

Acknowledgment

The authors thank Margaret Brew and Joseph O'Boyle for technical support, Sandra Spinks and Penny Pounder for illustrations, and Donna O'Neil for secretarial assistance.

References

Angiographic Findings 1 Month After Myocardial Infarction: A Prospective Study of 259 Survivors

AMADEO BETRIU, M.D., ANGEL CASTAÑER, M.D., GINES A. SANZ, M.D., J. CARLOS PARE, M.D., EULALIA ROIG, M.D., SANTIAGO COLL, M.D., JORGE MAGRINA, M.D., AND FRANCISCO NAVARRO-LOPEZ, M.D.

SUMMARY  Coronary anatomy as it relates to left ventricular function was assessed prospectively in patients who survived acute myocardial infarction. The study population included 259 consecutive male patients age 60 years or younger who underwent catheterization 30 days after the acute event. Coronary artery obstructive lesions (> 50% reduction in luminal diameter) were found in 241 patients (93%), 118 (45%) of whom had total and 76 (29%) subtotal (> 90%) stenosis) occlusion of at least one coronary artery. Normal coronary vessels were seen in eight patients (3%) and nonobstructive lesions in 10 (4%). One-, two- and three-vessel disease were present in 89, 86 and 66 patients, respectively. Patients with normal coronary arteries or nonobstructive lesions had higher ejection fractions than those with obstructive lesions in one, two or three vessels (p < 0.05). Ejection fraction was lower (p < 0.001) and the percentage of akinetic segments higher (p < 0.001) in patients with total or subtotal lesions and no collaterals. Adequate collaterals, seen in 29 patients (11%), significantly improved regional wall motion (p < 0.05) and decreased the percentage of akinetic segments (p < 0.001). Thus, in a substantial number of patients (32% in our series), the infarcted area is spontaneously reperfused by collaterals or through the involved artery. Both mechanisms ameliorate wall motion in corresponding areas.

CORONARY ARTERIOGRAPHY is not routinely performed after myocardial infarction. Most series, being retrospective, deal with selected patients catheterized at variable time intervals after the acute event. As a result, information from such studies may not represent the overall spectrum of lesions associated with myocardial infarction.

Prospective studies are scarce, and because they exclude a significant number of potential candidates (30–70%), their results might be subjected to bias. In 1975, we designed a prospective protocol that includes cardiac catheterization within 1 month after infarction. Our study entered 91% of all male patients age 60 years or younger who survived myocardial infarction. The results from the first 259 patients form the basis of the present report. The purposes of our investigation were to determine the prevalence of coronary artery lesions of different degrees, to analyze left ventricular function as it relates to the extent and severity of coronary artery lesions, and to assess the influence of collaterals on regional wall motion.

Methods

Patients

From January 1975 to March 1979, 300 male patients age 60 years or younger were admitted to the coronary care unit at the Hospital Clinico, University of Barcelona, with a definite myocardial infarction. There were 284 survivors, 25 of whom were excluded because they either refused cardiac catheterization (21 patients) or had life-threatening conditions (cancer in two patients and severe cor pulmonale in two others). The remaining 259 patients entered the study. At the time of this study, neither heparin nor lidocaine was routinely used.

Criteria for Myocardial Infarction

Acute myocardial infarction was diagnosed when at least two of the following were present: ischemic chest pain lasting more than 20 minutes, typical rise and fall of enzymes, and evolving Q-wave abnormalities with acute ST-segment and T-wave changes on the ECG. Previous infarction was diagnosed by a history of a hospital admission for documented myocardial infar-
The interval ejection fraction: a cineangiographic and radionuclide study.
A J Kemper, J A Bianco, R M Shulman, E D Folland, A F Parisi and D E Tow

_Circulation_. 1982;65:1094-1099
doi: 10.1161/01.CIR.65.6.1094

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 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/65/6/1094

**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 Permissios 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/