Relation between Contractile Reserve and Prognosis in Patients with Coronary Artery Disease and a Depressed Ejection Fraction

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SUMMARY
Postextrasystolic potentiation (PESP) and L-epinephrine infusion have previously been shown by the ventriculographic technique to augment left ventricular wall motion in patients with coronary artery disease. The present study relates the magnitude of this augmentation to short-term prognosis in 56 patients with coronary artery disease and a factor already identified with reduced life expectancy, i.e., an abnormal ejection fraction (EF < .50). Forty-two patients received PESP and 14 L-epinephrine infusion. Based on severity of symptoms and technical suitability, 37 were treated surgically and 19 medically. Mean follow-up times were 11.7 and 14.3 months, respectively. The mean increase in EF induced by PESP or L-epinephrine infusion was significantly greater in patients who subsequently had good results from either surgical or medical therapy than in those who died or had progressive cardiac deterioration. In addition, those patients with an increase in EF of 10 or greater had a statistically greater chance of doing well than patients with less augmentation. Evaluation of change in ejection fraction after inotropic stimulation in patients with depressed ejection fractions is helpful in identifying those patients with greatest contractile reserve and hence better short-term prognosis with either medical or surgical therapy. Because of its ease of performance and greater enhancement of contractility, PESP is preferred to L-epinephrine infusion as the inotropic stimulus of choice.

Additional Indexing Words:
Coronary artery surgery
Inotropic stimulation
L-epinephrine
Postextrasystolic potentiation

Two types of inotropic stimuli — postextrasystolic potentiation and L-epinephrine infusion — have previously been shown in our laboratory to augment left ventricular wall motion during cine-left ventriculography.1, 2 The degree of augmentation, as evidenced by change in ejection fraction and axis shortening, varies in normal controls as well as in patients with coronary artery disease. The purpose of the present study is to determine whether or not short-term prognosis in coronary artery disease can be related to the degree of improvement in overall ventricular function induced by the intervention. The ejection fraction was selected as the single most useful measurement to be studied. Patients with coronary artery disease and normal ejection fractions have been shown to have a good short-term prognosis, whether treated medically3, 4 or surgically.5, 6 In contrast, patients exhibiting a depressed ejection fraction have a reduced life expectancy,3, 5 and the present study will concern only this group in its analysis.

Methods
Patient Selection
The present series consists of 56 patients who were studied at the Peter Bent Brigham Hospital from 1971–1974. There were 49 men and seven women; average age was 47 years. Selection criteria included 1) angiographic evidence of obstructive coronary artery disease (in at least one major vessel system), 2) a ventriculographic ejection fraction less than 0.50, and 3) the use of inotropic stimulation during ventriculography as described in the subsequent section. These patients do not represent a truly consecutive series; instead each patient served as his own control for the measurements to be described.

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Catheterization Studies

Coronary arteriography was performed by either the Sones or Judkins technique. Seventy-five percent or greater stenosis of the vessel lumen was considered to be significant obstruction.

Left ventricular end-diastolic pressure was measured at high gain using fluid-filled catheters. Cardiac output was determined by the green dye indicator dilution technique.

Left ventriculography was performed with multi-holed angiographic catheters using power injections of 35 to 50 ml of 76% meglumine sodium diatrizoate over a 3-4 sec period. Systolic ejection fraction was calculated from the equation

\[ \text{Ejection fraction} = \frac{\text{End-diastolic volume minus end-systolic volume}}{\text{End-diastolic volume}} \]

with the appropriate volumes determined from sequential end-diastolic and end-systolic silhouettes of the left ventricle in either a single-plane (30 degrees right anterior oblique) projection or a biplane (30 degrees right anterior oblique and 60 degrees left anterior oblique) projection using a grid-calibration system and area-length formulae for a prolate ellipsoid as reported previously.\(^7\) The aortic valve and apex were used as reference points; no attempt was made to correct for downward displacement of the base or rotation of the heart nor was a regression equation used to correct to "true" volumes. The ejection fraction in normal subjects is 0.66 ± 0.15 (mean ± 2 SD) in our laboratory,\(^8\) using either single-plane or biplane techniques. Values less than 0.50 (more than 2 SD from the norm) are considered abnormal; this value is close to that cited as abnormal by the American Heart Association (0.45).\(^8\)

Propranolol had been discontinued 24-48 hr prior to catheterization to avoid effects of the drug on hemodynamic and ventriculographic measurements.

After informed consent, inotropic stimulation took one of two forms, either infusion of l-epinephrine or postextrasystolic potentiation (PESP). The techniques and protocols involved in both methods have been previously described in detail.\(^1\) Briefly, the epinephrine ventriculogram was performed in 14 subjects approximately 30 min after the control ventriculogram, and 9 min after a 1-4 μg/min infusion of l-epinephrine had begun. Ejection fraction in the epinephrine ventriculogram was compared to that of the same numbered beat in the control ventriculogram. PESP was employed in 42 subjects. Ejection fraction in the sinus beat preceding the ventricular premature contraction was compared to ejection fraction in the potentiated beat following it. In most patients the ventricular premature contraction was elicited using a bipolar pacing catheter positioned in the right ventricle and attached to an R-wave coupled stimulator (developed by B. Berkovits of the American Optical Company). This technique enables the investigator to introduce a single extrasystole at a known, safe interval from the preceding R wave during the first three beats after complete opacification of the ventricle, before there are significant hemodynamic changes due to the angiographic contrast medium.\(^9\) In this series, the R-to-stimulus interval averaged 400 msec with a range of 320 to 640 msec as measured by simultaneous ECG recordings, and the average current was 2.4 mA. Neither repetitive extrasystoles nor more serious arrhythmias were observed. There are two other methods for introducing ventricular premature contractions when this device is not available: 1) by pulling a catheter back through the right ventricle into the right atrium, and 2) as a result of the power injection of angiographic contrast medium into the left ventricle. Neither method is as reliable as the previously described technique because of the unpredictability of the number of extrasystoles and their R-to-R intervals. In the present study, extrasystoles induced by the alternate techniques were evaluated only if they 1) were single and occurred within the first three beats after complete opacification of the ventricle, and 2) occurred within approximately the same R-R interval (310-480 msec) obtained with the R-wave coupled stimulator. Twelve such cases were included in the total of 42 in the present study; in analyzing changes due to PESP we found no consistent pattern attributable to any one method of introducing extrasystoles.

Follow-up Data

All surgical patients had frequent out-patient hospital visits following discharge. However, patients not referred for surgery were usually returned to the care of their primary physician and had less frequent out-patient hospital visits. In these patients, medical regimens varied and chest X-rays could not always be obtained. For these reasons, different end points were employed in following the medical and surgical groups cited earlier\(^4,5\) and have been continued in the present study. Thus (as described below), although death was the end point in the medical group, death or continuing or progressive cardiac decompensation were end points in the surgical group. Operative and peri-operative mortality were defined as death at or during the first 30 days after surgery.

Surgical Group (37 Patients)

Thirty-five patients with severe angina underwent direct myocardial revascularization procedures. Seventeen of these 35 patients also had severe failure symptoms and six underwent aneurysmectomy. Two other patients with severe failure but without angina underwent only aneurysmectomy. (Since this was largely a retrospective study, the information obtained from it did not influence the surgical decision to revascularize or resect a given segment of ventricular wall.) The interval between catheterization and surgery averaged 33 days in this series and no new myocardial infarctions occurred during that period. Following discharge, patients were seen regularly in office visits. In addition to noting angina episodes (if any), patients were also classified according to the presence of symptoms of congestive failure using the same modification of the NYHA functional criteria employed previously.\(^9\) Furthermore, chest X-rays were obtained in all patients and postoperative heart size compared to the preoperative findings. Increase in the cardiothoracic ratio of more than 10% was taken as evidence of increasing heart size. Functional classification and evaluation of radiographic heart size were done without prior knowledge of the effect of inotropic stimulation on the ejection fraction. (One patient sustained a nonfatal myocardial infarction after discharge and had his follow-up period terminated as of the date of that episode, since such an event itself may result in heart failure.)

Medical Group (19 Patients)

One of the 19 patients followed medically refused surgery. Nine others had severe symptoms of angina and/or
congestive failure but were not considered good operable risks — not only because of their depressed ejection fractions but because of severely diseased distal coronary vasculature and/or areas of asynergy either too large or ill-defined to permit resection. The remaining nine patients were considered technically operable but their symptoms of angina and/or failure were not considered severe enough to warrant the higher-than-normal risk associated with their degree of ventricular dysfunction. Patients and/or their primary physicians were queried relative to their clinical status, and follow-up chest X-rays were requested.

Results

Surgical Group (37 Patients)

Mean follow-up time was 11.7 months (range 1–36 months).

Twenty-five patients (68%) did well, i.e., they survived the surgery and were free of class III-IV failure symptoms, including 12 patients with severe failure preoperatively. None of the 25 had a postoperative increase in heart size on X-ray. Twenty-three of the 25 had severe angina preoperatively and only two of the 23 reported no improvement in angina postoperatively.

Twelve patients (32%) did not do well. Seven (19%) died at or soon after surgery, including three with severe failure preoperatively. Most of the patients died in a low output state despite vigorous therapeutic measures including intra-aortic balloon counterpulsation. Five other patients (13%) were in class III-IV failure despite administration of digitalis and diuretics, including two with severe failure preoperatively. All had increases in heart size on X-ray. All five had severe angina preoperatively but only one of the five continued to have severe angina postoperatively.

The 25 patients who did well had a mean increase in ejection fraction following inotropic stimulation of .13 ± .03 compared to .06 ± .02 for the 12 patients who did poorly (P < .05) (fig. 1A). As listed in table 1, we analyzed various characteristics of the two groups that could have been responsible for this difference and found no significant difference in mean ejection fraction in the sinus beat, LVEDP or cardiac index. There was also no difference between the two groups in number of patients with sinus beat ejection fractions < .30, preoperative class III or IV failure, or multivessel coronary disease. Other possible sources of bias were also excluded: mean ages were similar in both groups as were the number of bypasses employed and incidence of peri-operative infarction. PESP rather than epinephrine infusion was used in 67% of both groups, biplane rather than single plane ventriculographic studies were performed in 56% of the patients doing well and 50% of those doing poorly, and aneurysmectomy was performed in five of 25 patients doing well compared to three of 12 patients doing poorly. Aneurysmectomy per se did not appear to affect prognosis since five of the eight patients un-

| Table 1 |

Factors Influencing Prognosis in Medically and Surgically Treated Patients with Coronary Artery Disease and Depressed Ejection Fractions

<table>
<thead>
<tr>
<th>A. Surgical group (N = 37)</th>
<th>Postoperative NYHA I-II (N = 25)</th>
<th>Postoperative NYHA III-IV &amp; operative mortality (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>.30 ± .03 NS</td>
<td>.33 ± .04</td>
</tr>
<tr>
<td>ΔEF with inotropic stimulation</td>
<td>.13 ± .02 P &lt; .05</td>
<td>.06 ± .02</td>
</tr>
<tr>
<td>LVEDP (mm/Hg)</td>
<td>18 ± 2.5 NS</td>
<td>20.1 ± 3.4</td>
</tr>
<tr>
<td>Cardiac index (1/min/m²)</td>
<td>2.2 ± 0.4 NS</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>No. of pts with EF &lt; .30</td>
<td>13 (52%) NS</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>NYHA III-IV pre-operatively</td>
<td>12 (48%) NS</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>21 (84%) NS</td>
<td>11 (93%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Medical group (N = 19)</th>
<th>Alive (N = 13)</th>
<th>Dead (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>.29 ± .03 P &lt; .01</td>
<td>.23 ± .03</td>
</tr>
<tr>
<td>ΔEF with inotropic stimulation</td>
<td>.12 ± .02 P &lt; .05</td>
<td>.05 ± .02</td>
</tr>
<tr>
<td>LVEDP (mm/Hg)</td>
<td>17.3 ± 2.4 P &lt; .05</td>
<td>23.1 ± 3.0</td>
</tr>
<tr>
<td>Cardiac index (1/min/m²)</td>
<td>2.2 ± .3 P &lt; .05</td>
<td>1.9 ± .2</td>
</tr>
<tr>
<td>No. of pts with EF &lt; .30</td>
<td>6 (46%) P &lt; .05</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>NYHA III-IV pre-operatively</td>
<td>4 (30%) NS</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>10 (77%) NS</td>
<td>5 (80%)</td>
</tr>
</tbody>
</table>

Abbreviations: EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure; CAD = coronary artery disease; NYHA = New York Heart Association functional classification modified for failure symptoms.
CONTRACTILE RESERVE AND PROGNOSIS IN CAD

Figure 1

Changes in ejection fraction following inotropic stimulation with either postextrasystolic potentiation (PESP) or l-epinephrine infusion (EPI) in 37 patients receiving surgical therapy (A) and 19 patients receiving medical therapy (B) for coronary artery disease. In both groups inotropic stimulation resulted in a significant increase in ejection fraction, but patients doing well had a greater change in ejection fraction than those doing poorly. NYHA = modified New York Heart Association functional criteria.

dergoing this procedure did well postoperatively, including both patients who did not undergo concomitant revascularization procedures.

Although patients doing well had a greater change in ejection fraction than those doing poorly there was considerable scatter (fig. 2A). However, using the statistical midpoint of the two group means (.095) as a convenient point of separation, we found that 18 of 25 patients doing well had an ejection fraction increase $\geq .10$ compared to two of 12 patients not doing well ($P < .001$). Thus, of the 20 patients with an increase in ejection fraction $\geq .10$, two died (10%); of the 17 patients with a change in ejection fraction $< .10$, five died (29%) and five had persistent failure symptoms (29%) (fig. 2B).

Medical Group (19 Patients)

The mean follow-up time was 14.3 months (range 5–35 months). Thirteen of the 19 (68%) were alive and reported their clinical status unchanged (nine were still in modified NYHA failure classes I-II and four were in classes III-IV). Nine of the 13 had follow-up X-rays: none had increases in heart size. Three of the 13 still complained of severe angina.

Six of the 19 (32%) were dead at the end of this period; all six died in a low output state, although one death was associated with an acute myocardial infarc-

tion. The mean increase in ejection fraction after inotropic stimulation was $12 \pm .02$ in the survivors, compared to $.05 \pm .02$ in those who died ($P < .05$) (fig. 1B). Unlike the surgical group, however, medically treated patients who survived had statistically significantly better left ventricular function initially (higher ejection fraction and cardiac index, and lower LVEDP) than those who died (table 1). The prevalence of severe failure symptoms and multivessel disease was similar in both survivors and nonsurvivors as was the frequency of biplane studies (67%), but PESP was used in 46% of the survivors compared to 100% of those dying.

Although surviving patients had a greater average increase in ejection fraction than those dying there was again considerable scatter in the two subgroups (fig. 3A). The midpoint of the mean values for change in ejection fraction was .085. Since this was similar to the midpoint in the surgical group (.095) we continued to use the value of .10 (rather than .09) as a convenient point of separation for the two subgroups. Eight of the 13 patients doing well had an increase in ejection fraction greater than .10 compared to none of the six patients who died ($P < .001$). Thus, all eight patients with increases in ejection fraction $\geq .10$ did well compared to five of 11 with increases $< .10$ ($P < .05$) (fig. 3B).
Figure 2

A) Comparison of the changes in ejection fraction with either postextrasystolic potentiation (PESP) or l-epinephrine infusion (EPI) in patients doing well or poorly after cardiac surgery. The mean values for the two groups are significantly different. The broken line represents the statistical midpoint of the two group means. B) Using the approximate midpoint of the means (10) as a convenient line of separation, we observed that 90% of the patients with increase in ejection fraction (EF) of .10 or greater did well after surgery. NYHA = modified New York Heart Association functional criteria.

Figure 3

Similar format as in figure 2 but considering only medically treated patients. Note again the statistically significant difference between the two groups in panel A, and the finding in panel B that all of the patients with increases in ejection fraction of .10 or more were alive at the end of the follow-up period.
CONTRACTILE RESERVE AND PROGNOSIS IN CAD

Discussion

Recent studies have indicated that prognosis in patients with coronary artery disease can be related to the presence or absence of impaired left ventricular function. This is true of both medically treated and surgically treated patients. Assuming the ventricle to be ellipsoidal, end-diastolic and end-systolic volumes can be determined via the area-length method and calculated ejection fraction can be used as a measurement of over-all ventricular function. Patients with normal ejection fractions generally have a much better short-term prognosis than those patients with abnormal values. In our hospital, for example, a poor result following direct myocardial revascularization and/or aneurysmectomy, i.e., operative mortality or development (or persistence) of moderate to severe heart failure in the year following surgery, was found in 40% of patients with a preoperative ejection fraction less than .50 (our lower limit of normal) compared to only 3% in patients with an ejection fraction above .50 (P < .001). Presence of severe angina postoperatively appeared to bear little relation to the preoperative ejection fraction in either the present group or our previously reported series. In regard to medical treatment 24% of patients with an ejection fraction below .50 were dead an average of one year after catheterization compared to 2% with ejection fraction greater than .50 (P < .001).

We have utilized other hemodynamic and angiographic measurements in an attempt to identify those patients with depressed ejection fractions who have a better prognosis, but with only limited success. Thus, we are still left with a large number of patients in both medically and surgically treated groups who have extensive vessel disease and multiple abnormal hemodynamic parameters. To better delineate these patients as to prognosis, we have recently employed inotropic stimulation (l-epinephrine infusion and postextrasystolic potentiation) in selected populations. Although the 56 patients with a depressed ejection fraction in the present study do not represent a truly consecutive series, the percentage of patients doing poorly after either medical or surgical therapy (32%) is similar to that noted in similar subjects in the previously cited consecutive series. Although experimentally induced myocardial ischemia in dogs, inotropic stimulation results in augmented wall motion in both normal areas and ischemic areas with potential contractile reserve. During inotropic stimulation in man, augmentation of ventricular wall motion occurs in normal areas and in hypokinetic (and presumably ischemic) areas composed of muscle, or a mixture of muscle and fibrous tissue, but not in scar. Although this augmentation has yet to be correlated with improved segmental wall motion after direct myocardial revascularization surgery, short-term (one year) prognosis does appear to be related to the magnitude of augmentation as expressed by the degree of improvement in the ejection fraction of patients with depressed values at rest. Patients with a marked increase in ejection fraction (>.10) induced by inotropic stimulation have considerable contractile reserve, i.e., much of their ventricular dysfunction can be attributed to reversible myocardial dysfunction rather than chronic scar formation. Prognosis in these patients appears to be equal to that of patients with a normal ejection fraction. Thus, the true high-risk group consists of those patients with little or no contractile reserve who augment poorly or not at all during inotropic stimulation; however, even a significant minority of these latter patients does well postoperatively.

If it appears that the difference in prognosis in patients undergoing operation is attributable to the difference in contractile reserve, as expressed by the change in ejection fraction, the same cannot be said with as much certainty in the medically treated patients since left ventricular function was significantly worse initially in the patients who subsequently died than in those still alive (table 1). It should be emphasized that the decision to operate or not in patients with depressed ejection fractions is not only a function of contractile reserve but also of severity of symptoms and technical problems. (At the present time, recommendations as to whether or not segments of ventricular wall should be revascularized or resected on the basis of PESP or epinephrine stimulation must await results of further postoperative catheterization studies.) Since eight of the nine patients not operated on because of mild symptoms did well the present series suggests that patients with milder symptoms have a good short-term medical prognosis, whether or not they have marked augmentation of wall motion with inotropic stimulation. Only four of the nine patients not operated on for technical reasons did well, suggesting also that the worst prognosis appears to be in the patients who augment poorly and have severe angina and/or failure symptoms, but have either severely diseased distal coronary vasculature or large or ill-defined aneurysms that preclude surgery.

A final word concerns choice of inotropic stimulation. We prefer PESP. In the present study, it produced a significantly larger change in ejection fraction than did l-epinephrine (.13 vs .06, P < .01). In addition, if patients receiving epinephrine are deleted from figures 2A and 3A, significant differences still remain between patients doing well and those doing poorly (fig. 2A: .15 vs .08, P < .05; fig. 3A: .16 vs .06,
This indicates that the PESP effect is the more important one. PESP is also easier to perform, requiring only a single ventriculogram.

References

Relation between contractile reserve and prognosis in patients with coronary artery disease and a depressed ejection fraction.
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