Prognostic Value of a Single Exercise Test 3 Weeks after Uncomplicated Myocardial Infarction

Dennis M. Davidson, M.D., and Robert F. DeBusk, M.D.

SUMMARY The prognostic value of exercise testing was assessed in 195 men, mean age 54 ± 8 years, 3 weeks after uncomplicated myocardial infarction. In the first 82 men, effort was terminated at a heart rate of 130 beats/min in the absence of limiting symptoms, exertional hypotension or ventricular tachycardia. In the last 113 men, heart rate was not used as an end point. No complications of exercise testing were noted. From 13 clinical and treadmill test characteristics, a stepwise multiple logistic regression program identified exercise-induced ST-segment depression (STI) ≥ 0.2 mV, angina pectoris and maximal work load < 4 multiples of resting energy expenditure (mets) as "risk factors" predictive of combined medical and surgical events (myocardial infarction, sudden death, cardiac arrest and coronary artery bypass surgery) in a subset of 92 patients followed 2 years or more. Clinical characteristics and exercise-induced ventricular ectopic activity were not predictive of such events. Life-table analysis in the entire population of 195 men confirmed the increased probability of combined medical and surgical events in patients with one or more "risk factors." For medical events alone, STI ≥ 0.2 mV and maximal work load < 4 mets were predictive, whereas angina pectoris was not. STI ≥ 0.2 mV and exercise-induced angina pectoris were predictive of surgical events. We conclude that patients without evidence of congestive heart failure 3 weeks after uncomplicated myocardial infarction can safely undergo symptom-limited exercise testing. Valuable prognostic information is gained that is independent of selected clinical characteristics.

IDENTIFICATION of patients soon after myocardial infarction who are at relatively high risk for subsequent cardiac events offers two major benefits. High-risk patients could be identified for more aggressive medical or surgical therapy to reduce their morbidity and mortality. Patients at low risk could be spared needless invasive studies and unwarranted restriction of their physical activities.

Routine clinical methods are sufficient to identify certain subgroups of patients at increased risk for subsequent cardiac events after acute myocardial infarction. A history of congestive heart failure or shock in the coronary care unit, cardiomegaly on chest x-ray, audible third heart sound (S₃) and a history of digitalis usage are all features of left ventricular dysfunction that have been associated with increased mortality during the year after myocardial infarction. In contrast, these abnormalities are absent in the majority of patients who survive myocardial infarction. Hypothetically, the risk of subsequent cardiac events in these clinically uncomplicated patients may be further stratified by treadmill exercise testing performed soon after the acute event. The present study was designed to determine whether treadmill exercise testing, performed soon after uncomplicated infarction, further defines the risk of subsequent cardiac events and, if so, which specific exercise test characteristics are most predictive of such events in this population.
Materials and Methods

Men aged 70 years or younger who were hospitalized at Stanford University Medical Center and associated hospitals for myocardial infarction during the years 1974–1978 were considered for the study. Patients with clinical or radiologic evidence of pulmonary congestion or cardiac enlargement during hospitalization and those with one or more of the following characteristics 3 weeks after hospital admission were excluded: rest or unstable angina pectoris, clinical congestive heart failure, an audible S₃ or digoxin or propranolol therapy, significant cardiac valvular disease, hypertension >180/100 mm Hg, pulmonary disease or musculoskeletal disorders limiting exercise capacity, previous coronary artery bypass graft surgery, and cardiac conditions complicating electrocardiographic interpretation, such as left bundle branch block or atrial fibrillation.

Men hospitalized at Stanford University Medical Center constituted 72% of the patients in the study population. Of 542 consecutive patients treated for myocardial infarction at our institution, 81 (15%) died in the hospital. Of the 461 survivors, 184 (40%) were excluded for medical reasons: 118 for the cardiac conditions listed above, 57 for pulmonary disease or musculoskeletal disorders limiting exercise, and nine because of digoxin or propranolol therapy. One hundred thirty-six other men (30%) whose medical characteristics were similar to those undergoing exercise testing were unavailable for the study (nonmedical exclusions): 42 for patient or physician refusal, 34 for transfer to other hospitals and 60 for residence outside the San Francisco Bay Area. The remaining 141 men (30% of survivors) joined the study. Because patients with nonmedical exclusions were similar to those who participated in the study, we concluded that the patients described in this report are representative of approximately 60% of the entire population of men aged 70 years or younger who were treated for myocardial infarction in our institution.

The final study population consisted of 195 patients. Infarction was inferior transmural in 119 patients (61%), anterior transmural in 56 (29%), and nontransmural in 20 (10%). The mean maximal elevation of serum creatine kinase was 833 ± 657 IU (normal range for men 5–90 IU). Complications during the first 5 days of hospitalization included ventricular tachycardia in 42 patients (22%), ventricular fibrillation in six patients (3%), second-degree atrioventricular block in 13 patients (7%) and third-degree atrioventricular block in six patients (3%). Twenty-five patients (13%) had experienced angina pectoris in the 3 months before infarction and 16 (8%) had a history of prior myocardial infarction. Eight patients (4%) were taking quinidine, mean daily dose 787 ± 203 mg, and four patients were taking procainamide, mean daily dose 1750 ± 645 mg. Two patients (1%) were taking long-acting nitrates in a daily dose of 20 mg each. These medications were withheld for 16–24 hours before exercise testing.

Before testing, patients were interviewed and examined by a physician and informed consent was obtained. A physician and a specially trained cardiovascular nurse conducted the test. All tests were performed between 1–5 p.m., at least 2 hours after eating or smoking. Twelve-lead ECGs were recorded at rest, at the end of each 3-minute stage of exercise, and at 1, 3, 5, 7 and 10 minutes of recovery. In addition, leads V₄ through V₆ were displayed continuously on a three-channel oscilloscopic monitor and recorded on magnetic tape for 3 minutes before exercise and during each minute of exercise and recovery. ST-segment depression was defined as horizontal or downsloping displacement of the ST segment measured 80 msec after the J point relative to a baseline drawn tangentially through the PQ segment. At rest, 55% of patients had no ST depression and 42% had ST depression less than 0.1 mV. During exercise, the maximal change from rest was measured to the nearest 0.05 mV in leads 2, 3, aVF, and V₆ through V₈. Systolic blood pressures were recorded by cuff sphygmomanometer at the end of each 3-minute stage of exercise and at 1-minute intervals if the systolic pressure did not rise from one stage of exercise to the next.

Exercise was performed on a motor-driven treadmill using the protocol given in table 1. Exercise commenced at a work load of 3 mets and work loads were increased every 3 minutes. The first 82 patients completed a “heart-rate-limited” protocol in which testing was stopped at an arbitrary heart rate of 130 beats/min (37 cases) unless any of the end points listed below occurred sooner (45 cases). Because no complications were noted in this group, the next 113 patients, clinically indistinguishable from the first 82, completed a “symptom-limited” protocol in which maximal heart rate was not used as an end point. End points included: 1) limiting symptoms of chest pain, dyspnea, fatigue, leg cramps or dizziness; 2) exertional hypotension, defined as a fall in systolic pressure of 10 mm Hg or more from the peak value attained earlier during exercise; and 3) ventricular tachycardia, defined as three or more consecutive premature ven-

<table>
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<tr>
<th>Table 1. Treadmill Exercise Test Protocol</th>
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<td><strong>Stage</strong></td>
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*3 minutes each.

Abbreviation: Mets = multiples of resting energy expenditure (estimated).
tricular complexes (PVCs). The magnitude of ST-segment depression was not used as an end point.

Patients returned for follow-up visits 11 weeks, 6 months and 1 year after infarction. After the first year of the study, contact with patients or their physicians was maintained by annual telephone calls or letters. Subsequent cardiac events were defined as medical (sudden death, ventricular fibrillation with survival, acute myocardial infarction) or surgical (coronary artery bypass graft surgery).

A stepwise logistic regression analysis was used to identify clinical and treadmill variables predictive of subsequent cardiac events (table 2). Because this analysis requires a standard follow-up period, a subset of 92 patients, followed for 24 months after infarction or until the occurrence of a medical or surgical event, was used. In the analysis, the variable that best predicts the outcome is selected and designated "most valuable." Each of the remaining variables is combined with the previously selected "most valuable" variable and that one is selected which in combination with the previously selected variable best predicts the outcome. This process continues until the addition of a variable does not significantly augment prognostic information, as assessed by a chi-square test. Some variables that are unilaterally associated with the outcome are not selected by this stepwise process because the information they contain is better expressed by previously selected variables. Thus, the value of a given variable in this analysis represents not only its correlation with outcome but also its independence from previously selected variables.

Variables significantly associated with clinical outcome in the subgroup of 92 patients with a 24-month follow-up were then used to stratify the risk of subsequent cardiac events within the entire population of 195 patients. Censored survival curves were compiled to estimate the probability of cardiac events in patients with one or more risk factors. Statistical significance was assessed by the method of Kaplan and Meier.

Because of the nonrandom process of selection for surgery and because of the uncertain influence of coronary artery bypass graft surgery on prognosis, clinical outcomes were defined in two ways: 1) combined medical and surgical events — tantamount to assuming that all patients undergoing surgery would have had medical events otherwise, and 2) medical events only — equivalent to assuming that no patient who had surgery would have otherwise had a medical event. The predictive power of clinical and treadmill test characteristics was evaluated within the bounds of these two extreme assumptions.

Table 2. Variables Used in Prognostic Stratification

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Treadmill Variables</th>
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<tr>
<td>Age</td>
<td>Maximal heart rate</td>
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<td>Previous MI</td>
<td>Maximal systolic blood pressure</td>
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<td>Angina within 3 months of MI</td>
<td>Maximal rate-pressure product</td>
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<td>Site of MI</td>
<td>Maximal work load</td>
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<td>Peak creatine kinase level</td>
<td>ST-segment depression</td>
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<td></td>
<td>Angina pectoris</td>
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<td></td>
<td>Exercise-induced hypotension</td>
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<td>Ventricular ectopic activity</td>
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Abbreviation: MI = myocardial infarction.

Results

Clinical Characteristics

Within the entire population of 195 patients, no significant differences in age, maximal level of creatine kinase activity, prevalence of angina pectoris before infarction or history of prior infarction were noted in comparing the following subgroups: 1) the 92 patients followed for 2 years compared with the 103 patients with shorter follow-up, 2) the 19 patients who underwent coronary artery bypass graft surgery compared with the 176 patients who did not, 3) the 56 patients with anterior infarction compared with the 119 patients with inferior infarction, and 4) the 82 patients who underwent a heart-rate-limited test protocol compared with the subsequent 113 patients who underwent a symptom-limited test protocol.

Treadmill Test Results

No complications of treadmill exercise were noted. Of the 82 patients who completed a heart-rate-limited protocol, 30 (37%) stopped because of dyspnea or fatigue, eight (10%) stopped for angina pectoris, six (7%) were stopped after exercise-induced hypotension was noted, one (1%) was stopped because of ventricular tachycardia and 37 (45%) had no symptoms before reaching the limiting heart rate of 130 beats/min. Of the 82 men, 15 (18%) had ST-segment depression ≥ 0.1 mV and 12 (15%) had ST depression ≥ 0.2 mV.

Of the 113 patients who completed a symptom-limited protocol, 86 (77%) stopped because of dyspnea or fatigue, 13 (11%) for angina pectoris, 14 (12%) because of exercise-induced hypotension and none for ventricular tachycardia. Of the 113 men, 29 (26%) had ST-segment depression ≥ 0.1 mV and 13 (12%) had ST depression ≥ 0.2 mV.

The mean duration of treadmill exercise after the appearance of 0.1 mV of ST-segment depression for the entire group was 1.9 ± 2.0 minutes (range 0–7 minutes).

Treadmill test characteristics for the total population of 195 patients are summarized in table 3. These characteristics were not significantly different 1) in the subgroup of patients followed for 2 years compared with those with a shorter follow-up, 2) in those who had coronary artery bypass graft surgery compared with those who did not, and 3) in patients with inferior infarction compared with those with anterior infarction. Exercise-induced angina pectoris was noted in one-third of patients with ST-segment depression ≥ 0.1 mV and in one-half of patients with ST-segment depression ≥ 0.2 mV. Ventricular ectopic activity was
not significantly more frequent in patients with exercise-induced ST-segment depression than in those without it.

Clinical Outcome (fig. 1)

The median duration of follow-up was 26 months (range 1–64 months). To date, 150 patients have been followed at least 1 year, 92 for at least 2 years, and 48 for at least 3 years. Of the 195 men, three died suddenly, two had nonfatal cardiac arrest, 12 had nonfatal myocardial infarction and 19 underwent coronary artery bypass surgery. In the 150 patients followed for at least 1 year, the rate of combined medical and surgical events within the first year of follow-up was 19%. The rate of medical events only within the first year of follow-up was 8%.

Prognostic Stratification

The stepwise multiple logistic regression analysis identified (in descending order of importance) ST-segment depression ≥ 0.2 mV, exercise-induced angina pectoris and a maximal treadmill work load < 4 mets as the most important “risk factors” associated with combined medical and surgical events in a subgroup of 92 patients followed for 2 years or more. Among the clinical and treadmill test characteristics listed in table 2, only ST-segment depression, low maximal work load and angina pectoris were identified as risk factors.

The relationship between risk factors and the probability of combined medical and surgical events in the entire population of 195 patients was evaluated by censored survival curves (fig. 2). ST-segment depression ≥ 0.2 mV was the variable most highly associated with combined events (p < 0.0001). ST-segment depression 0.1–0.19 mV was of no greater predictive value than ST-segment depression < 0.1 mV. In patients with < 0.2 mV ST-segment depression, those with exercise-induced angina or a maximal treadmill work load of < 4 mets had an increased probability of combined events (p < 0.0001) when compared with those with neither abnormality.

The risk of medical events alone was higher in patients with ST-segment depression ≥ 0.2 mV (p < 0.001) or maximal work load < 4 mets (p < 0.07) compared with patients with neither of these features. In contrast, exercise-induced angina pectoris was not associated with a significantly higher probability of subsequent medical events (fig. 2).

Nineteen of the 195 patients underwent coronary artery bypass surgery. This group includes two of 10 patients (20%) with exercise-induced angina and ST depression ≥ 0.2 mV, four of 22 (18%) with angina only, five of 13 (38%) with ST-segment depression ≥ 0.2 mV but no angina and eight of 150 (5%) with neither angina nor ST-segment depression ≥ 0.2 mV. Thus, surgery was ultimately performed in six of 32 patients (19%) with angina compared with 13 of 163 patients (8%) without exercise-induced angina.

Of the five episodes of sudden death or nonfatal ventricular fibrillation, three occurred 3–11 weeks after infarction. All three patients had ST-segment depression ≥ 0.2 mV on the treadmill test performed 3 weeks after infarction. No patients with < 0.2 mV ST segment depression had sudden death or ventricular fibrillation during this early posthospital period.

Discussion

We sought to evaluate the prognosis of postinfarction patients without clinical evidence of severe left ventricular dysfunction. Within this selected population, we found that certain treadmill test characteristics permitted prognostic stratification, but clinical characteristics such as age, extent of creatine kinase elevation, site of infarction and prior history of angina pectoris or infarction did not. Our study thus complements the prognostic evaluations of Bigger et al.4 in patients with a high prevalence of severe left ventricular dysfunction and of Moss et al.5 in a population with an intermediate prevalence of clinically severe left ventricular dysfunction.

The prognostic significance of ST-segment depression during exercise testing soon after infarction has not been reported. Granath et al.7 and Ericsson et al.8 performed bicycle exercise testing 3 weeks after infarction in a population with a high prevalence of left ventricular dysfunction, but the use of digitalis complicates the evaluation of ST-segment responses.

![Diagram of medical and surgical events in 195 men followed for 1–64 months after uncomplicated myocardial infarction. SD = sudden cardiac death; VF = ventricular fibrillation (successful resuscitation); MI = myocardial infarction; CABS = coronary artery bypass graft surgery.](image-url)
transmural ST-segment depression equivalent degree study, their patients to had the prognostic significance frequent less infarction. regions 2 within this group. Ibsen et al.9 noted ischemic responses in a large proportion of patients undergoing bicycle exercise testing 3 weeks after infarction, but the prognostic significance of this finding was not reported. Weld and Bigger,10 whose patients performed treadmill exercise tests 2 weeks after infarction, did not note an increased rate of subsequent coronary events in patients with "ST deviation" ≥ 0.2 mV.

The influence of recent myocardial infarction on the ST-segment response to exercise has only recently been examined. Castellanet et al.11 found that exercise testing had a low sensitivity (52%) for the detection of significant coronary artery stenosis in noninfarcted regions 2 months or more after anterior myocardial infarction. The authors attributed this low sensitivity to the opposing effects of anterior ventricular aneurysm on the exercise-induced ischemic vector. In their patients with inferior infarctions, aneurysm was less frequent and the sensitivity of exercise testing for the detection of coronary lesions was 84%. In the present study, the prevalence of exercise-induced ST-segment depression was not significantly different when patients with anterior and with inferior infarction were compared. The exclusion of patients with an audible S3 or radiologic evidence of cardiomegaly may have "normalized" our population, such that an equivalent degree of left ventricular dysfunction was present in patients with anterior and with inferior transmural infarctions. In fact, the site of infarction did not significantly influence the occurrence or degree of ST-segment depression in our patients.

In many exercise laboratories, tests are terminated at the onset of 0.1 mV of ST-segment depression. While this policy partly reflects a concern with safety, there are few data to substantiate the greater safety of this policy compared with that of testing to limiting symptoms, regardless of the extent of ST-segment depression. In addition, the present study indicated that ST-segment depression was of prognostic significance only when it was ≥ 0.2 mV. Thus, if the tests are terminated at 0.1 mV of ST depression or if an arbitrary heart rate limit is imposed, some patients may not have the opportunity to exhibit 0.2 mV of ST depression.

In the absence of ST depression ≥ 0.2 mV, exercise-induced angina pectoris was not associated with a higher likelihood of subsequent medical events. In contrast, the risk of combined medical and surgical events in patients with angina pectoris was increased, because patients with angina, regardless of ST depression, were three to four times more likely to undergo bypass surgery than patients with neither angina nor ST depression ≥ 0.2 mV.

We found a low maximal work load (< 4 mets) to be predictive of subsequent cardiac events in patients without ST depression ≥ 0.2 mV or angina pectoris. Weld et al.10 also noted that patients with a maximal work load of 3 mets or less 2 weeks after infarction had an increased risk of subsequent cardiac events. Factors contributing to peak work load include not only left ventricular function, but also physical activity patterns before infarction, natural endowment of the patient and the length of bedrest and reduced
physical activity after infarction. Nevertheless, good correlation between 1) the duration of exercise and 2) the ejection fraction and extent of regional wall motion abnormalities was documented by Paine et al. in patients tested several months after infarction. Because the extent of left ventricular dysfunction correlates with long-term prognosis, it is not surprising that our patients with a decreased maximal work load experienced a higher rate of subsequent cardiac events.

We found that ventricular ectopy on a single exercise test 3 weeks after infarction had no independent prognostic value, even in patients with complex configurations or a high frequency of PVCs. This experience is contrary to that of Weld et al., who noted an increased risk of subsequent cardiac events in patients with 1 or more PVCs on treadmill exercise testing performed 2 weeks after infarction. Granath et al. also noted an increased subsequent mortality in patients with exercise-induced PVCs 3 weeks after infarction. This difference probably reflects the prevalence of left ventricular dysfunction, because we excluded patients with clinically evident left ventricular dysfunction and those taking digitalis. In contrast, nearly half of the patients studied by Bigger et al. had cardiomegaly on chest x-ray and nearly half of the patients of Granath et al. were taking digitalis.

Several studies have shown a close relationship between the prevalence of PVCs and the extent of left ventricular dysfunction in patients with chronic ischemic heart disease. Previously we reported a lack of prognostic significance of PVCs recorded during exercise tests or on ambulatory ECGs 3 weeks after uncomplicated myocardial infarction. Our findings are similar to those of Schulze et al., who noted that complex PVCs recorded by ambulatory ECGs were not associated with an increased rate of sudden death in patients with an ejection fraction > 40% — patients likely to resemble those of the present study. Thus, the prognostic significance of PVCs appears to be closely related to the extent of left ventricular dysfunction.

Others have also shown that exercise testing can be safely performed as early as 3 weeks after infarction. Is there an advantage in performing testing this soon? During the month after their 3-week test, one of our patients died suddenly, one had a nonfatal cardiac arrest and one had a fatal reinfarction. All three of these patients showed exercise-induced ST-segment depression ≥ 0.2 mV 3 weeks after infarction. The identification of such high-risk patients soon after infarction is crucial to the evaluation of newer medical and surgical techniques for improving prognosis. The nonrandom process of selection for coronary artery bypass surgery and the uncertain influences of bypass surgery on prognosis complicate the evaluation of prognosis after myocardial infarction. To exclude the subgroup of patients having bypass surgery from analysis introduces a potential bias that we addressed by considering outcome events as combined medical and surgical events and as medical events only.

Because the exercise test results may have contributed to the decision to perform surgery, it was important to show that the treadmill test was predictive of medical events alone (sudden death, nonfatal cardiac arrest, myocardial infarction) as well as combined medical and surgical events. Indeed, ST-segment depression ≥ 0.2 mV and maximal treadmill work load < 4 mets were found to be predictive of subsequent medical events. Thus, consideration of clinical outcomes in these two ways helped to avoid any bias introduced by performance of coronary artery bypass surgery during the follow-up period.

We conclude that in patients with clinically uncomplicated myocardial infarction, treadmill exercise testing performed 3 weeks after the acute event further defines the risk of subsequent cardiac events, and that within this population, prognosis is more closely related to exercise-induced ischemic abnormalities (ST-segment depression ≥ 0.2 mV and angina pectoris) or to mechanical abnormalities (low maximal work load) than to electrical abnormalities (ventricular ectopic activity).

Addendum

While this manuscript was in press, Theroux et al. reported on 1-year follow-up of 210 patients without heart failure who had exercise testing before discharge from hospitalization for acute myocardial infarction (N Engl J Med 301: 341, 1979). They had no complications of testing. ST-segment depression was the exercise test variable of most prognostic significance. One-year mortality rates and the incidence of sudden death were both more than 10 times greater for patients who had 0.1 mV or greater ST-segment depression than for patients without this ST-segment response.

References

11. Castellanet MJ, Greenberg PS, Ellestad MH: Comparison of
Regional Assessment of Myocardial Metabolic Integrity in Vivo by Positron-emission Tomography with $^{11}$C-labeled Palmitate

MICHEL M. TER-POGOSIAN, PH.D., MILTON S. KLEIN, M.D., JOANNE MARKHAM, M.S., ROBERT ROBERTS, M.D., AND BURTON E. SOBEL, M.D.

SUMMARY To determine whether positron emission tomography (PET) after the combined administration of $^{11}$C-palmitate intravenously to image myocardium and $^{14}$CO by inhalation to image the cardiac blood pool with $^{14}$CO-hemoglobin provides quantitative delineation of the locus and extent of myocardial infarction, 28 patients with suspected myocardial infarction were studied. Twenty-one patients had electrocardiographically documented transmural infarction and in seven, the diagnosis of infarction was ultimately excluded based on enzymatic and electrocardiographic criteria. To assess reproducibility, four patients were studied on two occasions 1 month apart. Inferior and apical infarcts were readily localized with sagittal and coronal as opposed to transaxial reconstructions. Complete electrocardiographic and tomographic concordance was observed for the locus of all transmural infarcts. Reproducibility of tomographic estimates was within 10%. Tomographic estimation of the extent of infarction with $^{11}$C-palmitate in a subset of patients in whom right ventricular contributions to overall enzyme release could be excluded was facilitated by delineation of the endocardial border with the $^{12}$CO-hemoglobin cardiac blood pool image in the same plane. The correlation between enzymatic (serial plasma MB-CK method) and tomographic estimates of infarct size was close ($r = 0.92$). Thus, as has been shown in experimental animals, PET with $^{11}$C-palmitate permits quantification and localization of myocardial infarcts in patients.

THE EXTENT of myocardium undergoing irreversibly injury is an important determinant of prognosis after acute myocardial infarction. Because it may be possible to limit the extent of infarction during its early evolution, accurate, reliable and serially applicable objective indexes are needed to define both the extent of tissue jeopardized by ischemia and the magnitude of irreversible injury evolving ultimately.

During the past several years we have been exploring the possibility of assessing the metabolic integrity of myocardium quantitatively and noninvasively by positron tomography with radioactively labeled metabolic substrates of myocardium, based on the premise that prolonged depression of regional myocardial metabolism will quantitatively reflect underlying pathology. The application of this approach requires that the fate of the labeled substrate and of the radioactive label itself reflect changes in endogenous metabolites indicative of the altered metabolic state — a condition best fulfilled by radionuclides with chemical identities akin to physiologic substrates such as $^{13}$C, $^{18}$O and $^{15}$N, in contrast to the case when substrates such as fatty acids are labeled with an atom such as $^{13}$F$^-$. The brief physical half-lives of these radionuclides ($^{13}$C—20 minutes, $^{15}$N—10 minutes, $^{18}$O—2 minutes) permit repeated measurements within a brief interval and delivery of only a modest dose of radiation to the patient. Unfortunately, because of their fleeting existence, these isotopes must be prepared in the immediate vicinity of their application, generally requir-
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Circulation. 1980;61:236-242
doi: 10.1161/01.CIR.61.2.236

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 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:
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