Clinical and Angiographic Characteristics of Exertion-Related Acute Myocardial Infarction

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Context Vigorous physical exertion transiently increases the risk of acute myocardial infarction (MI), but little is known about the clinical characteristics of exertion-related MI.

Objective To compare the clinical and angiographic characteristics of patients who had an exertion-related acute MI vs those who experienced an MI not related to exertion.

Design and Setting Prospective observational cohort study of patients with an acute MI referred to a tertiary care hospital for primary angioplasty.

Patients Of 1048 patients with acute MI, 640 (64 who experienced an exertion-related MI and 576 who did not) were selected for treatment with primary angioplasty and admitted between August 1995 and November 1998.

Main Outcome Measures Clinical characteristics of the patients, including their habitual physical activity (determined by the Framingham Physical Activity Index and the Lipid Research Clinic Physical Activity Questionnaire), angiographic findings during coronary angiography, and the relative risk (RR) of MI during exertion.

Results Patients who experienced exertion-related MI were more frequently men (86% vs 68%), hyperlipidemic (62% vs 40%), and smokers (59% vs 37%), were more likely to present with ventricular fibrillation (20% vs 11%), Killip classification III or IV heart failure (44% vs 22%), single-vessel disease (50% vs 28%), and a large thrombus in the infarct artery (64% vs 35%) and were more likely to be classified as having very low or low activity (84% vs 66%). The RR of experiencing an MI during exertion was 10.1 times greater than the risk at other times (95% confidence interval [CI], 1.6-65.6), with the highest risk among patients classified as very low active (RR, 30.5; 95% CI, 4.4-209.9) and low active (RR, 20.9; 95% CI, 3.1-142.1).

Conclusion These results show that exertion-related MIs occur in habitually inactive people with multiple cardiac risk factors. These individuals may benefit from modest exercise training and aggressive risk-factor modification before they perform vigorous physical activity.

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Epidemiological studies have documented that habitual physical activity reduces the population incidence of coronary heart disease, including myocardial infarction (MI) and cardiac death.[1] On the other hand, vigorous physical activity can also acutely and transiently increase the risk of both of these cardiac events.[2-5] Between 4% and 15% of MIs occur during or soon after vigorous exertion,[6] making exertion one of the most common triggers of acute MI. Such events appear more frequent in patients with diabetes and habitually sedentary individuals,[2] but little else is known about who develops an exertion-related cardiac event. Most studies of exertion-related sudden death cannot develop a clinical picture of the victims because of small sample sizes.[4,5,7] The current study compared the clinical characteristics of patients who experienced an exertion-related MI with those who experienced MI not related to exertion.

METHODS

Study Design

The data are derived from the Hartford Hospital Acute MI Study, which was designed to evaluate prospectively the outcomes of patients with MI treated with primary angioplasty, the predominant treatment method for acute MI at our institution. Between August 1995 and November 1998, 1048 consecutive patients with acute MI were hospitalized within 12 hours of symptom onset at our institution. Of the 1048 patients who presented within the 12-hour time window, 225 were treated with thrombolysis, 12 underwent catheterization but proceeded immediately to coronary artery bypass graft surgery, 112 were transferred from another hospital for rescue angioplasty after failed thrombolytics, 42 had vein graft occlusion, 6 had absolute contraindications to coronary intervention, 6 had an unidentifiable infarct artery, and 5 declined participation, leaving 640 patients for this study. All patients provided verbal and written informed consent as approved by the institutional review board.

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Patients were interviewed during the hospital admission by a study physician using standardized forms. When patients were unable to be interviewed personally or during the admission, the information was obtained from interview with the spouse or a cohabiting family member in 26 (4.0%) or by telephone interview in 62 (9.7%) of the participants, respectively. Medical records were reviewed by a physician to obtain clinical characteristics of the patients. Angina was graded by the Canadian Cardiovascular Society criteria.[8] Height and weight were measured in hospital clothing.

The activity at the onset or 1 hour before the MI was determined by interview and classified as vigorous (>6 metabolic equivalents [METS]) or not using standard tables.[9] One *MET* is defined as the energy expenditure for sitting quietly or approximately 3.5 mL of oxygen per kilogram of body weight. An *exertion-related MI* was defined as an MI with symptom onset during or within 1 hour of vigorous exertion.

Evaluation of Physical Activity

Both the Framingham Physical Activity Index (PAI)[10] and the Lipid Research Clinics (LRC) Physical Activity Questionnaire[11] were used to estimate patients' usual physical activity. Subjects were asked the average amount of time in a typical day they spent sleeping, resting, and performing light, moderate, or heavy physical activity during the past year using a list of leisure and household activities.[9,12] Patients also were asked their physical activity during the preceding 24 hours and the past month. Activities were assigned an estimated caloric requirement using standardized tables[9,13] and multiplied by the time spent in each activity to estimate the energy expended during a typical day and the individual's PAI.[14] Total physical activity was also divided into time spent on heavy (>6 METS), moderate (4-6 METS), light (2-4 METS), and sedentary (<2 METS) activities.[12] Patients were also stratified by physical activity status into very low, low, moderate, or high activity groups using the modified scoring scheme of the LRC Physical Activity Questionnaire.[11] Patients graded their level of physical activity relative to their peers at work and leisure. Among patients who reported strenuous physical activity, those grading themselves as more active or equally active than their peers were classified as highly active and moderately active, respectively. Among patients who reported no strenuous physical activity, those grading themselves as equally or less active than their peers were classified as low active and very low active, respectively.

Calculation of the Relative Risk of Exertion-Related MI

A within-patient, case-crossover technique[15] was used to assess the relative risk (RR) of an MI during strenuous exertion compared with other times. Applying standard stratified data analysis, the case-crossover design treats the individual patient as the stratifying variable, as in a crossover experiment. The amount of person-time exposed to heavy exertion was estimated by multiplying the reported annual frequency of physical exertion by its duration. Unexposed person-time was calculated by subtracting the exposed time from the number of hours in a year. A 1-hour hazard period immediately before the onset of the MI was compared with the control data obtained from the patient's usual frequency of heavy physical exertion (>6 METS) during the past year.[2] The ratio of the observed frequency of strenuous exertion during the hazard period to the expected frequency was used to estimate RR.

Cardiac Catheterization and Quantitative Angiography

Coronary angiography and angioplasty were performed using standard techniques. Cineangiograms were interpreted in duplicate by experienced angiographers who were unaware of the patient's clinical or procedural characteristics. Cineangiographic frames were selected under uniform optical magnification with standardized illumination. Quantitative angiographic analysis was performed using an automated edge-detection algorithm (CMS Medical Imaging System, version 4.0, Wallingford, Conn)[16,17] to determine the "normal" or reference diameter of the infarct artery and the minimal luminal diameter of the culprit lesion. Anterograde flow in the infarct artery was assessed by the Thrombolysis in Myocardial Infarction (TIMI) trial grading system.[18] Lesion morphology was graded according to American College of Cardiology and American Heart Association criteria.[19] Intraluminal thrombus was identified angiographically and graded on a semiquantitative scale (none = 0, possible = 1, definite thrombus <3 mm = 2, definite thrombus ≥3 mm = 3).[20] For analysis, thrombus was categorized as possible (grades 0 and 1) or definite (grades 2 and 3) based on the largest thrombus noted before angioplasty.

Statistical Analyses

Continuous variables were compared using 2-tailed *t* tests. Categorical and dichotomous variables were analyzed using the χ^2 or Fisher exact tests. A 2-sided *P* value of <.05 was considered significant. The predictive value of clinical, lifestyle, and angiographic information for an exertion-related MI was evaluated by univariate and multivariate stepwise logistic regression analysis (SPSS 8.0, Chicago, Ill). Logistic regression coefficients and SDs were converted to odds ratios (ORs) and 95% confidence intervals (CIs).

RESULTS

Clinical Characteristics of Patients

Of the 640 patients with MI who were treated by primary angioplasty, 64 (10%) sustained the event during or within an hour of vigorous physical exertion. This exertion was predominantly aerobic activity such as running and jogging in 26 cases (40.6%), isometric or heavy lifting in 12 cases (18.8%), and a mixture of aerobic and lifting activities in 26 cases (40.6%). Patients with an exertion-related MI were more likely to have established coronary artery disease (CAD) risk factors including male sex, obesity, current cigarette smoking, hyperlipidemia, and hypertension (TABLE 1), and were less likely to use aspirin or β-blockers and tended to have less established cardiac disease ($P = .06$).

Levels of Habitual Physical Activity

By multiple measurement criteria, patients who experienced an exertion-related MI were significantly less physically active than patients with non–exertion-related MI (Table 1). Fifty-four (84%) of the exertion-related MI patients were classified as very low active or low active by LRC criteria, and only 1 was classified as highly active. Compared with patients in the group with MI not related to exertion, the annual Framingham PAI was significantly lower in the exertion-related MI group, and only 17% of the patients with exertion-related MI engaged in heavy exertion for 20 minutes or more at least weekly. The Framingham PAI was also lower during the prior year and 30 days for the patients with exertion-related MI, but was significantly higher for the 24 hours prior to their event, suggesting that the event occurred in association with unusual physical activity.

Relative Risk of MI During Vigorous Exertion

For all subjects, the RR of MI was 10.1 times greater (95% CI, 1.56-65.63) during vigorous exertion than at other times. Among the 4 LRC activity groups, however, the risk was significantly increased only among the very low active (RR, 30.5; 95% CI, 4.4-209.9) and low active subjects (RR, 20.9; 95% CI, 3.1-142.1) and was not significantly increased among those classified as moderately active (RR, 2.9; 95% CI, 0.5-15.9) and highly active (RR, 1.2; 95% CI, 0.3-5.2).

Clinical Course of Patients

Patients with an exertion-related MI were more likely to develop ventricular fibrillation during the event, to require blood pressure support, and to develop Killip class III and IV heart failure (TABLE 2). Peak creatine kinase values were also significantly higher in the exertion-related MI group, but there were no differences between the 2 groups in other clinical parameters or in the clinical outcome at 30 days.

Angiographic Characteristics

There were no differences in the identity of the infarct-related artery between the 2 patient groups (TABLE 3). Patients whose MI occurred during exertion were more likely to have single-vessel, and less likely to have triple-vessel, CAD. There was no difference between the 2 groups in infarct-artery calcification, lesion morphology, the frequency of total coronary occlusion, or initial TIMI flow grade, but patients with exertion-related MI were more likely to demonstrate definite angiographic thrombus (grades 2 and 3). Both the reference section of the infarct artery and the minimal luminal diameter before angioplasty were larger in the exertion-related MI group, but there were no other significant differences in the angiographic findings.

Predictors of Exertion-Related MI

On univariate analysis, a low or very low activity level, male sex, obesity, hyperlipidemia, current cigarette smoking, and absence of angina pectoris were predictive of exertion-related MI. In a stepwise logistic regression model that included other relevant demographic, clinical, and angiographic variables, the following variables independently con-

Table 1. Patient Clinical Characteristics and Measures of Habitual Physical Activity*

Characteristics	Exertion-Related AMI (n = 64)	Non–Exertion-Related AMI (n = 576)	*P* Value
Age, mean (SD), y	59 (13)	61 (14)	.26
Male	86	68	.002
White	97	90	.47
Body weight, mean (SD), kg	87 (14)	82 (14)	.005
Obesity (BMI ≥30 kg/m^2)	48	28	.002
Current smoker	59	37	.001
Hyperlipidemia†	62	40	.001
Hypertension‡	34	46	.08
Family history of premature CAD	36	35	.89
Diabetes mellitus‡	19	18	.92
Prior diagnosis of CAD	16	26	.06
Prior aspirin use	20	35	.02
Prior β-blocker use	9	30	.001
LRC 4-point scoring system			
Very low active	14	13	.02
Low active	70	53	
Moderately active	14	31	
Highly active	2	3	
Frequency of heavy exertion of >20 min/wk			
0	83	62	.03
1	6	21	
2	6	10	
3	5	4	
≥4	0	3	
Framingham Physical Activity Index, mean (SD)			
Annual	26.93 (1.69)	28.95 (3.30)	<.001
Preceding 30 days	26.40 (0.79)	28.00 (2.16)	<.001
Preceding 24 hours	32.68 (1.99)	29.43 (3.37)	<.001

*Data are expressed as percentage unless otherwise indicated. AMI indicates acute myocardial infarction; BMI, body mass index; CAD, coronary artery disease; and LRC, Lipid Research Clinic.
†Serum cholesterol level of greater than 6.21 mmol/L (240 mg/dL) or the use of cholesterol-lowering agents.
‡Physician diagnosis or the use of appropriate medications.

Table 2. Disease Severity at Presentation and Clinical Outcome*

Variables	Exertion-Related AMI (n = 64)	Non–Exertion-Related AMI (n = 576)	*P* Value
Ventricular fibrillation at presentation	20	11	.02
Need for inotropic support	36	24	.03
Killip class			
I	37	64	
II	19	15	.001
III or IV	44	22	
Peak creatine kinase, mean (SD), mg/dL	2466 (1606)	1607 (1413)	.001
Left ventricle ejection fraction, mean (SD), %†	41.7 (12)	42.8 (12)	.48
Clinical parameter or outcome at 30 days			
Mortality	5	7	.49
Recurrent infarction	8	3	.06
Any revascularization‡	13	9	.37
Coronary artery bypass graft surgery	9	6	.28
Composite clinical event§	16	22	.24

*Data are expressed as percentage unless otherwise indicated. AMI indicates acute myocardial infarction.
†Left ventricle ejection fraction was measured by ventriculography or echocardiogram performed within 12 hours of the angioplasty.
‡Includes percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery.
§Includes death, recurrent myocardial infarction, and any revascularization procedure.

Table 3. Coronary Morphology and Quantitative Coronary Angiographic Results*

Variables	Exertion-Related AMI (n = 64)	Non–Exertion-Related AMI (n = 576)	*P* Value
Infarct artery			
Left anterior descending	31	40	
Right coronary	48	45	.34
Left circumflex	20	16	
No. of diseased coronary vessels			
1	50	28	
2	42	32	.001
3	8	41	
Calcification			
None	75	72	
Mild	22	23	.72
Moderate	2	4	
Severe	2	1	
Lesion type†			
A/B1	44	39	
B2	41	41	.65
C	16	21	
Lesion length >20 mm	11	13	.61
Intracoronary thrombus ≥2 mm	64	35	.001
Initial TIMI flow grade			
0/I	86	81	.19
II/III	14	19	
Initial minimal luminal diameter, mean (SD), mm	0.21 (0.33)	0.15 (0.21)	.04
Initial % diameter stenosis, mean (SD)	93.0 (10.3)	94.4 (8.1)	.19
Reference diameter, mean (SD), mm	2.93 (0.45)	2.74 (0.46)	.002
Persistent no reflow	11	7	.27

*Data are expressed as percentage unless otherwise indicated. Coronary artery disease was defined angiographically as at least 50% diameter stenosis. AMI indicates acute myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction study.
†Lesion type graded according to American College of Cardiology/American Heart Association criteria.[19]

tributed to the prediction of exertion-related MI: a low or very low activity level (OR, 3.35; 95% CI, 1.58-7.10; *P* = .001), male sex (OR, 3.26; 95% CI, 1.53-6.92; *P* = .002), hyperlipidemia (OR, 2.27; 95% CI, 1.30-3.95; *P* = .004), current smoking (OR, 2.15; 95% CI, 1.24-3.74; *P* = .007), obesity (OR, 1.87; 95% CI, 1.06-3.32; *P* = .03), and stable angina (OR, 0.23; 95% CI, 0.09-0.60; *P* = .003).

COMMENT

In this study, 10% of the MIs treated with primary angioplasty occurred during or within an hour of vigorous exertion. We do not know how many other patients had exertion-related MI, but even if we assume no additional events, then at least 6% of all acute MIs evaluated at our institution were associated with physical exertion. The RR of experiencing an MI associated with vigorous physical activity was 10.1 higher than at other times. This risk was greatest for those individuals classified as very low active or low active by LRC criteria and was not significantly increased among those classified as moderately and highly active. Our definition of an exertion-related MI required physical exertion of at least 6 METS, but only 17% of subjects who sustained an exertion-related event routinely performed a similar level of sustained effort. In contrast, subjects who had an exertion-related MI had higher levels of physical exertion than comparison subjects during the 24 hours prior to the event. This higher energy expenditure is due in part to the requirement that such subjects be performing physical exertion at the time of the event, but does suggest that the MI occurred during unaccustomed physical activity.

These results are consistent with other studies demonstrating that exertion and exercise acutely increase the risk of cardiac events and that such events are more common in inactive people. Joggers in Rhode Island were 7 times more likely to die while jogging than during other activities,[4] and men in Seattle were 14 times more likely to develop cardiac arrest during vigorous activity than at other times.[5] In the

Seattle study, the RR of a cardiac arrest during exercise was 56 among the habitually least active subjects and 5 among the most active men. Other studies have documented that acute MI is 2^3 to 6^2 times more common during vigorous exertion than during less demanding activities, but that the RR decreases from 107 in people who exercise less than once per week to 2.4 in people who exercise more than 4 times weekly.[2] These findings do not impugn the benefits of regular exercise. Many epidemiological studies demonstrate that habitual physical activity reduces the incidence of cardiac events, and there are sufficient data to fulfill accepted criteria that the physical activity itself, and not some associated factor, is responsible for the reduced incidence of CAD.[21]

In addition to being physically inactive, patients who experienced an exertion-related MI were more likely to be male, obese, current smokers, and hyperlipidemic than patients who had MI not related to exertion.

The patients with exertion-related MI were also more likely to have single-vessel CAD and less likely to have triple-vessel disease. They had a significantly larger absolute diameter of the reference section of the infarct artery and more frequently had definite thrombus. The MI in the patients in whom the event was related to exertion, therefore, was associated with a larger thrombus burden and less triple-vessel disease.

Atherosclerotic plaque rupture and coronary thrombosis are the immediate precedents of most acute MIs in the general population. Studies of individuals who develop exertion-related cardiac complications[22] and of athletes who experience sports-related cardiac events[23] generally demonstrate the same pathological process. The mechanisms by which exercise triggers an acute cardiac event are not clear. Shear forces that increase the vascular wall stress may increase plaque fissuring and rupture. Plaques vulnerable to rupture are often lipid-enriched and covered by a thin fibrous cap.[24] Furthermore, plaques that subsequently produced an acute MI often occluded less than 70% of the coronary diameter when visualized by angiography and were regarded as hemodynamically insignificant prior to the event.[25]

Exertion acutely alters both the geometry and hemodynamic forces of the coronary arteries. Exercise increases systolic blood pressure and heart rate. Increased blood pressure augments shear forces in the coronary arteries and the elevated heart rate increases the frequency of the bending, twisting, and flexing motions required of the coronaries during cardiac contraction.[22] Increases in left ventricular end-diastolic volume and decreases in end-systolic volume during exercise also increase the excursion required of the epicardial arteries, which augments the stress on the less flexible atherosclerotic segments. Normal coronary arteries dilate during exercise, whereas atherosclerotic segments may constrict.[26] All of these mechanical forces may contribute to plaque disruption during exertion. Alternatively, spontaneous plaque rupture without subsequent coronary thrombosis may be a relatively common event in patients with coronary atherosclerosis,[27] and exertion may acutely increase the risk that plaque rupture will lead to clinical sequelae especially in sedentary individuals. Exercise increases fibrinolysis[28] and tissue plasminogen activator levels.[29] These changes are reduced in sedentary subjects, whereas exercise-induced platelet aggregation is increased.[30]

The higher prevalence of hyperlipidemia and cigarette smoking in patients with exertion-related MI suggests that these risk factors may act synergistically with exertion to produce acute cardiac events. This concept has support from other observations. Cigarette smoking increases coronary artery vasoconstriction,[31] which may exacerbate exercise-induced vasoconstriction in atherosclerotic coronary arteries. Both smoking and hyperlipidemia[32] increase platelet-thrombus formation in patients with CAD[33] and could potentiate platelet aggregation during physical exertion in sedentary subjects. Similarly, lipid-lowering therapy enhances flow-mediated brachial artery dilatation,[34] a surrogate measure of coronary artery vasomotion,[35] so that cholesterol reduction may reduce exercise-induced coronary vasoconstriction. The observation that exertion-related events occurred in subjects with more cardiac risk factors but less multivessel CAD raises the possibility that modifying CAD risk factors, specifically hyperlipidemia and cigarette smoking, is especially important in inactive people before they participate in vigorous exercise.

The clinical complications of an exertion-related acute MI in this study were more severe than nonexertion events. Despite less triple-vessel CAD, patients with exertion-related MI were more likely to present with congestive heart failure and ventricular fibrillation. These observations require confirmation, but the cardiac demands of exertion may exacerbate the damage produced by the acute MI. Despite the more ominous early course, however, there was no difference in the clinical outcome of patients with exertion-related and non–exertion-related MIs at 30 days' follow-up. Delay in presentation could have contributed to MI severity because the time from symptom onset to emergency department admission tended to be longer in patients with exertion-related MI (mean [±SD]: 223 [±118] vs 202 [±90] minutes, $P = .08$), as was the time to first angioplasty balloon inflation (mean [±SD]: 297 [±122] vs 279 [±94] minutes, $P = .15$).

This study has several limitations. Our analysis is based on patients admitted with acute MI who were selected for, and treated with, primary angioplasty. Thirty-eight percent of all patients with MI were excluded primarily because they were treated with thrombolytic therapy before transfer to our hospital. The assessment of physical activity was based on self-report and it is possible that patients who experienced an exertion-related event underestimated their habitual activity level. This potential problem is not unique to this study, however, because all previous studies of exertion-related MI are based on subjective reports of habitual physical activity. Coronary vessel diameter and the presence of thrombus is difficult to quantify with angiographic techniques, but all angiographic studies were interpreted by 2 cardiologists without knowledge of the patient characteristics and any errors in angiographic measurements should have similarly affected the results for both activity groups.

In conclusion, this study demonstrates that exertion-related acute MI occurs predominantly in habitually inactive individuals during unaccustomed physical activity. These results should reassure individuals who exercise regularly and public health advocates of physical activity. The American College of Sports Medicine and the Centers for Disease Control and Prevention recommend physical activity consisting of 3 to 5 METS of exertion on most, and preferably all, days of the week.[36] Such recommendations appear prudent since it is likely that the risk of exercise increases with intensity and these exercise recommendations are below the level of exertion used to define an exercise-related cardiac complication in this and other studies. Our results also suggest that other cardiac risk factors such as hyperlipidemia and smoking should be treated aggressively, especially in middle-aged adults who exercise vigorously. Although other evidence suggests that moderate exercise is beneficial, the current results suggest that habitually inactive adults with elevated cardiac risk should avoid unaccustomed vigorous exertion.

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REFERENCES

1. Powell KE, Paffenbarger RS Jr. Workshop on epidemiologic and public health aspects of physical activity and exercise: a summary. *Public Health Rep.* 1985;100:118-126.

2. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion: protection against triggering by regular exertion. *N Engl J Med.* 1993;329:1677-1683.

3. Willich SN, Lewis M, Lowel H, Arntz HR, Schubert F, Schroder R. Physical exertion as a trigger of acute myocardial infarction. *N Engl J Med.* 1993;329:1684-1690.

4. Thompson PD, Funk EJ, Carleton RA, Sturner WQ. Incidence of death during jogging in Rhode Island from 1975 through 1980. *JAMA.* 1982;247:2535-2538.

5. Siscovick DS, Weiss NS, Fletcher RH, Lasky T. The incidence of primary cardiac arrest during vigorous exercise. *N Engl J Med.* 1984;311:874-877.

6. Tofler GH, Stone PH, Maclure M, et al. Analysis of possible triggers of acute myocardial infarction (the MILIS study). *Am J Cardiol.* 1990;66:22-27.

7. Thompson PD, Stern MP, Williams P, Duncan K, Haskell WL, Wood PD. Death during jogging or running: a study of 18 cases. *JAMA.* 1979;242:1265-1267.

8. Campeau L. Grading of angina pectoris. *Circulation.* 1976;54:522-523.

9. Dafoe W. Table of energy requirements for activities of daily living, household tasks, recreational activities, and vocational activities. In: Pashkow F, Dafoe W, eds. *Clinical Cardiac Rehabilitation: A Cardiologist's Guide, I.* Baltimore, Md: Williams & Wilkins; 1993:359-376.

10. Kannel WB, Sorlie P. Some health benefits of physical activity: the Framingham Study. *Arch Intern Med.* 1979;139:857-861.

11. Ainsworth BE, Jacobs DR Jr, Leon AS. Validity and reliability of self-reported physical activity status: the Lipid Research Clinics questionnaire. *Med Sci Sports Exerc.* 1993;25:92-98.

12. Haskell WL, Brachfeld N, Bruce RA, et al. Task Force II: determination of occupational working capacity in patients with ischemic heart disease. *J Am Coll Cardiol.* 1989;14:1025-1034.

13. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc.* 1993;25:71-80.

14. Garcia-Palmieri MR, Costas R Jr, Cruz-Vidal M, Sorlie PD, Havlik RJ. Increased physical activity: a protective factor against heart attacks in Puerto Rico. *Am J Cardiol.* 1982;50:749-755.

15. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol.* 1991;133:144-153.

16. Lesperance J, Hudon G, White CW, Laurier J, Waters D. Comparison by quantitative angiographic assessment of coronary stenoses of one view showing the severest narrowing to two orthogonal views. *Am J Cardiol.* 1989;64:462-465.

17. Kimball BP, Cohen EA, Adelman AG, for the CCAT Investigators. Influence of stenotic lesion morphology on immediate and long term (6 months) angiographic outcome: comparative analysis of directional coronary atherectomy versus standard balloon angioplasty. *J Am Coll Cardiol.* 1996;27:543-551.

18. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. *N Engl J Med.* 1985;312:932-936.

19. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease: implications for patient selection. *Circulation.* 1990;82:1193-1202.

20. Bresnahan DR, Davis JL, Holmes DR Jr, Smith HC. Angiographic occurrence and clinical correlates of intraluminal coronary artery thrombus: role of unstable angina. *J Am Coll Cardiol.* 1985;6:285-289.

21. Powell KE, Thompson PD, Caspersen CJ, Kendrick JS. Physical activity and the incidence of coronary heart disease. *Annu Rev Public Health.* 1987;8:253-287.

22. Black A, Black MM, Gensini G. Exertion and acute coronary artery injury. *Angiology.* 1975;26:759-783.

23. Ciampricotti R, Deckers JW, Taverne R, El Gamal M, Relik-van Wely L, Pool J. Characteristics of conditioned and sedentary men with acute coronary syndromes. *Am J Cardiol.* 1994;73:219-222.

24. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). *N Engl J Med.* 1992;326:242-250.

25. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation.* 1988;78:1157-1166.

26. Gordon JB, Ganz P, Nabel EG, et al. Atherosclerosis influences the vasomotor response of epicardial coronary arteries to exercise. *J Clin Invest.* 1989;83:1946-1952.

27. Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J.* 1985;53:363-373.

28. Kvernmo HD, Osterud B. The effect of physical conditioning suggests adaptation in procoagulant and fibrinolytic potential. *Thromb Res.* 1997;87:559-569.

29. Szymanski LM, Pate RR, Durstine JL. Effects of maximal exercise and venous occlusion on fibrinolytic activity in physically active and inactive men. *J Appl Physiol.* 1994;77:2305-2310.

30. Kestin AS, Ellis PA, Barnard MR, Errichetti A, Rosner BA, Michelson AD. Effect of strenuous exercise on platelet activation state and reactivity. *Circulation.* 1993;88:1502-1511.

31. Winniford MD, Whelan KR, Kremers MS, et al. Smoking-induced coronary vasoconstriction in patients with atherosclerotic coronary artery disease: evidence for adrenergically mediated alterations in coronary artery tone. *Circulation.* 1986;73:662-667.

32. Lacoste L, Lam JY, Hung J, Letchacovski G, Solymoss CB, Waters D. Hyperlipidemia and coronary disease: correction of the increased thrombogenic potential with cholesterol reduction. *Circulation.* 1995;92:3172-3177.

33. Hung J, Lam JY, Lacoste L, Letchacovski G. Cigarette smoking acutely increases platelet thrombus formation in patients with coronary artery disease taking aspirin. *Circulation.* 1995;92:2432-2436.

34. Stroes ES, Koomans HA, de Bruin TW, Rabelink TJ. Vascular function in the forearm of hypercholesterolaemic patients off and on lipid-lowering medication. *Lancet.* 1995;346:467-471.

35. Anderson TJ, Uehata A, Gerhard MD, et al. Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol.* 1995;26:1235-1241.

36. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA.* 1995;273:402-407.

tension of applying the concepts seemingly embraced by this article, in which economics drive health care decisions.

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1. Showstack J, Katz PP, Lake JR, et al. Resource utilization in liver transplantation: effects of patient characteristics and clinical practice. *JAMA*. 1999;281:1381-1386.
2. Williams JW, Vera S, Evans LS. Socioeconomic aspects of hepatic transplantation. *Am J Gastroenterol*. 1987;82:1115-1119.
3. United Network for Organ Sharing. *1997 Report of Center Specific Graft and Patient Survival Rates.* Washington, DC: US Dept of Health and Human Services; 1998.
4. Whiting JF, Martin J, Zavala E, Hanto D. The influence of clinical variables on hospital costs after orthotopic liver transplantation. *Surgery*. 1999;125:217-222.

In Reply. Due to changes in clinical practices over time, the data cited by Dr Fung from UNOS center-specific graft and patient survival rates for 1997 are not necessarily comparable with our data for patients who received transplants during 1990 to 1995. For example, hepatitis B immunoglobulin was not used routinely by any of the 3 centers during the first years of the study, and there was little difference among the 3 centers in the number of patients with hepatitis B. Cytomegalovirus prophylaxis did not differ significantly among the 3 centers; all centers used regimens that consisted of intravenous ganciclovir, acyclovir, or both; and analyses controlled for donor and recipient CMV status. Finally, the transfer of patients from the transplantation hospital to a lower-cost facility rarely occurred in this era. Thus, the differences found in resource use among the 3 centers were unlikely to have been caused by the factors suggested by Fung.

Currently, the clinical profile of patients undergoing transplantation in the United States is dictated largely by the criteria used for organ allocation. These criteria represent the efforts of the transplantation community to develop objective criteria by which suitable patients with the most advanced disease can be identified and given the highest priority for transplantation. The current scheme for prioritizing patients is based on the Child-Pugh score.[1] In our study, the most important contributor to increased resource use was more advanced liver disease, defined as patients with a Child-Pugh score of at least 10. In fact, in most parts of the country, few patients with a score of less than 10 have sufficient priority to be offered livers. Thus, national policy is already committed to transplanting livers in patients who are likely to consume greater resources. Moreover, the Institute of Medicine recently acknowledged that if broader sharing of livers for transplantation were to occur, as it recommended, then a greater number of transplantations would be performed in patients with more advanced disease, and the costs of liver transplantation would increase.[2]

As patients with more advanced disease receive a higher proportion of transplants, there will be increased pressures to deliver cost-effective care, which requires that a program be able to quantify the costs of transplantation, and patient characteristics and clinical services affect those costs. The issue is whether we are most effectively and efficiently using our limited clinical and financial resources for organ transplantation.

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1. Pugh RWH, Murray-Lyon IM, Dawson JL, et al. Transaction of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1983;60:646-649.
2. Committee on Organ Procurement and Transplantation Policy, Institute of Medicine. *Organ Procurement and Transplantation: Assessing Current Policies and the Potential Impact of the DHHS Final Rule*. Washington, DC: National Academy Press; 1999. Available at: http://www.nap.edu/books/030906578X/html/index.html. Accessed November 1999.

CORRECTIONS

Omission of Investigator Names: In the Original Contribution entitled "The Effect of Raloxifene on Risk of Breast Cancer in Postmenopausal Women: Results From the MORE Randomized Trial," published in the June 16, 1999, issue of THE JOURNAL (1999;281:2189-2197), the names of the study investigators were inadvertently omitted and not acknowledged for their contributions to the article. A full list of the investigators of the study has been subsequently published in the Original Contribution entitled "Reduction of Vertebral Fracture Risk in Postmenopausal Women With Osteoporosis Treated With Raloxifene: Results From a 3-Year Randomized Clinical Trial," published in the August 18, 1999, issue of THE JOURNAL (1999;282:637-645).

Incorrect Wording: In the Original Contribution entitled "Reduction of Vertebral Fracture Risk in Postmenopausal Women With Osteoporosis Treated With Raloxifene: Results From a 3-Year Randomized Clinical Trial," published in the August 18, 1999, issue of THE JOURNAL (1999;282:637-645), there was incorrect wording in 2 tables and 1 figure. On page 640 in Table 2, for study group 1, the relative risk for raloxifene 120 mg/d that read "0.5" should have read "0.6," and the total relative risk for raloxifene 120 mg/d that read "0.6" should have read "0.5." On page 641 in Table 3, the title that read "Nonvertebral Fractures in 4536 Women Receiving Raloxifene Hydrochloride Therapy and 2292 Women Receiving Placebo" should have read "Nonvertebral Fractures in 5129 Women Receiving Raloxifene Hydrochloride Therapy and 2576 Women Receiving Placebo." On page 642 in the legend for Figure 3, the sentence that read "This represents 2292 women who received placebo and 4536 women who received raloxifene therapy for osteoporosis" should have read "This represents 2576 women who received placebo and 5129 women who received raloxifene therapy for osteoporosis."

Incorrect Wording: In the Original Contribution entitled "Clinical and Angiographic Characteristics of Exertion-Related Acute Myocardial Infarction" published in the November 10, 1999, issue of THE JOURNAL (1999;282:1731-1736), there was incorrect wording in the last sentence of the "Results" section on pages 1732-1733. The sentence should read as follows: Patients with an exertion-related MI were more likely to have established coronary artery disease (CAD) risk factors including male sex, obesity, current cigarette smoking, and hyperlipidemia (TABLE 1), and were less likely to use aspirin or β-blockers and tended to have less hypertension ($P = .08$) and established cardiac disease ($P = .06$).

