The role of exercise testing for evaluating patients with unstable angina

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Exercise testing is used to assess the degree of demand that results in myocardial ischemia and the functional result of induced ischemia, thus providing physiologic data that complement the anatomic information available from coronary angiography. Exercise testing has been shown to be useful for evaluating patients with stable coronary artery disease. The results of an exercise test can be used to evaluate patients presenting with chest pain,[1] for estimation of the extent of disease and the prognosis,[1-4] or for determining the likelihood of benefit from surgical versus medical therapy.[1-6] With respect to acute coronary syndromes, many studies have evaluated the use of exercise testing following myocardial infarction.[7] This report reviews the role of exercise testing for evaluating patients with unstable angina.

Natural history and pathophysiology. Unstable angina embraces a spectrum of presentations, including new-onset angina, crescendo angina, and rest pain.[8,9] Patients with unstable angina have an increased incidence of myocardial infarction and mortality[10]; studies of patients with unstable angina who are treated with rest and minimal medication show a cardiac mortality of 8% to 10% and an incidence of nonfatal myocardial infarction of 12% to 14% over a 1-year follow-up.[11,12] In a 10-year prospective follow-up study of patients with unstable angina, Gazes et al.[13] noted an 82% 12-month survival and a 48% survival 120 months after diagnosis. The reported incidence of cardiac events associated with unstable angina varies as a function of the patient population studied[14]; patients presenting with rest pain have a particularly poor prognosis.[9]

Pathologic and angiographic evidence suggest that acute coronary syndromes most commonly occur as a consequence of a sudden decrease in myocardial oxygen supply resulting from plaque rupture and superimposed thrombosis.[15-22] Whether this plaque transformation results in Q wave myocardial infarction, non-Q wave myocardial infarction, or unstable angina is a function of factors such as the length of time of total occlusion (which may be affected by natural or pharmacologic thrombolysis) and the collateral supply to the jeopardized area.[17,18,20]

Angiography and unstable angina. Angiographic studies have shown that 90% of patients presenting with unstable angina have significant coronary artery obstruction in one or more coronary arteries; the distribution of lesions is similar to that seen in patients with chronic coronary disease.[23-25] Left main coronary disease has been reported to occur in from 4% to 20% of patients with unstable angina.[26] Patients presenting with crescendo angina or rest pain have a higher incidence of multivessel disease and left main coronary artery stenosis.[26,27]

Patients with unstable angina who continue to have pain or signs of myocardial ischemia despite medical therapy require cardiac catheterization and angioplasty or coronary artery bypass surgery should be considered.[28-30] However, most patients with unstable angina respond to medical therapy,[28] and some have questioned if these patients should undergo coronary angiography.[31]

The National Cooperative Study Group for Unstable Angina Pectoris[32] found no benefit for urgent coronary artery bypass surgery in patients stabilized on medical therapy, regardless of whether patients had one-, two-, or three-vessel disease. However, progressive symptoms occurred significantly more commonly in the medically treated group and 36% of the medical group crossed over to surgical therapy. Furthermore, patients with left main coronary disease were excluded from this study.[33]

One reason to perform angiography following medical stabilization would be to determine if the patient was in a subset that large multicenter trials of patients with chronic stable angina have identified as

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Table I. Exercise testing in patients with unstable angina who respond to medical therapy: Predictive value for adverse cardiac events over long-term follow-up

Study	*No.*	*Protocol*	*End point*	*Independent variable*	*SENS*	*SPEC*	*+PV*	*−PV*
Nixon[40]	55	Upright bicycle; exercise stopped for ECG changes, symptoms, or target heart rate	Severe angina, unstable angina	ECG changes	71%	70%	71%	70%
Butman[41]	125	Modified Naughton treadmill; exercise stopped for ECG changes, symptoms, or target heart rate	Severe angina, CABG, MI, death	ECG changes or chest pain	76%	85%	88%	71%
Swahn[42]	275	Upright bicycle; exercise stopped for symptoms (or target heart rate for non-Q MI, $n = 74$)	CABG, MI, death	ECG changes, limiting chest pain, or RPP <13,500	92%	70%	40%	98%
Wilcox[43]	107	Modified Naughton treadmill; exercise stopped for ECG changes or symptoms	Unstable angina, MI, death	ECG changes and RPP <18,000	38%	85%	48%	79%
				ECG changes and RPP <18,000, or ECG changes alone or RPP <18,000 alone	86%	32%	32%	86%
Brown[44]	52	Treadmill, Bruce symptom-limited	Unstable angina, MI, death	ECG changes	30%	80%	55%	59%
				Reversible thallium defect	70%	76%	70%	76%

SENS, Sensitivity; *SPEC*, specificity; *+PV*, positive predictive value; *−PV*, negative predictive value; *MI*, myocardial infarction; *non-Q MI*, non-Q wave myocardial infarction; *CABG*, coronary artery bypass grafting (surgery); *RPP*, rate-pressure product.

benefiting from revascularization.[33-37] Another reason to consider angiography in the medically responsive patient is the possibility of performing angioplasty.[38]

Studies of exercise testing and unstable angina. It would seem prudent to consider angiography in a significant percentage of patients with unstable angina,[14, 38, 39] particularly those presenting with rest pain or crescendo angina. Investigators have studied the use of exercise testing for further stratifying patients with unstable angina who respond to medical therapy to identify a subset most likely to benefit from angiography and subsequent revascularization (Table I).

Nixon et al.[40] performed upright bicycle exercise testing on 55 patients diagnosed with either new onset angina or crescendo angina who had stabilized on medical therapy. Exercise was stopped because of myocardial ischemia (either chest pain or significant ST changes) or upon the patient's attaining a target heart rate of 120 beats/min. There were no complications from exercise. The results showed that exercise-related chest pain or significant ST depression had a 71% positive predictive value and a 71% negative predictive value for the development of severe angina or recurrent unstable angina over the follow-up period (mean 18 weeks).

Butman et al.[41] performed submaximal exercise tests on 125 patients with unstable angina after a pain-free period on medications of at least 3 days; therapy included nitrates (85%), β-blockers (53%), and calcium antagonists (3%). Patients with congestive heart failure or myocardial infarction within the 3 months before admission were not included in the study. The test was discontinued for symptoms, significant ST depression, or upon the patient's reaching 70% of the predicted heart rate. There were no complications from exercise testing. In over 1 year of follow-up, 87% of patients with angina or more than 1 mm ST segment depression on the electrocardio-

Table II. Exercise testing in patients with unstable angina who respond to medical therapy: Predictive value for multivessel disease

Study	*No.*	*Protocol*	*End point*	*Independent variable*	*SENS*	*SPEC*	*+PV*	*−PV*
Butman[45]	78	Modified Naughton treadmill; exercise stopped for symptoms, ECG changes, or 70% pred. max. heart rate	Multivessel disease	ECG changes or angina	65%	85%	92%	57%
Freeman[46]	67	Bruce treadmill, symptom-limited	Multivessel disease	ECG changes or exercise <6 minutes	82%	66%	97%	73%
				Exercise <6 minutes and abnormal thallium	78%	100%	100%	62%

Pred max, Predicted maximum; other abbreviations as in Table I.

gram (ECG) had an unfavorable outcome (including unstable angina, myocardial infarction, or death) compared with 29% of the 65 patients with a negative test.

In a study of 400 patients with either unstable angina or non-Q wave myocardial infarction (which represented 26% of the study population) who responded to medical therapy, Swahn et al.[42] performed upright bicycle testing before hospital discharge. The test was stopped because of symptoms (or when the patient attained a maximal heart rate of 130 beats/min or a work load of 130 W in patients with non-Q wave myocardial infarction). There were no adverse effects from exercise testing. Over a 1-year follow-up, 45 of 114 men with limiting chest pain, more than 1 mm of ST segment depression associated with exercise, or a rate pressure product below 13,500 died, had a myocardial infarction, or required bypass surgery (positive predictive value 40%). In contrast, 98% of patients without these findings had a favorable outcome. There was no prognostic significance derived from exercise testing in women. The authors concluded that men with induced ischemia on exercise testing should be considered for coronary reperfusion.

Wilcox et al.[43] studied 107 patients who had unstable angina and no rest pain for 3 days after treatment with medical therapy, which included nitrates, calcium channel antagonists (58%), β-adrenergic blocking agents (50%), and aspirin (35%). The test was stopped because of angina or a strongly positive ECG. There were no complications. The data indicated that two exercise test variables—a positive exercise ECG and low rate-pressure product—were independent predictors of adverse outcome. Patients who had both exercise-related ST segment depression and a rate-pressure product below 18,000 had a 48% incidence of unstable angina, myocardial infarction, or death over 1 year of follow-up. In contrast, only 14% of patients with neither finding during exercise had an unfavorable outcome. Using a regression formula that included three clinical variables and two exercise variables, a low-risk group with a 5% risk could be identified.

In another study, Brown[44] found that thallium perfusion scanning along with symptom-limited exercise testing significantly improves the ability to identify high and low risk in patients with unstable angina who respond to medical therapy. The exercise ECG had a 55% positive predictive value and a 59% negative predictive value for a cardiac event (including unstable angina, nonfatal myocardial infarction, or cardiac death). In comparison, patients with reversible thallium defects had a 70% incidence of cardiac events over the mean 39-month follow-up period, while only 20% of patients with a normal scan had a cardiac event. Of particular note, only 1 of 29 patients without reversible thallium defects had either cardiac death or nonfatal myocardial infarction (MI).

Two studies have evaluated the use of exercise testing for predicting multivessel disease in patients with unstable angina who have responded to medical therapy (Table II). Butman et al.[45] reported that angina or significant ST changes associated with submaximal testing (target heart rate limited on Naugh-

ton protocol) following stabilization of unstable angina had a 92% positive predictive value and a 57% negative predictive value for multivessel disease. In another study, Freeman et al.[46] demonstrated that the addition of thallium imaging increased the ability to predict the extent of coronary artery disease. Symptom-limited treadmill exercise (standard Bruce protocol) was performed by 67 patients admitted with unstable angina who responded to medical therapy. No complications of exercise testing were noted. Exercise duration less than 6 minutes or a significant thallium defect (or both) was present in all patients with multivessel coronary artery disease, and neither was present in 18 of 29 patients with less severe coronary disease. The authors noted that more rigorous exercise improved sensitivity, and proposed that symptom-limited exercise testing be performed after medical stabilization.

These studies demonstrate that in selected patients exercise testing following presentation with unstable angina is a safe procedure. It is important to carefully select which patients are to be tested so as to minimize risk of exercise-related complications. A wide variety of exercise protocols was used in the studies mentioned above; the best protocol remains to be determined.

The data indicate that patients at increased risk for multivessel disease can be identified, and that patients can be stratified with respect to risk for cardiac events over long-term follow-up. Thus exercise testing of patients with unstable angina who respond to medical therapy may help identify patients who should be considered for angiography and patients who could initially be managed with medical therapy.

It is important to note that there are several variables influencing the predictive value of a test, including the testing protocol, the population tested, the parameters used for prediction, and the end point followed. Although the high negative predictive value in some studies indicates a very low risk for a certain cardiac event over long-term follow-up, the negative predictive values in other studies indicate that patients without certain exercise-related abnormalities may still be at significant risk for a cardiac event despite an apparent response to medical therapy. The addition of thallium perfusion scanning appears to significantly improve risk stratification, but there is limited information on this point. More studies are needed to determine the best method for noninvasive evaluation of patients presenting with unstable angina who respond to medical therapy.

In addition to potentially functioning as a screening test to determine which patients should have angiography, a role that should be considered is the use of exercise testing as an adjunct to angiography to further stratify stabilized patients once the anatomic extent of the disease is determined. Similar to the patients with stable coronary disease, the results of an exercise test may be used to identify high and low risk groups from among patients with an "equivalent" degree of coronary stenosis[47-51] and should help to identify patients with the greatest potential benefit from revascularization.

REFERENCES

1. American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Exercise Testing). Guidelines for exercise testing. J Am Coll Cardiol 1986;8:725-38.
2. Weiner DA. Exercise testing for the diagnosis and severity of coronary disease. J Cardiac Rehabil 1981;1:438-44.
3. Weiner DA, McCabe CH, Ryan TJ. Identification of patients with left main and three vessel coronary disease with clinical and exercise test variables. Am J Cardiol 1980;46:21-7.
4. Goldschlager N, Selzer A, Cohn K. Treadmill stress tests as indicators of presence and severity of coronary artery disease. Ann Intern Med 1976;85:277-86.
5. Weiner DA, Ryan TJ, McCabe CH, Chaitman BR, Sheffield LT, Fisher LD, Tristani F. Value of exercise testing in determining the risk classification and the response to coronary artery bypass grafting in three-vessel coronary artery disease: a report from the Coronary Artery Surgery Study (CASS) registry. Am J Cardiol 1987;60:262-6.
6. Weiner DA, Ryan TJ, McCabe CH, Chaitman BR, Sheffield LT, Fisher LD, Tristani F. The role of exercise testing in identifying patients with improved survival after coronary artery bypass surgery. J Am Coll Cardiol 1986;8:741-8.
7. O'Rourke RA. Noninvasive and invasive testing after myocardial infarction. Curr Probl Cardiol 1991;16:723-63.
8. Farhi JI, Cohen M, Fuster V. Broad spectrum of unstable angina pectoris and its implications for future controlled trials. Am J Cardiol 1986;58:547-50.
9. Bertolasi CA, Tronge JE, Mon GA, Turri D, Lugones MI. Clinical spectrum of "unstable angina". Clin Cardiol 1979; 2:113-20.
10. Cairns JA, Fantus IG, Klassen GA. Unstable angina pectoris. Am Heart J 1976;92:373-86.
11. Mulcahy R, Daly L, Graham I, Hickey N, O'Donoghue S, Owens A, Ruane P, Tobin G. Unstable angina: natural history and determinants of progress. Am J Cardiol 1981;48:525-8.
12. Mulcahy R, Hai Al Awadhi A, de Buitleor M, Tobin G, Johnson H, Contoy R. Natural history and prognosis of unstable angina. Am Heart J 1985;109:753-8.
13. Gazes PC, Mobley EM, Faris HM, Duncan RC, Humphries GB. Preinfarctional (unstable) angina—a prospective study—ten year follow-up. Prognostic significance of electrocardiographic changes. Circulation 1973;58:331-7.
14. Scanlon P. The intermediate coronary syndrome. Prog Cardiovasc Dis 1981;23:351-64.
15. Falk E. Morphologic features of unstable atherothrombotic plaques underlying acute coronary syndromes. Am J Cardiol 1989;63:114E-20E.
16. Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985;53:363-73.
17. Ambrose JA, Winters SL, Arora RR, Haft JI, Goldstein J, Rentrop KP, Gorlin R, Fuster V. Coronary angiographic morphology in myocardial infarction: a link between the pathogenesis of unstable angina and myocardial infarction. J Am Coll Cardiol 1985;6:1233-8.
18. Gorlin R, Fuster V, Ambrose JA. Anatomic-physiologic links between acute coronary syndromes. Circulation 1986;74:6-9.

19. Forrester JS, Litvack F, Grundfest W, Hickey A. A perspective of coronary disease seen through the arteries of living man. Circulation 1987;75:505-13.
20. Fuster V, Badimon L, Cohen M, Ambrose JA, Badimon JJ, Chesebro J. Insights into the pathogenesis of acute ischemic syndromes. Circulation 1988;77:1213-20.
21. Ambrose JA, Winters SL, Stern A, Eng A, Teichholz LE, Gorlin R, Fuster V. Angiographic morphology and the pathogenesis of unstable angina. J Am Coll Cardiol 1985;5:609-16.
22. Ambrose JA, Winters SL, Arora RR, Eng A, Riccio A, Gorlin R, Fuster V. Angiographic evolution of coronary artery morphology in unstable angina. J Am Coll Cardiol 1986;7:472-8.
23. Roberts WC, Virmani R. Quantification of coronary arterial narrowing in clinically-isolated unstable angina pectoris. An analysis of 22 necropsy patients. Am J Med 1979;67:792-9.
24. Alison HW, Russell RO, Mantle JA, Kouchoukos NT, Moraski RE, Rackley CE. Coronary anatomy and arteriography in patients with unstable angina pectoris. Am J Cardiol 1978;41: 204-9.
25. Fuster V, Frye RL, Connolly DC, Danielson MA, Elveback LR, Kurland LT. Arteriographic patterns early in the onset of the coronary syndromes. Br Heart J 1975;35:1250-5.
26. Plotnick GD, Greene HL, Carliner NH, Becker LC, Fisher ML. Clinical indicators of left main coronary artery disease in unstable angina. Ann Intern Med 1979;91:149-53.
27. Plotnick GD, Fisher ML, Carliner NH, Becker LC. Cardiac catheterization in patients with unstable angina. Recent onset vs crescendo pattern. JAMA 1980;244:574-6.
28. Plotnick GD. Approach to the management of unstable angina. AM HEART J 1979;98:243-55.
29. Faxon DP, Detre KM, McCabe CH, Fisher L, Holmes DR, Cowley MJ, Bourassa MG, Van Raden M, Ryan TJ. Role of percutaneous transluminal coronary angioplasty in the treatment of unstable angina. Report from the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty and Coronary Artery Surgery Study registries. Am J Cardiol 1983;53:131C-5C.
30. de Feyter PJ, Serruys PW, van den Brand M, Balakumaran K, Moghtar B, Soward AL, Arnold AER, Hugenholtz PG. Emergency coronary angioplasty in refractory unstable angina. N Engl J Med 1985;313:342-6.
31. Brown BG, Dodge HT. Unstable angina: guidelines for therapy based on the last decade of clinical observations. Ann Intern Med 1982;97:921-3.
32. Unstable Angina Pectoris Study Group. Unstable Angina Pectoris National Cooperative Study Group to Compare Surgical and Medical Therapy. II. In-Hospital experience and initial follow-up results in patients with one-, two-, and three-vessel disease. Am J Cardiol 1978;42:839-48.
33. Unstable Angina Pectoris Study Group. Unstable Angina Pectoris National Cooperative Study Group to Compare Medical and Surgical Therapy. I. A report of protocol and patient population. Am J Cardiol 1976;37:896-902.
34. The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eleven-year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina. N Engl J Med 1984;311:1333-9.
35. Varnauskas E, and the European Coronary Surgery Study Group. Twelve-year follow-up of survival in the Randomized European Coronary Surgery Study. N Engl J Med 1988; 319:332-7.
36. Alderman EL, Bourassa MG, Cohen LS, Davis KB, Kaiser GG, Killip T, Mock MB, Pettinger M, Robertson TL, for the CASS Investigators. Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. Circulation 1990;82:1629-46.
37. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Coronary Artery Bypass Graft Surgery). Guidelines and indications for coronary artery bypass graft surgery. J Am Coll Cardiol 1991;17:543-89.
38. Leeman DE, McCabe CH, Faxon DP, Lorell BH, Kellett MA, McKay RG, Varricchione T, Baim DS. Use of percutaneous transluminal coronary angioplasty and bypass surgery despite improved medical therapy for unstable angina pectoris. Am J Cardiol 1988;61:38G-44G.
39. ACC/AHA Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures. Guidelines for coronary angiography. J Am Coll Cardiol 1987;10:935-50.
40. Nixon JV, Hillert MC, Shapiro W, Smitherman TC. Submaximal exercise testing after unstable angina. AM HEART J 1980;99:772-8.
41. Butman SM, Olson HG, Gardin JM, Piters KM, Hullett M, Butman L. Submaximal exercise testing after stabilization of unstable angina pectoris. J Am Coll Cardiol 1984;4:667-73.
42. Swahn E, Areskog M, Berglund U, Walfridsson H, Walletin L. Predictive importance of clinical findings and a predischarge exercise test in patients with suspected unstable coronary artery disease. Am J Cardiol 1987;59:208-14.
43. Wilcox I, Freedman SB, Allman KC, Collins FL, Leitch JW, Kelly DT, Harris PJ. Prognostic significance of a predischarge exercise test in risk stratification after unstable angina pectoris. J Am Coll Cardiol 1991;18:677-83.
44. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging in patients with unstable angina who respond to medical treatment. J Am Coll Cardiol 1991;17:1053-7.
45. Butman SM, Olson HG, Butman LK. Early exercise testing after stabilization of unstable angina: correlation with coronary angiographic findings and subsequent cardiac events. AM HEART J 1986;111:11-8.
46. Freeman MR, Chisholm RJ, Armstrong PW. Usefulness of exercise electrocardiography and thallium scintigraphy in unstable angina pectoris in predicting the extent and severity of coronary artery disease. Am J Cardiol 1988;62:1164-70.
47. McNeer JF, Margolis JR, Lee KL, Kisslo JA, Peter RH, Kong Y, Behar VS, Wallace AG, McCants CB, Rosati RA. The role of the exercise test in the evaluation of patients for ischemic heart disease. Circulation 1978;57:64-70.
48. Kent KM, Rosing DR, Ewels CJ, Lipson L, Bonow R, Epstein SE. Prognosis of asymptomatic or mildly symptomatic patients with coronary artery disease. Am J Cardiol 1982;49:1823-31.
49. Gohlke H, Samek L, Betz P, Roskamm H. Exercise testing provides additional prognostic information in angiographically defined subgroups of patients with coronary artery disease. Circulation 1983;68:979-85.
50. Weiner DA, McCabe CH, Ryan TJ. Prognostic assessment of patients with coronary artery disease by exercise testing. AM HEART J 1983;105:749-55.
51. Bonow RO, Kent KM, Rosing DR, Lan KKG, Lakatos E, Borer JS, Bacharach SL, Green MV, Epstein SE. Exercise-induced ischemia in mildly symptomatic patients with coronary artery disease and perserved left ventricular function. Identification of subgroups at risk of death during medical therapy. N Engl J Med 1984;311:1339-45.