

Early exercise testing to stratify risk for development of restenosis after percutaneous transluminal coronary angioplasty

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Restenosis after percutaneous transluminal coronary angioplasty (PTCA) usually occurs 3 to 6 months after the procedure.¹⁻³ The process underlying restenosis is believed to involve elastic recoil; platelet accumulation and thrombus formation; release of platelet-derived growth factors; and fibrocellular migration and proliferation.⁴⁻⁹ Smooth-muscle proliferation may occur as early as several days to weeks after PTCA.^{10, 11} Thus, to identify effectively an increased risk for restenosis, a marker must be present and recognizable early after the procedure. Studies have shown that clinical and angiographic variables (recent onset angina, unstable angina, coronary spasm, anatomic location, nonacute total occlusions, balloon size, pressure used for inflation, and intimal dissections) may be used to identify an increased risk for restenosis.¹² However, no variable that reliably stratifies risk has been determined.^{8, 13}

Early exercise testing after PTCA has been shown to be safe,¹⁴⁻¹⁶ but the value of the results for prediction of later restenosis is variable.¹⁷ This article evaluates questions about exercise performed early after PTCA as a method for stratifying risk for restenosis.

USE OF STANDARD EXERCISE ELECTROCARDIOGRAPHY FOR PREDICTING RESTENOSIS

El-Tamimi et al.¹⁴ performed sequential post-PTCA exercise tests beginning 3 days after the pro-

cedure and angiography at 6 months in 31 patients with single-vessel disease who had undergone PTCA. Among the 14 patients with an abnormal result on exercise testing at 3 days, 11 were found to have angiographic restenosis at follow-up (positive predictive value of 78.5%). Among the 17 patients with a negative result on early exercise testing, 3 had restenosis on follow-up angiography (negative predictive value of 82%). In contrast, Wijns et al.¹⁶ performed exercise tests 4 weeks after PTCA with angiographic follow-up within 6 months and found that the standard exercise test had a positive predictive value of 54% and negative predictive value of 63% for restenosis.

De la Morena¹⁵ performed exercise tests 2 to 4 days after PTCA in 51 patients with single-vessel disease and 24 patients with multivessel disease who had undergone single-vessel PTCA; angiograms were performed within 1 to 8 weeks in patients with an abnormal exercise-test result. In patients with single-vessel disease, 7 of 10 patients with an abnormal post-PTCA exercise-test result early after the procedure had >70% stenosis on the follow-up angiogram. In comparison, among patients with multivessel disease, 0 of 8 patients with an abnormal result on the early post-PTCA exercise test had restenosis. Thus the positive predictive value for restenosis of an abnormal result on the exercise test in patients with single-vessel disease in this study was 70%, whereas an abnormal result had no predictive value for restenosis in patients with multivessel disease; the negative predictive value of exercise testing could not be determined from this study because patients with a negative exercise-test result did not have angiography. Given these observations it is noteworthy that a study by Deligonul et al. of the prognostic value of early post-PTCA exercise testing showed that abnormal findings on the exercise electrocardiogram was associated with an increased risk of cardiac events in patients with

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multivessel disease but not in patients with single-vessel disease.¹⁸

EXERCISE-GATED RADIONUCLIDE VENTRICULOGRAPHY

Exercise-gated radionuclide ventriculography after successful PTCA usually shows an exercise-related increase in left ventricular ejection fraction.^{19, 20} However, factors such as cardiomyopathy, previous myocardial infarction, and submaximal exercise may result in a lack of exercise-related increase in ejection fraction despite a good PTCA result.¹⁹

In a study by DePuey et al.,²¹ patients had exercise-gated radionuclide ventriculography within 4 days of PTCA and returned for follow-up angiography. Patients with an abnormal response (defined as <5-point increase in ejection fraction or a deterioration in wall motion in response to exercise) had a higher degree of angiographic restenosis than patients with a normal response; 75% of patients with $\geq 50\%$ restenosis had had abnormal findings, compared with 18% of patients with $\leq 20\%$ restenosis. This result showed the predictive accuracy of this test immediately after PTCA to be 73%, and this test was a better predictor of restenosis than recurrence of symptoms, angina, or exercise-induced changes in the electrocardiogram. O'Keefe et al.²² performed exercise radionuclide ventriculograms within 1 month of PTCA and also found that a normal result identified a very low risk for future restenosis.

EXERCISE THALLIUM TESTING

Exercise thallium testing is often performed after PTCA to evaluate the adequacy of revascularization.^{17, 19, 23} In addition, studies have shown that early exercise thallium testing is predictive of restenosis.^{16, 17, 24, 25} Breisblatt et al.²⁵ performed early post-PTCA exercise thallium testing and showed that an abnormal result on thallium scanning at 4 to 6 weeks was highly predictive of future restenosis; 86% of asymptomatic patients with abnormal findings on exercise thallium scanning 4 to 6 weeks after PTCA became symptomatic and were found to have restenosis by 6 months after PTCA. Wijns et al.^{16, 24} found that patients with an abnormal early post-PTCA exercise thallium scan result (5 weeks after the procedure) had a high likelihood of restenosis and that patients with a normal early post-PTCA exercise thallium scan result had a low likelihood for development of restenosis, regardless of whether exercise-related electrocardiographic changes were present. The authors noted that the improved predictive value of thallium scanning may be related to

the greater sensitivity of the test as detector of a pathophysiologic process (such as fibrocellular proliferation) that has not led to sufficient stenosis to result in exercise-related changes in the electrocardiogram but that has led to sufficient abnormality in coronary flow reserve to result in abnormalities on the perfusion scan.

These studies indicate that patients with an early post-PTCA abnormality on thallium scanning are at high risk for development of restenosis and should be observed closely. However, the timing of early post-PTCA exercise thallium scanning is important. Thallium scan abnormalities very early after PTCA (within the first 2 weeks after the procedure) may be transient.¹⁹ For example, Manyari et al.²⁶ found that 12 (28%) of 42 patients had an abnormal scan result 9 days after PTCA, but all exercise-related perfusion scans subsequently normalized at 2 to 4 months. In the Breisblatt et al.²⁵ study, 4 of 7 patients who had an abnormal scan result 1 to 2 weeks after PTCA were found to have a normal scan result at 4 to 6 weeks. Given the findings of these studies, diagnostic evaluation with exercise thallium testing should probably not be done before 4 to 6 weeks after PTCA.

COMMENTS

Restenosis remains a major limiting factor after PTCA. Estimates of the prevalence of restenosis vary widely^{9, 13} and are complicated by the definition of the end point, restenosis, by varying angiographic criteria. Criteria for restenosis that have been used include an increase of $\geq 30\%$ from the immediate post-PTCA stenosis to the follow-up PTCA stenosis; an immediate post-PTCA stenosis of $< 50\%$ that increases to $\geq 70\%$ at follow-up; an increase in stenosis at follow-up to $\leq 10\%$ below predilatation stenosis; and a loss of $\geq 50\%$ of the gain achieved at PTCA.^{2, 3, 9, 12} The varying definition of restenosis influences the evaluation of sensitivity, specificity, and predictive value of functional tests such as exercise testing among studies.

Besides the problem associated with a lack of a uniform definition for restenosis, the results of studies that stratify risk for restenosis are influenced by the method by which restenosis is evaluated. Patients may have angiographic restenosis without symptoms^{8, 27, 28}; in a series of 557 patients, Holmes et al.³ found that 24% of patients who had angiographic restenosis did not have clinical restenosis. Whether a study includes restenosis determined as the result of mandatory follow-up angiography (which would include asymptomatic restenosis) or includes only restenosis detected after angiography performed because of clinical indications (such as

recurrent chest pain) affects the properties of the test (i.e., sensitivity, specificity, predictive value) and the derived implications of the test for clinical practice. Thus conclusions from a post-PTCA exercise study that includes angiography only for clinical indications (e.g., recurrent chest pain) are limited to this symptomatic group, whereas studies that include mandatory angiography can be generalized to the predictive value for restenosis in general. Another factor to consider is the timing of testing; some studies include very early testing (a few days to 2 weeks), whereas others denote early testing as 4 to 6 weeks after the procedure.

An abnormal result on exercise testing after PTCA indicates an imbalance in coronary flow reserve. This condition can result from fixed disease or from fixed disease or from a dynamic abnormality such as coronary artery spasm. In the absence of a coronary angiogram to follow up the postprocedure exercise test it is not possible to exclude definitively the possibility that a patient with an abnormal early post-PTCA exercise test already has anatomic restenosis, although this diagnosis is unlikely in the majority of cases.¹ An abnormal result on post-PTCA exercise testing may result from procedure-related changes in coronary flow reserve^{29,30} or may be related to small-vessel disease or dynamic vasoreactivity.^{31,32} These functional abnormalities may then contribute to the pathophysiologic processes involved in restenosis. This concept is supported by the work of Hardoff et al.,³³ who showed that reversible thallium-test defects associated with atrial pacing 12 to 24 hours post-PTCA identify a high risk for the development of restenosis 6 to 12 months later.

The question as to whether post-PTCA exercise testing should be part of routine follow-up remains unanswered, and the best method for testing remains undetermined. Two factors need to be considered when deciding whether to use exercise testing as part of routine follow-up post-PTCA to stratify risk for restenosis. First, restenosis rarely presents as a cardiac emergency (i.e., sudden death or myocardial infarction).³⁴ Thus identification of high risk for restenosis does not identify a risk for an acute cardiac event. Second, currently there is no treatment that could be targeted for use in a high-risk group to prevent restenosis. This situation raises the question as to the usefulness of identifying a high risk.

If exercise testing is to be done, the initial postprocedure exercise test should be delayed for 4 to 6 weeks after the PTCA. It seems advisable to do an imaging test, such as thallium scanning, with the exercise test, particularly for patients with multi-

vessel disease. At least, a negative test result provides a useful baseline for comparison with a subsequent test and provides information about functional capacity. An abnormal test result indicates the patient may be at increased risk for restenosis and therefore may need closer clinical follow-up. The results of each test need to be individualized for the presence of multivessel disease.

The best method for approaching the problem of restenosis after angioplasty will change with rapid advancements in the technique. The use of intracoronary stents has been shown to lower the risk of restenosis significantly,³⁵⁻³⁷ and further refinements of the technique will have additional effect on the incidence of recurrence. Future areas of study include the use of exercise testing to examine patients after stent deployment and the use of techniques such as exercise echocardiography for postprocedure evaluation.

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