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Limitations of the exercise test as a screen for acute cardiac events in asymptomatic patients

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Acute cardiac events such as myocardial infarction or sudden death affect hundreds of thousands of patients each year, and may be the initial manifestation of coronary artery disease. This has prompted efforts to screen asymptomatic subjects in an effort to identify the presence of disease before the occurrence of a serious problem. The exercise test is frequently used for this purpose.[1] However, major limitations have been noted when the exercise test is used in an asymptomatic population, including a large number of abnormal tests that represent false positive results, and failure to identify the majority of patients who have serious cardiac events (including myocardial infarction and sudden death) over a long-term follow-up.[2, 3]

Any test of a group with a low pre-test probability of disease—such as asymptomatic patients with no risk factors for coronary disease—results in a large number of false positive responses that lower the predictive value of a positive test.[4] This has been discussed in detail in the literature,[3-5] and will not be considered further here.

Failure to identify patients who have acute cardiac events is a more serious limitation for a screening test. A study by McHenry et al.[6] involving long-term follow-up after a screening exercise test in 908 asymptomatic men, illustrates the magnitude of the problem. The absolute number of patients with acute cardiac events in the group of 833 patients with a

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negative stress test (25 myocardial infarctions and seven sudden deaths) far exceeded the number of acute events seen in the group of 75 patients with a positive exercise test (one myocardial infarction/ one death). The patients with a positive stress test had a higher risk for sudden death than the patients with a negative stress test (1.4% versus .8%), but more patients in the negative stress test group actually experienced sudden death. Similarly, Epstein and Maron[7] demonstrated that a screening program that used exercise testing and risk factor evaluation would miss the majority of patients who will actually have clinical manifestations of disease. This paper examines the pathophysiology of acute cardiac events to determine why the exercise test fails to detect patients who have myocardial infarction and sudden death, and discusses implications for screening and primary prevention.

Pathophysiology. The electrocardiographic exercise test is designed to detect ischemia resulting from an imbalance of myocardial oxygen supply and demand during exercise. This usually occurs secondary to a flow-limiting obstruction in a coronary artery. Failure of an exercise test to identify a patient at risk for an acute cardiac event may result from failure to perform adequate exercise or from inadequate sensitivity of the test to detect ischemia.[3] However, there are several lines of investigation that suggest that many victims of sudden death or myocardial infarction may not have had antecedent flow-limiting coronary artery stenosis,[8-14] and that acute coronary syndromes develop secondary to an active process that can rapidly change a nonocclusive stenosis to one associated with total obstruction.[12, 15-17] Thus the mechanism responsible for the screening exercise test's failure to show signs of myocardial ischemia may be that at the time of the test there was no "critical" obstruction present.

Clinical-pathologic correlations. Davies and Thomas[12] found that patients who died within 6 hours of acute coronary ischemia showed evidence of an acute coronary lesion (either intraluminal thrombus or plaque fissuring) in 95 of 100 autopsies; 74 of 95 had plaque disruption with overlying occlusive thrombosis. Levin and Fallon[18] compared the histologic appearance of atherosclerotic plaques in patients dying of myocardial infarction evaluated by postmortem angiography or in those undergoing coronary bypass surgery and found that complicated coronary lesions (characterized by plaque rupture, plaque hemorrhage, superimposed partially occluding thrombus, or recanalized thrombus) resulted in a characteristic angiographic morphology that included irregular borders and intraluminal lucencies. Extending these observations, Ambrose et al. showed that patients with unstable angina[19] and acute myocardial infarction[20] frequently had angiographic evidence of a complicated coronary lesion.

Plaque rupture is an unpredictable event, probably resulting from the effects of various forces (including wall shear stress, coronary spasm, etc.) on a fragile atherosclerotic plaque.[17] The disrupted plaque exposes collagen and other factors to the blood, which promotes platelet adhesion and aggregation. In addition, plaque rupture results in the release of tissue factor, which initiates the coagulation cascade and leads to the generation of thrombin and fibrin; this further induces platelet aggregation and thrombosis. The final result is that a nonocclusive plaque (which itself would not lead to an abnormal exercise test) may be transformed by overlying thrombus into a severe occlusion. This may lead to sudden death, particularly in the absence of collaterals.[21]

Sequential angiographic studies: nonlinear progression of atherosclerosis. The concept that acute cardiac syndromes occur secondary to sudden change in plaque morphology is supported by sequential angiographic studies which demonstrate that atherosclerosis may show a nonlinear progression. Ambrose et al.[8] showed that patients with unstable angina frequently demonstrated angiographic signs of sudden progression from a previously insignificant lesion or a normal-appearing artery. A subsequent study demonstrated that myocardial infarction, particularly Q wave myocardial infarction, frequently develops from a previously nonsevere lesion.[10] Little et al.[11] showed that in 28 of 29 cases myocardial infarction occurred secondary to new occlusion of a site previously demonstrated to have less than a 70% stenosis; 19 of 29 had shown progression from a site having less than 50% stenosis. In addition, in two thirds of the patients, myocardial infarction did not occur secondary to occlusion of the previously patent artery with the most severe stenosis.

Thrombolysis studies. The importance of mild to moderately stenotic plaques leading to acute myocardial infarction is also evident from the results of reperfusion trials.[9, 13, 14] Hackett et al.[13] noted a residual stenosis of less than 60% obstruction in 28 of 60 patients. Studies by Brown et al.[9] and Serruys et al.[14] show that mild to moderate stenosis may underlie acute thrombotic occlusion, and in addition their studies demonstrate that residual thrombus partially accounts for the stenotic lesion seen on early post-thrombolysis catheterization. Thus the degree of obstruction secondary to the atherosclerotic lesion may be less severe than is reported in some thrombolysis studies.

Implications for screening and primary prevention. The fact that acute coronary syndromes may result from acute change in a nonocclusive plaque, leading to sudden reduction in coronary blood flow, explains the limited effectiveness of the exercise test when used as a screening test in asymptomatic patients. In addition, it has implications for strategies to develop better screening techniques and for primary prevention. For example, would techniques more sensitive to the presence of coronary artery lesions than the electrocardiogram be useful for screening? Hakki et al.[22] noted that 75% of patients with false negative electrocardiographic stress tests had abnormal thallium scans. However, since rupture of an atherosclerotic plaque that may previously have been of insufficiently high profile to result in an abnormal thallium scan appears to be the predominant mechanism initiating acute ischemic syndromes, thallium scanning would be predicted to offer limited improvement in our ability to identify patients at risk for sudden death.

Newer techniques may further improve our ability to detect atherosclerotic plaque,[23, 24] but they would also be of questionable utility unless therapy that effectively interrupts the cascade associated with rapid evolution of the arterial lesion is developed.[16, 17] Current attempts at primary prevention are centered on interruption of the thrombotic component with antiplatelet agents.[25-27] In the future, modification of the lipid component of atherosclerotic plaque[28, 29] may provide a means for preventing acute coronary syndromes.

Conclusions. Sudden cardiac death frequently results from an acute arterial process that may transform a non-flow-limiting stenosis into a total occlusion. This explains why techniques relying on demonstrating myocardial ischemia or flow heterogeneity, such as exercise testing, fail to identify many patients who experience sudden death. Effective screening for a high-risk population and primary prevention of sudden death depend upon developing diagnostic techniques that detect nonocclusive lesions, along with therapy that interrupts the cascade associated with acute occlusion.

Summary. The exercise stress test has been shown to have limited effectiveness when used to screen asymptomatic patients at risk for acute cardiac events, failing to detect many patients who have sudden death or myocardial infarction over long-term follow-up. The explanation may be found in studies that show that acute cardiac events frequently occur secondary to rapid transformation of an atherosclerotic lesion (secondary to plaque rupture and thrombosis), which may change a previously "non-critical" lesion into a total occlusion. Furthermore, the risk of plaque disruption may not be related to the preexisting severity of coronary artery stenosis, making it difficult to screen patients with techniques such as exercise stress testing, which rely on demonstrating myocardial ischemia or flow heterogeneity resulting from a flow-limiting lesion. Effective reduction in the incidence of sudden death will depend upon the development of diagnostic techniques that are sensitive to the presence of nonocclusive (as well as occlusive) coronary lesions and upon treatment that will prevent the cascade associated with rapid arterial occlusion.

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