Exercise-Induced Myocardial Ischemia

Importance of Coronary Blood Flow

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The onset of ischemia is thought to occur when myocardial oxygen demand exceeds supply. In an individual patient the ischemic threshold might be a reproducible measure that could be used in the short term to establish the efficacy of therapy. In clinical studies the operational definition of the onset of ischemia has been 0.1 mV of ST depression on the electrocardiogram. In earlier investigations it was assumed that coronary supply was relatively fixed in patients with chronic ischemic heart disease and that changes in the onset of ischemia during exercise were mainly determined by changes in demand. Traditionally demand has been estimated by heart rate or the rate-pressure product. Clinical investigations have shown relatively constant rate-pressure products at the time of onset of ischemic ST segment changes; these observations confirmed the theory that supply was relatively fixed and explained the efficacy of agents that lowered demand, such as β-blockers. However, in individual patients the test-to-test variability of rate-pressure product at the time of ischemia onset may be great.

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When drugs with coronary vasodilation potential were administered during exercise testing, a different relation between demand and ischemic threshold was noted. For example, if rate-pressure product was plotted on the abscissa and the amount of ST depression on the ordinate, after diltiazem administration the curve was displaced downward so that at any given rate-pressure product there was less ST depression. These data support the concept that in addition to producing changes in demand, calcium-channel blockers increase coronary blood flow. β-Blockers were not observed to have this effect. Also, there is evidence to suggest that there are spontaneous changes in coronary tone in some patients with ischemic heart disease, which might also alter the relation between demand and ischemic threshold. Therefore, measures of myocardial oxygen demand may not be good markers of ischemia threshold. Are there good markers of coronary blood supply during exercise?

Experimental studies have suggested that the majority of coronary blood flow occurs during diastole and that decreases in diastolic coronary flow time reduce coronary blood flow. A group of investigators in Naples, Italy, noted that patients with syndrome X (symptomatic ischemia with normal epicardial coronary arteries) had reduced diastolic times during exercise compared with controls even when diastole was normalized for heart rate. They hypothesized that the reduced diastolic time resulted in decreased subendocardial blood flow and contributed to the development of ischemia. To explore this hypothesis further they performed another study reported in this issue of Circulation (Ferro et al). In this investigation, measures from serial exercise studies in patients with ischemic heart disease were evaluated for variability by testing the consistency of these measures at the electrocardiographically designated onset of ischemia. Diastolic perfusion time at 0.1 mV of ST depression, determined by polygraphic recordings, varied the least compared with heart rate, rate-pressure product, and exercise duration. These data suggest that diastolic perfusion time is an excellent measure of myocardial oxygen supply, which may be the most important determinant of myocardial ischemia.

Other studies have supported this concept. Guth et al demonstrated in a conscious canine chronic myocardial ischemia model that the mechanism of improvement of exercise ischemia and wall motion abnormalities by β-blockers was an increase in subendocardial blood flow produced by reduced heart rate. A subsequent study, from the same laboratory, by Indolfi et al confirmed these results using a specific non-β-blocker heart-rate-reducing drug (UL-FS 49) in a swine acute ischemia model. They found that abrupt decreases in heart rate during ischemia caused a major augmentation in contractile function associated with increases in subendocardial blood flow per minute and per beat. Although decreases in subendocardial oxygen demand due to bradycardia undoubtedly played a role, it is unlikely that the marked increase in contractile function observed during bradycardia reduced oxygen demand

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significantly. These observations have redirected our thinking about the mechanisms of exercise-induced myocardial ischemia.

Thus, it appears that subendocardial blood flow rather than oxygen demand may be the major determinant of exercise-induced myocardial ischemia. In fact, because diastolic time is related to heart rate, the relation between heart rate and ischemic threshold during exercise may be explained by reductions in diastolic time as heart rate increases. Interestingly, Ferro et al.⁹ had shown earlier that diastolic time correlates with heart rate at rest in normal subjects and in patients with chronic coronary artery disease, but only in the latter patients during exercise. Also, diastolic time is shorter during exercise in coronary patients. These data may explain the close relation of heart rate to ischemic threshold observed during exercise in patients with chronic coronary artery disease.

Although these results are interesting with regard to the mechanism of exercise ischemia and the effects of pharmacological agents, polycardiography during exercise is probably not going to become widely used clinically. In fact, Ferro et al.⁶ rejected the data from 17% of their patients because of inadequate recordings. Diastolic time was measured by Ferro et al as the RR interval minus the systolic ejection period as determined by phonocardiography. Aortic Doppler recording, which has a 95% success rate, could be substituted for phonocardiography in the determination of systolic ejection period. However, Doppler recording includes isovolumic systole, during which there is probably little coronary flow. In addition, isovolumic systole may be longer in ischemic heart disease patients. Diastolic time can also be measured by mitral valve Doppler blood flow recordings during exercise, but this determination excludes isovolumic diastole, when coronary blood flow may be at its highest. Thus, a better noninvasive measure of diastolic coronary perfusion time during exercise is needed.

Ultimately, a technique for directly measuring subendocardial blood flow in exercising humans may be the most reliable method of estimating the ischemic threshold.¹⁰ Current radionuclide perfusion imaging techniques do not achieve this goal. Perhaps contrast echocardiography could detect reductions in subendocardial flow during exercise, but currently an intracoronary injection is needed for optimal imaging. Therefore, until better technology is developed, we will have to continue to use heart rate to estimate myocardial oxygen demand, realizing that it is a measure of exercise ischemic perfusion time and subendocardial blood flow as well.

References


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