Antianginal medications and diagnostic accuracy of myocardial perfusion imaging

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The effect of antianginal drugs on myocardial perfusion imaging (MPI) has been hotly contested since the technique was first developed.[1,2] In this issue of the *Journal*, Bøttcher et al[3] have added to the continuing debate by comparing myocardial blood flow, measured by positron emission tomography (PET), in areas subtended by atherosclerotic arteries in patients receiving different anti-ischemic agents. In particular, they assessed the attenuation in dipyridamole-induced hyperemic flow resulting from various anti-ischemic agents. The effect of nitroglycerin (NTG) was to increase flow in both stenosed and nonstenosed areas of myocardium. Metoprolol reduced both resting and hyperemic flow in all areas of the myocardium. Amlodipine did not affect resting or hyperemic flow in areas of myocardium subtended by either stenosed or nonstenosed coronary arteries. This reduction in myocardial blood flow with certain anti-ischemic agents has led investigators to conclude that β-blockers may reduce diagnostic sensitivity in the setting of MPI with vasodilator stress. Although this study was performed using PET, by far the greatest clinical use of MPI is with single photon emission computed tomography (SPECT).

In the pharmaceutical armamentarium there are many commonly prescribed agents with varying therapeutic effects on myocardial ischemia. The current list runs to β-blockers, calcium channel blockers, nitrates, potassium channel activators (nicorandil), and newer agents such as fatty acid oxidase inhibitors (ranolazine).[4] β-Blockers and certain calcium channel blockers (diltiazem and verapamil)[5] exert much of their antianginal effect by reducing heart rate, thereby decreasing myocardial oxygen demand. Calcium channel blockers (eg, amlodipine) and nitrates[6,7] act mainly by producing vasodilatation and afterload reduction. Calcium channel blockers also have a direct effect on the ischemic myocyte. Nicorandil has a nitrate-like action and also inhibits calcium entry into myocytes via the activation of potassium efflux, resulting in arteriolar and venous dilatation. Ranolazine is a new directly acting anti-ischemic agent that does not affect heart rate or blood pressure and has no negative inotropic effect.

In those with significant obstructive coronary artery disease (CAD), dynamic exercise produces a supply-demand mismatch with subsequent ST-segment depression, the hallmark of myocardial ischemia. All of the drugs mentioned above have a potent effect on increasing exercise capacity[8] and reducing both anginal attacks and the magnitude of ST-segment depression.[9-11] These changes may be brought about by a myriad of pharmacologic effects. It is likely that these agents, at adequate doses, will reduce angina and the total ischemic burden during exercise treadmill testing. Anti-ischemic drugs may blunt this flow heterogeneity but are unlikely to reduce the magnitude of flow difference between regions supplied by diseased and non–flow-limiting vessels. Therefore it is not surprising that the total ischemic burden will be reduced. Exercise MPI may therefore fail to induce flow differences and thus fail to detect or underestimate the extent of underlying CAD.

However, many patients undergo pharmacologic MPI because of inadequate levels of exercise stress, usually attenuated by physical disability, chronic respiratory disease, chronotropic incompetence, or rate-slowing drugs. In these situations vasodilator stress (dipyridamole or adenosine) is used. Vasodilators do not usually induce ischemia per se; however, coronary flow increases 3 to 5 times above baseline levels, which is higher than that achieved with dynamic exercise.[12] Nevertheless, the supply-demand mismatch inherent in exercise stress will not be present during vasodilator stress. Because β-blockers mainly work through attenuation of heart rate response, conventional thought leads us to believe that flow heterogeneity resulting from vasodilator stress should not be affected by concurrent use of these agents.

Another proposed indicator of ischemic risk[13]—exercise-induced left ventricular (LV) chamber dilatation—is usually not detected by the use of solitary

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vasodilator stress. LV chamber dilation is a recognized phenomenon at peak stress with dobutamine echocardiography[14] and more recently with post-stress gated technetium 99m SPECT.[15] Therefore dipyridamole and adenosine do not mimic exercise stress in terms of flow mismatch and chamber dilation. Vasodilators are thus disadvantaged by the lack of functional data (exercise time and ST-segment changes) and by the rarity of ischemia-induced LV volume changes. Because of the multiple pharmacologic effects of dobutamine, one has to consider that various anti-ischemic drugs will also affect this stress modality.

The overall annual cardiac mortality rate for patients with a normal SPECT study is well established at less than 1% for exercise MPI.[16-20] However, for vasodilator stress, outcome studies seem to suggest a slightly higher overall cardiac mortality rate for a normal scan.[21-25] The results from the well-designed study of Bøttcher et al[3] suggest that metoprolol reduces resting and dipyridamole-induced hyperemic myocardial blood flow. This has significant implications for the withdrawal of β-blockers and other rate-limiting compounds before stress testing, as well as documenting the use of these drugs on any MPI report produced by a nuclear cardiology laboratory. There is understandable clinical unease among the cardiology community in withdrawing β-blockers before stress testing, especially if withdrawn too abruptly.[26]

When MPI is performed for prognostic reasons (eg, after myocardial infarction,[27] success of revascularization, and heart failure), it is probably appropriate to study these patients while undergoing maximal medical therapy, because the scan outcome will provide a clinically relevant diagnosis. In contrast, when MPI is used to provide or confirm a diagnosis of obstructive CAD in those with an intermediate pretest likelihood, then it will be prudent to discontinue β-blockers, diltiazem, and verapamil for at least 3 to 5 half-lives before stress testing so that an adequate heart rate response is obtained.

The study from Bøttcher et al[3] clearly confirms the original work by Brown et al[28] demonstrating that diseased and normal coronary arteries and arterioles both dilate with NTG. Nitrates have a clear and important use in clinical cardiology and perfusion imaging, especially in augmenting flow in hibernating myocardium to assess viability.[29] As mentioned previously, nitrates dilate epicardial coronary arteries and arterioles and decrease LV preload and afterload, decreasing subendocardial compression and improving subendocardial perfusion. This would increase delivery of tracer in low-flow states, reducing total ischemic burden, which is disadvantageous in the diagnosis of obstructive CAD. Clearly, nitrates, especially NTG, can be safely reduced in most cases; because the drug has a relatively short half-life, a 24-hour nitrate-free period should suffice. However, it is imperative that a well-constructed and large-scale prospective study is designed to assess fully the implications of antianginal drugs and MPI. In the meantime we should revisit this area in our own practice and probably withdraw rate-slowing anti-ischemic drugs in patients referred for diagnostic testing but maintain these drugs when testing patients for prognosis. Meanwhile, the debate continues.

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