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EDITORIAL

Exercise-Dipyridamole Myocardial Perfusion Imaging: The Circle Is Now Complete

The use of vasodilator pharmacologic stress as an adjunct for myocardial perfusion imaging has grown steadily, particularly since FDA approval of the intravenous preparation of dipyridamole. It allows a broader application of a now time-tested approach to evaluating patients with coronary heart disease who are unable to exercise optimally. A growing number of studies have demonstrated that vasodilator pharmacologic-stress myocardial perfusion imaging has comparable value to exercise perfusion imaging for the diagnosis of coronary artery disease as well as for risk stratification across a wide clinical spectrum of patients (*1,2*).

However, along with this increasing use has come recognition of drawbacks and limitations of this approach:

1. *Increased Splanchnic Uptake of Tracer.* Resting dipyridamole-myocardial perfusion imaging is associated with substantial uptake of ^{201}Tl in the liver, spleen and gut which, because of their close proximity to the heart, can confound image interpretation. This phenomenon is particularly problematic with planar imaging where overlap on the inferior wall commonly occurs. However, adjacent, intense uptake of ^{201}Tl can cause difficulty with SPECT imaging as well. Even modest levels of exercise can substantially decrease splanchnic blood flow and, consequently, uptake of ^{201}Tl, which can improve image quality and ease of interpretation. Splanchnic uptake, particularly in the liver, tends to be greater with ^{99m}Tc-sestamibi and although it diminishes with exercise it can remain problematic, especially with planar imaging.
2. *Inability to Evaluate Efficacy of Medications.* One of the drawbacks of vasodilator pharmacologic-stress myocardial perfusion imaging is that any ameliorating effects of anti-anginal medications cannot be evaluated in patients with coronary artery disease because coronary hyperemia is induced independent of myocardial oxygen demand. With exercise myocardial perfusion imaging, anti-anginal medications can blunt the hemodynamic response to exercise and reduce or eliminate stress-induced hypoperfusion. It has become common practice to evaluate the potential efficacy of medications in patients with known coronary artery disease by using symptom-limited exercise myocardial perfusion imag-

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ing. There is recent evidence that normal myocardial perfusion in patients taking anti-anginal medications, even with known anatomic coronary disease, predicts a very benign prognosis (*4,5*). Anti-anginal medications would be expected to have no impact on vasodilator pharmacologic-stress myocardial perfusion imaging since they do not interfere with vasodilator-induced coronary hyperemia. Thus, the efficacy of anti-anginal medications cannot be evaluated with this approach.

3. *Lack of Exercise Data.* In addition to data regarding regional uptake of myocardial tracers, exercise studies provide information regarding exercise capacity, heart rate and blood pressure response to exercise and development of provokable symptoms such as chest pain and shortness of breath. Such data have important clinical implications of their own, independent of the myocardial perfusion data, and are not available with pharmacologic stress.
4. *Side Effects.* As the use of vasodilator pharmacologic stress studies increased, it became apparent that such an approach had its own set of adverse effects (*5*). Hypotension, headache, dizziness, nausea and chest pain were all recognized as potentially inducible by dipyridamole or adenosine. However, from a practical perspective, these adverse effects are rarely a significant clinical problem because of the very short half-life of adenosine and because of the efficacy of theophylline as an antidote for dipyridamole (which also has a lower adverse effect rate).

Combining exercise with vasodilator pharmacologic stress has become increasingly recognized as a way to overcome some of the shortfalls of using vasodilators alone (*6,7*). In the current issue of the *Journal*, Ignaszewski and colleagues present their experience with combining exercise with dipyridamole ^{201}Tl imaging for the evaluation of patients with known or suspected coronary artery disease (*8*). Particularly with ^{201}Tl imaging, even modest levels of exercise can reduce splanchnic uptake of ^{201}Tl dramatically and improve the technical quality of the study (*7*). If combined with symptom-limited exercise, information regarding exercise capacity and provokable symptoms will be available.

In addition, there is evidence that noncardiac adverse effects with dipyridamole may be less frequent or severe if combined with exercise (*9*). However, the efficacy of medications cannot be evaluated with exercise when combined with vasodilator stress since, unlike exercise alone, the hyperemic response is dissociated from myocardial oxygen demand. It is possible that adrenegeric pharmacologic stress such as dobutamine may be closer to exercise in this respect.

Safety

Intravenous dipyridamole stress has been now shown to be quite safe when used with discretion and is thus applicable to a wide spectrum of patients with coronary heart disease. The study by Ignaszewski and colleagues suggests that exercise can be safely combined with dipyridamole, although their data allow no determination of the additional risk of exercise, if any. Nevertheless, dipyridamole has been associated with serious adverse effects, including death and myocardial infarction, and therefore requires proper patient selection to optimize safety. Two of the most important patient groups requiring circumspection are those with an unstable anginal pattern and those with severe bronchospastic disease.

Administration of dipyridamole in these settings can lead to myocardial infarction or life-threatening pulmonary insufficiency, respectively. Although there is less experience with adenosine, it would be expected to have similar dangers. Therefore, the clinical use of vasodilator myocardial perfusion imaging requires a commitment to careful screening of patients referred for evaluation.

Timing of Exercise and Vasodilator

Because of its longer duration of action, dipyridamole is the preferred agent when combining exercise with vasodilator myocardial perfusion imaging. The very short half-life of adenosine would require its administration throughout exercise. Combined with its higher side effect profile (particularly chest pain), this would make an exercise-adenosine protocol difficult. With dipyridamole, exercise can be started after completion of the infusion protocol.

To maximize the diagnostic value of dipyridamole myocardial perfusion imaging, one would want to inject the myocardial tracer agent at the time of peak coronary hyperemia. Thus, in designing a combined exercise-dipyridamole stress protocol, it would be important to ensure that the addition of exercise would still allow optimal timing of tracer injection. Unfortunately, there are very little available data regarding the *duration* of peak coronary hyperemic effects of dipyridamole, and none are available with combined exercise.

We have found that peak coronary hyperemic effects of dipyridamole begin to wane approximately 10–15 min after initiation of the standard 4-min infusion at 0.14 mg/kg · min^{-1} in a dog model (unpublished data). This suggests that the timing of tracer injection would require that exercise be completed in this time frame. Using a lower dose of 0.25 mg/kg dipyridamole over 1–2 min, Granato and colleagues found that peak coronary hyperemia began to decline after 20 min (*10*) in dogs. However, in a very small sample of patients, peak coronary hyperemic effects have been found to last at least 35 min (Kern M, *personal communication*).

In deference to our experimental data, exercise is begun in our protocol at 6 min after initiation of dipyridamole infusion and terminated by 12 min, with injection of myocardial tracer at approximately 1 min before

the end of exercise. Thus, exercise generally consists of two stages of a Bruce protocol with the specific levels tailored for each patient, depending on their physical condition and estimated predicted exercise capacity. If the duration of peak hyperemic effect is greater than 30 min, however, there is much more flexibility for combining exercise with the dipyridamole protocol. More data are clearly needed regarding the duration of action of intravenous dipyridamole on coronary blood flow in man.

In summary, although vasodilator pharmacologic stress is generally chosen as an adjunct to myocardial perfusion imaging because patients are unable to exercise optimally, the large majority of patients are able to perform at least some low-level exercise. Incorporating such exercise into a standard dipyridamole myocardial perfusion imaging protocol can lead to improved image quality, fewer and less severe adverse effects and provide at least some functional capacity data.

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