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EDITORIAL

Exercise Supplementation of Dipyridamole for Myocardial Perfusion Imaging

Intravenous dipyridamole provides a good alternative to treadmill exercise. Several studies have demonstrated that the diagnostic accuracy of ^{201}Tl scintigraphy performed with intravenous dipyridamole is equivalent to that performed in conjunction with treadmill exercise.

Dipyridamole infusion is technically simple and is associated with a low incidence of both cardiac and non-cardiac side effects. A threefold increase in coronary blood flow is achieved, comparable to that associated with maximal treadmill exercise (*1*). So why do some investigators feel that intravenous dipyridamole alone is insufficient and that supplementation with handgrip or treadmill exercise is advantageous? The following arguments have been offered:

1. The additive influence of exercise in further increasing coronary blood flow theoretically should allow for better differentiation of normal myocardium from vascular territories that are infarcted or supplied by stenotic coronary arteries. A similar argument has been offered to support the use of intravenous adenosine, a coronary vasodilator more potent than dipyridamole. However, at high coronary flow rates, exceeding 3.5 ml/min/gm of myocardial tissue, ^{201}Tl uptake begins to plateau despite further increases in blood flow, so the theoretical advantage of higher coronary flow rates might not be realized clinically with ^{201}Tl scintigraphy.

2. A minority of patients are dipyridamole "non-responders." In 12 patients in whom coronary blood flow reserve associated with dipyridamole infusion was measured, Rossen et al. demonstrated that two patients (17%) achieved peak flow rates of less than 2.0 ml/min/gm, compared to a mean ± s.d. of 3.7 ± 1.2 ml/min/g in the entire group (*2*). Poor coronary vasodilatory response to dipyridamole is also seen occasionally in routine ^{201}Tl studies and may be manifested by a poor myocardial-to-background ratio and diffusely diminished myocardial washout. The reason for such a poor coronary vasodilatory response in some patients is unknown. However, the addition of exercise to intravenous dipyridamole theoretically has the potential of improving test sensitivity by decreasing the number of "non-responders."

3. Dipyridamole decreases not only coronary but also systemic vascular resistance. Brown et al. measured systemic vascular resistance before and after dipyridamole infusion and measured a decrease from 15 ± 5 mmHg/liter/min to 10.9 ± 4.0 mmHg/liter/min ($p < 0.001$) mean ± s.d. (*1*). This results in increased ^{201}Tl uptake in tracer-avid organs other than the heart, including the liver. Since the liver lies immediately below the inferior wall of the left ventricle, myocardial image quality can be degraded due to Compton scatter and even actual overlap of the superior portion of the liver and the inferior wall of the left ventricle. Moreover, linear interpolative background subtraction algorithms used for exercise ^{201}Tl planar studies which demonstrate relatively little liver uptake may introduce error into dipyridamole studies. Because of the high count density in the liver, background will be oversubtracted from the inferior wall, resulting in artifactual inferior

Received Apr. 30, 1991; accepted Apr. 30, 1991.
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wall defects. Such factors affecting image quality are more problematical with planar studies than with SPECT since the tomographic technique is advantageous in visually separating adjacent structures (Figs. 1 and 2). However, even with SPECT, occasionally it may not be possible to separate adjacent liver or particularly bowel activity from the myocardium (*3*).

Since exercise results in shunting of blood away from the abdominal viscera to the working musculature, the addition of exercise to intravenous dipyridamole results in less ^{201}Tl liver uptake and improved image quality. Since treadmill exercise recruits a much larger muscle mass than handgrip, its effect in improving image quality is more marked. In this issue of the *Journal*, Stern et al. indeed document that the addition of treadmill exercise to dipyridamole improves the heart-to-liver ratio for planar ^{201}Tl imaging.

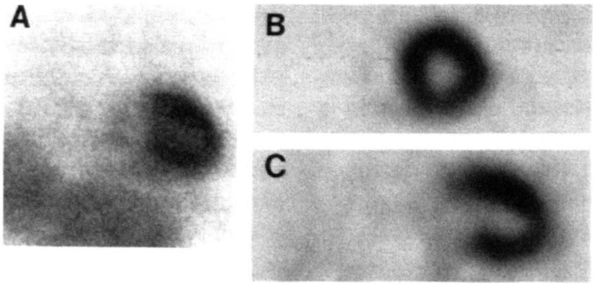

FIGURE 1. Thallium-201 scan performed in a 45-yr-old male following intravenous dipyridamole infusion (0.142 mg/kg/min for 4 min) supplemented by isometric handgrip exercise (33% maximal force for 4 min). An anterior planar image (A) was obtained 5 min following ^{201}Tl injection. immediately thereafter SPECT acquisition was performed. Midventricular short-axis (B) and vertical long-axis slices (C) are shown. Whereas moderate liver uptake characteristic of dipyridamole/handgrip studies is noted in the planar image, there is minimal, if any, image degradation in the tomographic slices. Image quality is comparable to that with treadmill exercise (Fig. 2).

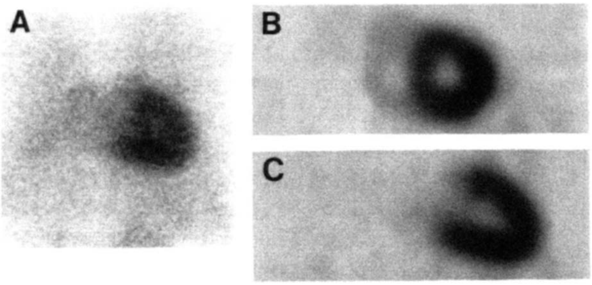

FIGURE 2. Thallium-201 scan performed in a 50-yr-old female following maximal (90% age-predicted heart rate) treadmill exercise. Five-minute anterior (A) and subsequent SPECT midventricular short-axis (B) and vertical long-axis (C) slices are shown. Tracer concentration in the liver is minimal.

EXERCISE SUPPLEMENTATION

With regard to the issues of augmentation of coronary blood flow, dipyridamole "non-responders," and image quality and also side effects, diagnostic accuracy, and logistics let us consider the potential application of either handgrip or treadmill exercise supplementation.

Handgrip Supplementation

Handgrip exercise supplementation of intravenous dipyridamole infusion is logistically attractive since both interventions can be performed with the patient supine in one location. However, considerable patient cooperation and effort are required. Cardiac and non-cardiac side effects and the incidence of ST segment depression have been noted to be similar with and without handgrip supplementation. (*4*).

Two studies have been published that evaluated the effect of handgrip exercise supplementation of intravenous dipyridamole to augment coronary blood flow. Unfortunately, the conclusions of the two studies are in disagreement with one another. Brown et al. measured coronary blood flow indirectly in 24 patients with coronary artery disease by means of a flow-sensitive thermodilution catheter placed in the coronary sinus (*1*). These investigators demonstrated a 2.4-fold increase in coronary sinus blood flow (compared to baseline) with dipyridamole, a 1.7-fold increase with handgrip alone (25% maximal force for 4 to 5 min), and a 3.3-fold increase with dipyridamole supplemented with handgrip. They found no similar additive effect of handgrip plus dipyridamole in decreasing coronary vascular resistance. In contrast, Rossen et al. measured coronary flow reserve (peak/resting coronary flow velocity ratio) in 12 patients with angiographically normal coronary arteries using intracoronary Doppler flow catheters (*2*). Isometric handgrip exercise supplementation (33% maximal force for 3–4 min) was not associated with an additional increase in coronary arterial blood flow compared to intravenous dipyridamole alone (flow reserve ± s.d. = 3.8 ± 1.1 before handgrip versus 4.0 ± 1.1 after handgrip, p = n.s.). Likewise, there was no change in coronary artery caliber measured by quantitative angiography associated with the addition of handgrip exercise. Technically, these conflicting studies differ significantly. Criticisms of the technique used in Brown's study put forth by Rossen et al. include potential errors due to movement of the thermodilution catheter particularly during labored respiration which occurs toward the end of handgrip exercise, and reflux of blood from the right atrium into the coronary sinus, resulting in overestimation of coronary blood flow. However, the potential hemodynamic effects of handgrip supplementation in the perfusion bed distal to a coronary stenosis cannot be assessed using the intracoronary Doppler flow catheter technique and may be better reflected by coronary sinus flow measurements. Differences in the results of these two studies also may in part be due to differences in the patient populations—all patients had coronary disease in the study by Brown et al., whereas patients had angiographically normal coronaries in the study by Rossen et al. In fact, Brown et al. noted coronary arterial vasoconstriction with handgrip to be most marked in small-to-moderate-sized arteries [18% ± 15% constriction of small-to-moderate-sized arteries ($p < 0.001$) versus 5% ± 12% construction of large, normal segments (p = n.s.)], which were not evaluated by Doppler measurements in Rossen's study.

In dipyridamole "non-responders" in whom coronary blood flow does not sufficiently increase to allow scintigraphic differentiation of myocardium supplied by normal and stenotic coronary arteries, there is limited data regarding the benefit of handgrip supplementation. In the two patients in the study by Rossen et al. in whom coronary flow reserve was less than 2.0 and in another four subjects in whom it was less than 3.0, handgrip supplementation had no significant effect in increasing flow reserve (*2*).

Handgrip exercise has been demonstrated to induce regional abnormalities in left ventricular function. Equilibrium radionuclide angiocardiography performed with isometric stress has been used to identify patients with coronary disease. In one report, the sensitivity of an exercise-induced regional wall motion abnormality was 67%, with abnormalities in regional ejection fraction present in 91% of patients (*5*). Likewise, for exercise echocardiography handgrip exercise is a potentially attractive form of stress since patient motion can be minimized. In patients with normal resting ventricular function, the sensitivity of a regional wall motion abnormality induced with handgrip exercise in detecting coronary stenosis has been reported to be as high as 65%, with a specificity of 100% (*6*).

However, physiologic mechanisms resulting in regional left ventricular dysfunction associated with handgrip exercise may be in part unrelated to changes in coronary perfusion. Brown et al. measured a mean ± s.d. increase in aortic pressure from a baseline value of 127/75 mmHg to a maximal value of 145/88 mmHg with handgrip exercise (*1*). This increase in systemic pressure may also be associated with an increase in left ventricular intracavitary pressure, increased wall tension, and increased myocardial oxygen demand, resulting in regional dysfunction. In a series of 27 patients with aortic valve disease, Huikuri et al. demonstrated that ^{201}Tl SPECT performed in conjunction with combined intravenous dipyridamole and handgrip exercise was highly sensitive (85%) and specific (86%) in determining the presence of coexistent coronary artery disease (*7*). The effects of dipyridamole on coronary blood flow and handgrip on wall stress in these patients with elevated baseline ventricular afterload most likely were additive in producing such excellent diagnostic accuracy of the myocardial perfusion scan.

Information is limited regarding the potential benefit of handgrip supplementation in improving the diagnostic accuracy of dipyridamole/thallium scintigraphy. For planar ^{201}Tl imaging, Ranhosky et al. demonstrated no additional increase in either test sensitivity or specificity associated with the addition of handgrip (*8*). For two-dimensional echocardiography, using deterioration of regional left ventricular function as the sole criterion of abnormality, Mandysova et al. observed a test sensitivity of 53% and specificity of 100% in detecting coronary stenoses ≥ 70% in a group of 53 patients studies with dipyridamole infusion alone (*9*). When dipyridamole stress was supplemented with handgrip (50% maximal force for up to 5 min), test sensitivity increased to 78% ($p < 0.001$) with no decrease in specificity. A diagnosis of coronary disease was made in 10 of 19 patients in whom studies would have been false-negative with dipyridamole alone. However, as postulated above, this increase in diagnostic sensitivity of ventricular functional imaging observed with handgrip may be possibly attributable to increased ventricular afterload and wall stress with accompanying regional asynergy.

In the article by Stern et al., heart-to-liver ratios were compared in patients undergoing dipyridamole/^{201}Tl planar imaging to a separate group who also performed handgrip exercise (*4*). No significant increase in the heart-to-liver ratio was demonstrated with the addition of handgrip, and the authors observed no improvement in image quality. However, the handgrip force performed by these patients was not very strenuous (25% of maximal force for 4 min) and less than that employed by other investigators. From my own unreported observations, more vigorous handgrip force (50% of maximal force for 3 to 4 min) may result in improvement in the heart-to-liver ratio as compared to dipyridamole alone.

Low-Level Treadmill Exercise Supplementation

The addition of upright treadmill exercise to intravenous dipyridamole infusion is logistically somewhat more difficult and more labor intensive than the addition of handgrip exercise. The patient must be moved from the supine position in which the dipyridamole was infused onto the treadmill, then back to the imaging table or SPECT pallet. Moreover, electrocardiographic monitoring must be duplicated for the two stress interventions. However, there are documented as well as theoretical advantages of treadmill exercise supplementation compared to handgrip supplementation or dipyridamole alone that may justify these relatively minor additional steps.

The incidence of non-cardiac side effects of dipyridamole is lower when the infusion is supplemented by treadmill exercise. In 100 patients who received intravenous dipyridamole, Casale et al. reported non-cardiac side effects (lightheadedness, headache, nausea, and vomiting) in 12%, whereas in a separate group of 100 patients who had the infusion supplemented by low level treadmill exercise (Bruce protocol, Stage 1 or 2, for 6 min) only 4% had noncardiac side effects (*10*). Similarly, Laarman et al. observed non-cardiac side effects in 43% of 101 patients receiving dipyridamole but only 11% of 200 patients with low-level bicycle exercise supplementation (60 rpm/30 watts for 3 min supine) ($p < 0.05$) (*11*). Although no significant increase in chest pain was observed with low-level exercise in either of these studies, the incidence of ST-segment depression was approximately double with low-level exercise in both series (26% versus 12% in Casale's report, and 25% versus 12% in Laarman's report). The increased incidence of ST segment changes with exercise supplementation may not necessarily be an unfavorable result, but may in fact be associated with increased test sensitivity for coronary artery disease.

The report by Stern et al. in this issue of the *Journal* and the previous report by Casale et al. clearly document that exercise supplementation increases the heart-to-liver count density ratio (*4,10*). The mean ratios ± s.d. reported in these two series was 1.22 ± 0.22 and 1.2 ± 0.3 for dipyridamole alone and 1.76 ± 0.50 and 2.1 ± 0.7 for dipyridamole plus low-level treadmill exercise (p's < 0.001 and < 0.0001, respectively). Such an increase in the target-to-background ratio results in improved image quality, especially for planar studies.

It is not known what the effect of low-level treadmill exercise is with regard to coronary blood flow. Experiments similar to those performed with thermodilution and Doppler flow catheters during dipyridamole infusion handgrip exercise would be difficult, if not impossible, to reproduce during treadmill or even bicycle dynamic exercise. Whereas maximal dynamic exercise results in a three- to fourfold increase in coronary blood flow, the hemodynamic effect of low level exercise is not known and may be variable among patients. Furthermore, the effect of low level exercise with regard to coronary blood flow in dipyridamole "non-responders" is unknown. The decrease in liver uptake associated with low level treadmill exercise is associated with shunting of blood to the working musculature and similar assumptions cannot be made regarding the coronary circulation.

Also, the effect of low-level treadmill augmentation on the diagnostic accuracy of ^{201}Tl scintigraphy has not been thoroughly investigated. In the studies cited above by Stern and Casale, the numbers of patients undergoing correlative coronary angiography were too small to draw meaningful conclusions (*4,10*). In an abstract by Ranhosky et al. reporting results in 1093 patients, neither handgrip (42 patients), bicycle ergometry (27 patients), nor walking in place for 5 min (222 patients) produced a significant increase in sensitivity or specificity compared to dipyridamole infusion alone (*8*). Test sensitivity was 86.6% in patients who performed any form of exercise compared to 84.2% for those who did not ($p = 0.40$).

Thus, apart from improved image quality for planar studies and an increase in the incidence of ischemic ST segment changes, the hemodynamic or diagnostic benefit of low-level exercise supplementation of dipyridamole/thallium scintigraphy has not been demonstrated.

Why Not Combine Intravenous Dipyridamole and Maximal Treadmill Exercise in All Patients?

One study reported by Walker et al. combined coronary vasodilatation with oral dipyridamole (300 mg) and maximal treadmill exercise for planar thallium scintigraphy (*12*). Results were compared to exercise imaging alone in 38 patients with documented coronary disease and/or a high pretest likelihood of disease. Perfusion defects were visualized in 76% of scans obtained after exercise alone and 89% with exercise plus oral dipyridamole (p = n.s.). No increase in side effects was observed when the two stress modalities were combined. Whereas 76% of patients had > 1 mm ST-segment depression during maximal, symptom-limited treadmill exercise alone, 84% had ischemic changes with oral dipyridamole supplementation (p = n.s.). Although these differences were not statistically significant, an interesting trend is noted. It is also possible that intravenous dipyridamole, now routinely available, might enhance these promising results.

The combination of intravenous dipyridamole and maximal, symptom-limited treadmill exercise may be an attractive option for the following reasons:

1. As noted above, in patients who are exercise-limited, dipyridamole provides adequate coronary vasodilatation in most cases, and test sensitivity and specificity are equivalent to exercise/thallium imaging.
2. Maximal treadmill exercise produces a three- to fourfold increase in coronary blood flow. Dipyridamole may augment the vasodilatory response even in patients who exercise maximally.
3. Suboptimal coronary vasodilatation and presumably decreased test sensitivity in patients who could exercise but not achieve a peak heart rate ≥ 85% of their age-predicted maximum would be less likely.
4. The likelihood of a patient being a dipyridamole "non-responder" would be less likely.

However, there are potential limitations to this combined dipyridamole-exercise approach:

1. The addition of dipyridamole to exercise increases the cost of each test by approximately $100.
2. With augmentation of coronary blood flow there is a potential for increased "coronary steal"

and thus increased myocardial ischemia with associated side effects.

3. Dipyridamole infusion is generally performed supine, whereas treadmill exercise is upright. The logistical limitations described above for dipyridamole/low-level exercise would apply to all patients and would thereby doubtlessly decrease laboratory efficiency.

SUMMARY

The substitution of intravenous dipyridamole for symptom-limited treadmill exercise has provided a noninvasive means to diagnose coronary artery disease with ^{201}Tl scintigraphy in patients unable to adequately exercise. Limitations of dipyridamole/thallium imaging are primarily due to suboptimal image quality secondary to hepatic tracer concentration and decreased test sensitivity in patients who are dipyridamole "non-responders." Low-level treadmill exercise supplementation improves image quality, whereas handgrip has little, if any, benefit. The effect of low-level exercise in augmenting coronary blood flow is unknown and reports regarding the effect of handgrip are conflicting. The diagnostic benefit of these maneuvers in improving test sensitivity and decreasing the number of "non-responders" has not been documented. The combination of maximal, symptom-limited treadmill exercise and intravenous dipyridamole is a theoretically attractive option to improve overall test sensitivity, but the physiologic consequences and potential side effects should be more thoroughly investigated.

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