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Editorial: Pharmacologic Stress with Dipyridamole: How Lazy Can One Be?

Even though dipyridamole is still an investigational drug, its application for pharmacologic stress testing in conjunction with thallium-201 (^{201}Tl) imaging has gained wide acceptance over the last few years (*1–6*). The diagnostic efficacy of ^{201}Tl-dipyridamole imaging for detecting significant coronary artery disease (CAD) has been shown to be comparable to treadmill exercise ^{201}Tl imaging.

Although ^{201}Tl-dipyridamole imaging is often referred to as "pharmacologic stress," this description is not entirely correct. In most instances, no real myocardial stress, resulting in increased metabolic demand, is provoked. The basic principle of ^{201}Tl-dipyridamole imaging is to visualize pharmacologically induced *heterogeneity* of myocardial blood flow (*7*).

Intravenous administration of dipyridamole blocks

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the transmembrane transport of adenosine and, in this manner, indirectly increases endogenous plasma adenosine levels. At adenosine receptor sites, adenosine is activated into an extremely potent dilator of the coronary resistance vasculature. Under normal conditions, coronary blood flow is autoregulated to meet myocardial metabolic demand by adjusting peripheral coronary resistance. Usually, only a fraction of maximally available coronary flow is recruited. The remaining amount of recruitable blood flow is commonly referred to as "coronary reserve" (*8*). In patients without significant CAD, infusion of dipyridamole may increase coronary blood flow three to five times above baseline levels. (It is of interest that during physical exercise coronary blood flow probably only increases two to three times resting levels).

In patients with significant coronary artery stenosis, the resistance vessels are already dilated to a certain degree in order to maintain normal resting flow. When dipyridamole is infused in these patients, no significant further vasodilatation may occur in the diseased vascular bed. However, in adjacent myocardium supplied by normal coronary arteries, near maximal vasodilatation and substantial increase in myocardial blood flow occurs. In this manner, *regional heterogeneity* of myocardial blood flow is created. The territory supplied by diseased arteries is relatively hypoperfused, compared to normal regions. This can be imaged with a gamma camera employing radioactive myocardial flow imaging agents such as ^{201}Tl or technetium-99m-SESTAMIBI, that accumulate proportional to regional myocardial blood flow.

Not only is ^{201}Tl-dipyridamole imaging comparable to physical exercise for the detection of angiographically significant CAD, abnormal ^{201}Tl-dipyridamole images have similar prognostic clinical value (*1, 6, 9–11*).

Indications to employ this alternative imaging modality for detection of CAD is in patients who are unable to perform physical exercise because of orthopedic, neurologic, or peripheral vascular problems. Furthermore, patients with CAD on beta-blocking medication who are unable to adequately increase their heart rate by physical exercise, have been studied successfully with dipyridamole.

As outlined above, the basic principle of ^{201}Tl-dipyridamole imaging is to create heterogeneity of coronary blood flow. True ischemia may develop in only a small proportion of patients. Myocardial ischemia can occur when blood flow is shunted away from areas supplied by diseased vessels. The underlying pathophysiologic mechanism may be either reversal of flow through collaterals toward normal regions with high flow, or by shunting of blood away from subendocardial to subepicardial regions (*12*). These patients have "coronary steal" and may experience chest pain and/or have electrocardiographic ischemic ST-T-segment changes. The reported incidence of these ischemic side effects varies (*1, 4, 6, 13*). Chest pain has been reported to occur in ~25% of patients, whereas electrocardiographic changes occur in ~20% of patients. These ischemic episodes usually can be reversed by i.v. aminophylline, which blocks adenosine receptor sites and inhibits adenosine activation. In occasional patients with coronary steal, myocardial ischemia can be severe and prolonged, resulting in pulmonary edema or even myocardial infarction. Overall, the incidence of *serious* side effects is relatively low (<1%).

Extensive clinical experience in thousands of patients has shown that ^{201}Tl-dipyridamole imaging is safe and of considerable diagnostic usefulness (*1–6, 9–11, 14–16*). Contraindications to perform ^{201}Tl-dipyridamole imaging are few. Patients with severe bronchospastic disease should not be studied because of high risk of provoking acute asthma. As one would assume, unstable angina is a relative contraindication. Nevertheless, some investigators have safely studied patients with unstable angina and recent (4–5 days) myocardial infarction (*11, 17*). A reasonable rule of thumb is that patients, who are too sick to perform physical exercise, probably should not be studied by dipyridamole infusion.

Interference of Various Drugs

Various drugs may have an antagonistic effect on the pharmacologic action of dipyridamole and may give false-negative results. Aminophylline, theophylline, and also caffeine block adenosine receptor sites and thus inhibit the vasodilatory effect of dipyridamole. Preliminary clinical studies have shown that patients who took either theophylline or caffeine prior to dipyridamole infusion had significantly less reversible ^{201}Tl defects, than when they were studied without these substances (*18, 19*).

In this issue, Brown et al. report the findings in a experimental model on the effect of yet another widely used prescription drug in patients with peripheral arterial disease, pentoxifylline (*20*). Pentoxifylline (Trental) is a methylxanthine derivative and potential adenosine antagonist. Many patients, referred for ^{201}Tl-dipyridamole imaging, have peripheral arterial disease and may be taking pentoxifylline at the time of study. The work by Brown and coworkers indicates that in experimental animals the vasodilatory effect of dipyridamole is not significantly altered by Trental. Assuming that their experimental findings are fully applicable to patients, these results suggest that this treatment does not need to be discontinued before ^{201}Tl-dipyridamole imaging.

Can Dipyridamole Infusion Replace Physical Treadmill or Bicycle Exercise?

Thallium-201-dipyridamole imaging has certain attractive aspects in comparison to ^{201}Tl imaging in conjunction with physical exercise. No expensive exercise

equipment is needed. The test can be performed on a stretcher in the nuclear medicine department. Infusion of dipyridamole is performed according to a standardized protocol and can be administered to all patients in a similar manner, whereas physical exercise for obvious reasons is variable and may have different end points and workload in different patients. No active patient participation is required for dipyridamole infusion. In fact, the patient is comfortably lying supine on the imaging table during the infusion. Patient motivation does not play an important role in successful dipyridamole imaging, whereas this is important for physical exercise.

Although by and large similar diagnostic *scintigraphic* information is acquired after dipyridamole infusion as after physical exercise, other important physiologic parameters are not available. For instance, the following additional information is useful to the cardiologist for complete evaluation of patients with heart disease:

1. Many patients are referred for evaluation of exertional symptoms. To address the question whether these symptoms represent anginal equivalents, it is important to observe and interrogate a patient during physical exercise. It is helpful to witness provocation of chest discomfort and judge its characteristics. In doing so, a more objective evaluation of the patient's symptoms can be made.
2. The duration and level of exercise is a powerful prognostic indicator (*21*). Patients who can not complete Stage III of the standard Bruce Protocol have a significantly poorer prognosis than patients who can exercise longer.
3. Furthermore, peak exercise heart rate, the change in heart rate from baseline-to-peak exercise, are of prognostic value (*22*).
4. The blood pressure response to exercise is of importance (*23*). A decrease in blood pressure during exercise is a poor prognostic sign, usually indicating severe CAD.
5. Although the exercise electrocardiogram in comparison to ^{201}Tl imaging is less sensitive and less specific for diagnosing CAD, it nevertheless provides important additional information (*24.*). The more positive the electrocardiogram, with typical horizontal or downsloping ST-T-segment depression, the more likely the patient has significant CAD (*25*). Exercise-induced ventricular ectopy is an important risk factor for death after acute myocardial infarction (*26*).

Several studies have demonstrated the incremental diagnostic and prognostic value of various exercise parameters (*21, 27*). This useful additional information is not available from dipyridamole testing. Therefore, *if* a patient is capable of performing, even limited, physical exercise, this is preferable, in comparison to "passive" dipyridamole infusion. One cannot allow a patient to be too lazy when the diagnosis of ischemic heart disease is considered.

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