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REVIEW ARTICLES

Dobutamine Stress Myocardial Perfusion Imaging

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In patients with limited exercise capacity and (relative) contraindications to direct vasodilators such as dipyridamole or adenosine, dobutamine stress nuclear myocardial perfusion imaging (DSMPI) represents an alternative, exercise-independent stress modality for the detection of coronary artery disease (CAD). Nondiagnostic test results (absence of reversible perfusion defects with submaximal stress) do occur in approximately 10% of patients. Serious side effects during DSMPI are rare, with no death, myocardial infarction or ventricular fibrillation reported in three DSMPI safety reports for a total of 2,574 patients. On the basis of a total number of 1,014 patients reported in 20 studies, the sensitivity, specificity and accuracy of the test for the detection of CAD were 88%, 74% and 84%, respectively. Mean sensitivities for one-, two- and three-vessel disease were 84%, 95% and 100%, respectively. The sensitivity for detection of left circumflex CAD (50%) was lower, compared with that for left anterior descending CAD (68%) and right CAD (88%). The sensitivity of predicting multivessel disease by multiregion perfusion abnormalities varied widely, from 44% to 89%, although specificity was excellent in all studies (89% to 94%). In direct diagnostic comparisons, DSMPI was more sensitive, but less specific, than dobutamine stress echocardiography and comparable with direct vasodilator myocardial perfusion imaging. In the largest prognostic study, patients with a normal DSMPI study had an annual hard event rate less than 1%. An ischemic scan pattern provided independent prognostic value, with a direct relationship between the extent and severity of the perfusion defects and prognosis. In conclusion, DSMPI seems a safe and useful nonexercise-dependent stress modality to detect CAD and assess prognosis. (J Am Coll Cardiol 2000;36:2017–27) © 2000 by the American College of Cardiology

Confirming or excluding coronary artery disease (CAD) in patients with chest pain remains a challenge because this disease is still the leading cause of death in the western world (1). Traditionally, exercise stress testing is performed as a first-line noninvasive diagnostic stress test (2). However, large numbers of patients referred for evaluation of chest pain are unable to perform adequate exercise testing, mainly because of deconditioning or neurologic, respiratory, peripheral vascular or orthopedic limitations (3). In these patients, pharmacological stress nuclear myocardial perfusion imaging (MPI) represents an alternative, exercise-independent stress modality. Usually, dipyridamole or adenosine is used as a stressor because of their superiority in creating blood flow heterogeneity (4) and the extensive experience with these stress modalities. For patients with (relative) contraindications to these direct vasodilators, such as severe obstructive airway disease (particularly patients with active wheezing or recent hospitalization for an exacerbation), high-grade atrioventricular block, arterial hypotension, ingestion of caffeine-containing beverages <12 h before testing or the use of dipyridamole or theophylline-containing compounds or medications <24 h before testing, dobutamine stress myocardial perfusion imaging (DSMPI) represents an alternative stress modality. Since its clinical introduction in 1984, DSMPI is increasingly used for detecting CAD and assessing prognosis (5–32). This review article deals with the: 1) methodology, 2) feasibility and safety, 3) diagnostic value for the detection of CAD and 4) prognostic value of DSMPI.

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METHODS AND STATISTICAL ANALYSIS

A Medline search on DSMPI (search terms dobutamine and thallium or technetium) studies published in the major English language journals until the end of 1998 was performed. Studies were only included for diagnostic analysis if these studies included patients with and without angiographically defined CAD and if it was stated how many patients with and without CAD had negative and positive DSMPI results. Reports indicating that the patients included were subsets of larger published studies were excluded. Also excluded from the primary diagnostic analysis were studies describing special issues, such as the value of DSMPI in patients with left bundle branch block (LBBB) or left ventricular hypertrophy (LVH) and studies involving only patients with prior myocardial infarction (MI). These subgroups were discussed separately. When DSMPI was compared with other stress modalities, only those studies making direct comparisons in the same patients were included.

Sensitivity was defined as the number of true positive tests divided by the total number of patients with angio-

Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
DSE = dobutamine stress echocardiography
DSMPI = dobutamine stress myocardial perfusion imaging
ECG = electrocardiogram or electrocardiographic
LBBB = left bundle branch block
LVH = left ventricular hypertrophy
MI = myocardial infarction
MPI = myocardial perfusion imaging

graphically significant CAD. Specificity was defined as the number of true negative tests divided by the total number of patients without angiographically significant CAD. Accuracy was defined by the total number of true positive and true negative tests divided by the total number of patients. Mean values for sensitivity, specificity and accuracy were calculated by combining the results of individual patient data from multiple studies. Comparisons of sensitivity, specificity and accuracy were performed using the standardized normal distribution test. Statistical significance was defined at $p < 0.05$.

TEST METHODOLOGY

Dobutamine: pharmacology and mechanism of action. Dobutamine is a synthetic catecholamine with a relatively short plasma half-life of approximately 2 min due to rapid metabolization in the liver to inactive metabolites (33,34). It has strong β_1-receptor and mild α_1- and β_2-receptor agonist activity. When used at low dose (up to 10 μg/kg body weight per min), marked inotropic effects (mediated by both α_1- and β_1-receptor stimulation) are encountered. These effects are extensively used for treatment of heart failure and the identification of dysfunctional, but viable, cardiac muscle. When used at high-dose (up to 40 μg/kg/min), heart rate is progressively increased (mediated by β_1-receptor stimulation). Despite a clear increase in cardiac output, systemic blood pressure increases only minimally due to a decrease in systemic vascular resistance because of peripheral vasoconstrictive effects (mediated by α_1-receptor stimulation) overwhelmed by vasodilative effects (mediated by β_2-receptor stimulation). In patients without a sufficient increase in heart rate, the addition of atropine has been proposed to further increase heart rate by its vagolytic effects (25,35). As a result of the hemodynamic changes, there is an increase in oxygen demand resulting in a secondary dilation of the coronary arteries and, thus, an increase in blood flow. Additionally, dobutamine may also have a (minor) direct vasodilatative effect on coronary vessels. For high-dose dobutamine infusion, this increase in blood flow in normal coronary arteries has been reported as three times baseline (36). However, in myocardial regions supplied by a coronary artery with a critical stenosis, the increase in oxygen demand cannot be met by an adequate increase in blood flow (37). For successful MPI, dobutamine should not only create an adequate flow disparity between myocardial regions supplied by normal and stenotic arteries, but the radionuclide tracer (thallium-201 or technetium-99m) must be distributed in the myocardium in proportion to blood flow over the range of flows induced by dobutamine also. Several studies (4,38) have shown that dobutamine-induced cardiac thallium-201 uptake expressed as a percentage of whole body uptake is intermediate between exercise and direct vasodilator stress and that heart-to-background ratios of thallium-201 uptake are similar to direct vasodilator stress (but less than exercise stress). Recently published studies on dogs, however, reported that myocardial technetium-99m uptake underestimated the relative blood flow deficit induced by dobutamine, and it was suggested that dobutamine adversely affects myocardial technetium-99m binding (39,40).

Protocol. Protocols for DSMPI vary from institution to institution, particularly with regard to dobutamine dose (range 20 to 50 μg/kg/min), atropine addition (range 0 to 2 mg) and stage duration (range 3 to 5 min) (Table 1). Usually, centers that use lower peak doses of dobutamine (used mainly in the early reports) use longer infusion stage durations and stop beta-adrenergic blocking agent treatment more often before the test (Table 1). To date, the most widely used protocol uses dobutamine up to 40 μg/kg/min, with the addition of atropine up to 1 mg.

According to this protocol, a rest electrocardiogram (ECG) is acquired; intravenous access is secured, and dobutamine is then administered intravenously by an infusion pump, starting at 10 μg/kg/min for 3 min, increasing by 10 μg/kg/min every 3 min up to a maximum of 40 μg/kg/min. For patients not achieving 85% of their theoretical maximal heart rate (220 − age) and without symptoms or signs of myocardial ischemia, atropine is administered on top of the maximal dose of dobutamine starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 min, with continuation of dobutamine infusion. The radionuclide tracer should be injected at peak heart rate, and dobutamine infusion should be continued for at least 1 min. Throughout dobutamine infusion, the ECG (3 leads) is continuously monitored and recorded (12 leads) at 1-min intervals. Blood pressure is measured and recorded by sphygmomanometry or automatic device every 3 min. Reasons for interruption of the test are: horizontal or downsloping ST segment depression >0.2 mV at an interval of 80 ms after the J point compared with baseline, ST segment elevation >0.1 mV in patients without a previous MI, severe angina, a symptomatic reduction in systolic blood pressure ≥40 mm Hg from baseline, hypertension (blood pressure ≥240/120 mm Hg); significant tachyarrhythmias and any serious side effect was regarded as due to dobutamine. A beta-adrenergic blocking agent that can be injected intravenously must be available to reverse the effects of dobutamine if they do not revert spontaneously and quickly. For patients with obstructive airway disease (and in