Safety and diagnostic accuracy of intravenous accelerated high-dose dipyridamole-atropine stress echocardiography

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Background. **In the present study, the safety and diagnostic accuracy of a modified protocol with accelerated high-dose dipyridamole-atropine stress echocardiography, utilized in an attempt to significantly shorten the test imaging time with respect to the standard protocol, were evaluated.**

Methods. **Three hundred and thirty-seven patients (231 men, 106 women, mean age 63 ± 9 years) with known or suspected coronary artery disease underwent 404 tests. The ECG and blood pressure were continuously monitored during constant infusion of 0.21 mg/kg/min of dipyridamole over 4 min; atropine (0.50 mg at 5 and 6 min) was given in order to reach ≥ 85% of the age-predicted heart rate. The wall motion score index and the 16-segment model were used to evaluate contractility. Eighty-nine patients underwent selective coronary angiography. Coronary artery stenosis was considered significant if the vessel diameter was < 50% of the normal value.**

Results. **Eighty-eight out of 404 tests were positive: 72 for echocardiographic criteria, 11 for ECG criteria, 2 for clinical symptoms, and 3 for combined criteria. Three hundred and sixteen tests were negative. In 303 tests atropine was administered and 380 tests were performed in pharmacological wash-out. The maximal heart rate was 105.8 ± 9 b/min and the maximal blood pressure was 128 ± 19/78 ± 9 mmHg. No major side effects nor life-threatening complications were observed. In 24 tests (5.9%) only minor side effects occurred and in no case did these effects cause premature suspension of the test. The sensitivity, specificity and diagnostic accuracy of angiographically assessed coronary artery disease were 56, 86 and 73% respectively.**

Conclusions. **Accelerated high-dose dipyridamole echocardiography is practical, feasible and safe and allows for a significant reduction in the imaging time, with an increased cost-effectiveness and tolerance of the patients. In our experience the diagnostic accuracy of this new protocol was quite good and similar to that of the standard test.**

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Introduction

The dipyridamole echocardiography test (DET) is, especially in Europe, a widely used diagnostic procedure for the diagnosis and prognostic stratification of coronary artery disease. Several studies have demonstrated the safety and the diagnostic and prognostic accuracy of standard DET (up to 0.84 mg/kg over 10 min)[1-8]. In the quest of user-friendliness and of an optimal diagnostic accuracy in specific clinical conditions, over the last 15 years various modifications of the standard protocol have been proposed: the infra-dose protocol (0.28 mg/kg in 2 min), the low-dose protocol (0.56 mg/kg)[9,10], the high-dose protocol (0.84 mg/kg over 10 min), the atropine protocol (1 mg in 4 min, after high-dose)[11,12], and the accelerated high-dose protocol (0.84 mg/kg in 6 min)[13]. The last protocol has been proposed with the aim of shortening the test imaging time (which is about 20 min in the standard protocol), without detrimentally affecting the safety, feasibility and accuracy of this diagnostic modality. This study reports the safety and feasibility of a new accelerated DET protocol, utilized in a single center by cardiologists who had passed the quality control procedures of stress echocardiographic reading and have entered the network of the Echo-Persantine International Cooperative (EPIC) studies[2].

Methods

Three hundred and thirty-seven patients with known or suspected coronary artery disease and with a satisfactory baseline echocardiographic study underwent 404 tests; 49 patients were submitted to > 1

DET study in the early and late follow-up of coronary angioplasty. The patient's characteristics are described in table I.

Three hundred and eighty tests were performed on patients who were off antianginal treatment; the remaining 24 tests were performed on patients who were on beta-blockers, nitrates, calcium antagonists, and combined therapeutic regimens.

Within 2 months of testing, 89 patients underwent selective right and left coronary angiography using the Judkins' technique. Coronary artery stenosis was considered significant if the vessel diameter was < 50% of the normal value. The decision to perform coronary angiography was made on the basis of the individual patient's needs and independently of the results of stress echocardiography by the referring physician. Of these 89 patients, 24 were on and 65 were off antianginal therapy at the time of stress echocardiography.

Table I. Patient's characteristics.

No. patients	337
Age (years)	63 ± 9
Sex (M/F)	231/106
Unstable angina	68
Prior MI and PTCA	98
Early MI	20
Primary PTCA	25
Prior bypass graft	20
Others*	34

MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty. * = patients with atypical chest pain or candidates for risk stratification before major vascular surgery.

Dipyridamole echocardiography test. All patients gave their informed consent and the local ethical committee approved the study protocol. Patients were instructed to fast for > 3 hours before the test and specifically to avoid tea, coffee and cola drinks for the preceding 12 hours. Two-dimensional echocardiography and standard 3-lead ECG monitoring were performed during constant infusion of 0.21 mg/kg/min of dipyridamole over 4 min (the cumulative dose was therefore 0.84 mg/kg over 4 min). When no endpoint was reached at 1 min after the end of infusion, atropine (in two divided doses of 0.50 mg up to a maximum of 1 mg at 5 and 6 min) was given in order to reach > 85% of the age-predicted heart rate. During the test, the blood pressure and 12-lead ECG were recorded each minute. The left ventricular wall motion was continuously analyzed in multiple standard views and recorded on the videotape at baseline and over the 10 min after the onset of dipyridamole infusion. Aminophylline, which promptly reverses the effects of dipyridamole, was readily available and routinely administered intravenously (up to a maximum of 240 mg) at the end of the test (8th min). The left ventricle was divided into 16 segments according to the American Society of Echocardiography criteria[14] and a semiquantitative index (wall motion score index) based on a 4-point scale (1 = normal, 2 = hypokinesia, 3 = akinesia, 4 = dyskinesia) was calculated at rest and during peak stress. The echo-positivity for ischemia was based on the detection of transient wall motion abnormality that was either absent or of a lesser degree at baseline; angina or ECG abnormalities were considered separately. The ECG positivity was based on the onset of an ST segment depression ≥ 0.1 mV in at least 2 leads.

In the presence of at least one of the following diagnostic signs the test was interrupted: new kinesis abnormalities, severe chest pain, diagnostic ST segment changes. Otherwise, the test was stopped after the maximum atropine dose or when the targeted heart rate (≥ 85%) was reached or in the presence of severe side effects: intolerable headache or nausea, hypotension (> 30 mmHg fall in blood pressure); bradycardia (< 50/min); supraventricular arrhythmias (supraventricular tachycardia or atrial fibrillation) or life-threatening complications.

Statistical analysis. Data are expressed as the mean value ± SD. The calculation of the sensitivity, specificity, positive and negative predictive values and accuracy was performed according to standard definitions.

Results

Stress echocardiography results. Of 404 tests, 72 (17.8%) were positive for echocardiographic criteria, 11 (2.7%) for ECG criteria, 2 (0.5%) for clinical symptoms, and 3 (0.8%) for combined criteria; 316 (78.2%) were negative. In 303 (75%) out of 404 tests atropine was co-administered. Of the 101 tests in which atropine was not administered, 30 (30%) were positive for ischemia, in 34 (34%) the targeted heart rate had already been reached, and in 37 (36%) atropine was contraindicated. In 380 (94%) patients, the tests were performed in pharmacological wash-out.

The maximal heart rate reached was 105.8 ± 9 b/min; the maximal blood pressure was 128 ± 19/78 ± 9 mmHg.

The average test imaging time of a negative test was 8 to 10 min.

Stress tolerability. Neither life-threatening complications nor side effects requiring hospitalization or specific treatment nor the above described severe side effects were observed. The only minor side effects observed are summarized in table II. In no case did these effects necessitate premature interruption of the test. All side effects promptly resolved following administration of aminophylline; beta-blockers were administered to patients with persistent tachycardia.

Table II. Complications.

Side effects	24 (5.9%)
Minor	24 (100%)
Nausea	5 (21%)
Headache	7 (29%)
Bradycardia/hypotension	3 (12%)
Supraventricular arrhythmias	2 (8%)
Ventricular beats	5 (21%)
Right/left bundle branch block	2 (8%)
Major (life-threatening)	0

Angiographic data. Of the 89 patients who underwent coronary angiography within 2 months of testing, 50 had normal arteries and 39 had > 50% coronary artery stenosis (4 with one-, 19 with two-, and 16 with three-vessel disease).

Correlation between the angiographic data and the stress result. Among the 50 patients without significant coronary artery stenosis, the test was positive in 7 patients and negative in 43; among the 39 patients with angiographically assessed coronary artery stenosis, the test was positive in 22 and negative in 17 (sensitivity 56%, specificity 86%, positive predictive value 76%, negative predictive value 72%, overall diagnostic accuracy 73%).

Discussion

In the last 15 years, protocols for dipyridamole stress testing have been proposed with the aim of optimizing the diagnostic accuracy in the setting of coronary artery disease[1-8]. Picano and co-workers[9,10] have supported this quick evolution, publishing several single and multicenter studies. The protocols have progressively incremented the dipyridamole doses and administration time (from 0.56 mg/kg in 4 min to 0.84 mg/kg in 8 min) and have added atropine (1 mg)[11,12], consequently prolonging the imaging time to 10 min. In the last 3 years, Picano and co-workers decreased the time of infusion (up to 6 min) on the basis of the pharmacodynamic assumption that "when vasodilator stress is coupled with echo, larger (dose) and faster (infusion rate) is probably better". Our protocol is more aggressive, decreasing the test time up to 6 min when atropine is added. The results demonstrate that the new protocol (accelerated high-dose dipyridamole-atropine echo-test) is practical, feasible and safe (Table II). A previous multicenter study[13] reported a significant occurrence of minor side effects (3%) and three major complications (0.23%): myocardial infarction, transient ischemic attack and ventricular tachycardia and brief asystole, confirming the safety and tolerability of the new fast test. However, further studies are needed to definitively verify the safety and tolerability of this new protocol. Previous studies[2,15-17] using the standard protocol reported a similar incidence of major or minor side effects (0.07-0.2 and 1.2-3% respectively).

Our study demonstrated that this accelerated protocol is appealing for the short imaging time with a reduction of 40% in comparison with the standard protocol. This significant reduction in time allows for an increased tolerability to the test and for a noticeable reduction in costs (the time employed by the physician is reduced from 25 min for the standard protocol with atropine to 10 min for the accelerated high-dose dipyridamole protocol with atropine). Furthermore, in 101 patients (25%) atropine was not co-administered. This resulted in a further reduction in imaging time (6 min). Finally, there was no need for drug cocktails.

With regard to the diagnostic accuracy of the test, the present study confirmed our previous data referring to patients with a Q-wave acute myocardial infarction for whom the standard protocol was used. Previous studies showed a slightly increased sensitivity, specificity and diagnostic accuracy, with a similarly acceptable safety profile[13,15-18]. However, these data largely refer to patients without regional dysfunction at rest and without therapy. Comparison of our data with those obtained for patients with similar characteristics (previous myocardial infarction, known coronary artery disease, multivessel coronary artery disease, etc.) and on therapy (27% of cases) reveals that the sensitivity, specificity and diagnostic accuracy are similar[13].

Where, among the indications for vasodilator stress tests, can this promising and time saving protocol be applied? Could this protocol substitute the "classical and standardized protocol" in defining and grading the severity of induced myocardial ischemia? Probably, this test may increase our diagnostic chances and flank others, so tailoring the best stress to the individual patient's needs. We suggest that this test could be initially performed in echocardiographic laboratories with high level expertise and in those clinical conditions where a "binary" response (positive/negative) is requested: patients in whom the diagnosis of ischemic heart disease is uncertain (i.e. with atypical chest pain) and patients submitted to primary or elective angioplasty, and in their long-term follow-up. Furthermore, a single shot vasodilator stress could be ideal when a combined functional-vasodilator effect is requested, i.e. in the simultaneous assessment of the regional wall motion and either perfusion with on-line contrast echo or left anterior descending artery flow.

A possible limitation of our study is represented by the small number of enrolled patients, while, as it is known, the safety of diagnostic procedures should be tested on thousands of patients. Moreover, tests were made by trained cardiologists belonging to an expert institution and could reflect local experience, not necessarily representative of daily clinical practice in the real world of the cardiological community.

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