Inhibition of Dipyridamole-Induced Ischemia by Antianginal Therapy in Humans
Correlation With Exercise Electrocardiography

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Background. Dipyridamole echocardiography test (DET: two-dimensional echocardiographic monitoring with dipyridamole infusion up to 0.84 mg/kg in 10 minutes) is a useful tool for the noninvasive diagnosis of coronary artery disease. Aims of the present study were to assess the effects of antianginal drugs on dipyridamole-induced ischemia and to evaluate whether drug-induced changes in DET response may predict variations in exercise tolerance.

Methods and Results. Fifty-seven patients with angiographically assessed significant coronary artery disease (>70% lumen reduction in at least one major coronary vessel) performed a DET and an exercise echocardiography test (EET) in random order both off treatment and on antianginal drugs (β-blockers, calcium antagonists and nitrates, alone or in various combinations). The criterion for DET positivity was a transient dyssynergy of contraction absent or of a lesser degree in the baseline examination. In DET, two parameters were evaluated: the dipyridamole time (i.e., the time from onset of dipyridamole infusion to obvious dyssynergy) and the wall motion score index. DET sensitivity was 91% off therapy and fell to 65% under therapy (p<0.01). In the 37 patients who had a positive DET both off and on therapy, the dipyridamole time increased from 6±3 (off therapy) to 8±3 minutes (on therapy) (p<0.01). The wall motion score index at peak dipyridamole went from 1.38±0.14 to 1.31±0.14 (p<0.01). EET and DET yielded concordant (positive versus negative) results in 41 of 57 (71%) patients off and in 35 of 57 (61%) on therapy (p=NS). In the subgroup of 38 patients with both positive DET and EET without treatment, the therapy-induced variations in exercise time were significantly correlated with the variations in dipyridamole time (r=0.5; p<0.01), not with variations in wall motion score index (r=0.3; p=NS).

Conclusions. 1) Antianginal therapy can protect from dipyridamole-induced ischemia and 2) the therapy-induced changes in DET response parallel variations in exercise tolerance and might be useful for the objective, exercise-independent assessment of the therapy efficacy. (Circulation 1991;83:1256–1262)

The results of diagnostic tests for noninvasive detection of coronary artery disease can be variably affected by antianginal therapy. Nuclear medicine myocardial perfusion imaging (during exercise or dipyridamole) is influenced little, if at all, by anti-ischemic therapy. On the other hand, exercise electrocardiography testing (EET) (which requires myocardial ischemia as a diagnostic end point) is profoundly affected by medical therapy, and changes in exercise tolerance represent an established clinical tool to assess objectively the efficacy of antianginal drugs.

The dipyridamole echocardiography test (DET) has been proposed as an exercise-independent tool for the diagnosis of coronary artery disease. The test positivity is linked to the development of a transient regional dyssynergy, and myocardial ischemia is, therefore, the desired diagnostic end point.

The results of anti-ischemic drugs on DET have not been systematically investigated up to now. Aims of the present study were to assess the effects of various antianginal drugs on dipyridamole-induced ischemia and to evaluate whether drug-induced changes in DET response may predict variations in exercise tolerance. Therefore, 61 patients with effort angina pectoris and angiographically documented coronary artery disease performed in random order two DETs, one off treatment and one on antianginal drugs (β-blockers, calcium antagonists, and nitrates,
alone or in various combinations). A subset of 57 patients also performed two EETs, one off therapy and one on the same treatment as DET.

**Methods**

Fifty-seven in-hospital patients (50 men and seven women; mean age, 56±9 years) with a history of effort chest pain and angiographically assessed coronary artery disease were considered for this study; 20 had a history of stable effort chest pain, 22 of mixed angina, 10 of recent unstable angina, and five of recent myocardial infarction (range, 21–60 days). Twenty-two (39%) patients had a history of previous myocardial infarction (Q wave in 19, non-Q wave in three), involving the anterior wall of the left ventricle in three patients, the anterolateral wall in one, the anterior wall and septum in two, the lateral wall in one, the apex in three, the apex and septum in three, and the inferoposterior wall in nine. The mean time from acute event and first dipyridamole study was 13±13 months.

No patient was receiving xanthines at the time of the study.

**Dipyridamole Echocardiography Test**

Two-dimensional echocardiographic monitoring was performed in combination with dipyridamole infusion: 0.56 mg/kg during 4 minutes, no dose for 4 minutes, and then, if the test remained negative, 0.28 mg/kg during 2 minutes. The cumulative dose was therefore 0.84 mg/kg during 10 minutes. During each minute of the procedure, blood pressure and the 12-lead electrocardiogram were recorded. Two-dimensional echocardiograms were continuously monitored and were intermittently recorded during and up to 10 minutes after dipyridamole administration. Commercially available imaging systems (models 77020, Hewlett-Packard Co., Andover, Mass., and SSA 270A, Toshiba Sonolayer, Otawara, Japan; both with 2.5- and 3.5-MHz transducers) were used. The test was terminated if new wall motion dyssynergy was detected by two-dimensional echocardiography or if symptoms were judged to be unacceptable by the cardiologist performing the test.

Aminophylline was administered (80–240 mg i.v. during 1–3 minutes) as soon as dyssynergy was demonstrated. Also, in negative tests, patients received aminophylline (40–70 mg i.v. during 1 minute) at the end of the test to reverse or prevent side effects. In the baseline studies as well as during stress testing, all standard echocardiographic views were obtained when possible. During the test, new areas of abnormal wall motion were identified on multiple views by rapidly moving the ultrasound transducer through various positions. The videotapes were analyzed by one experienced observer unaware of clinical, angiographic, EET, and therapy data. Positivity of the test was based on the detection of a transient dyssynergy of contraction, which was absent or of a lesser degree in the baseline examination.

A wall motion score index was derived for rest and peak dipyridamole echocardiograms in each patient. The left ventricle was divided into 11 segments, according to a segmentation proposed by the Italian Society of Echocardiography and already adopted in the GISSI 2 multicenter trial, in the subproject “Residual Ischemia” which included performing DET early after uncomplicated acute myocardial infarction. The 11 segments are apex, anterior septum (proximal and distal), inferior septum (proximal and distal), anterior wall (proximal and distal), lateral wall (proximal and distal), and inferior wall (proximal and distal). Segmental wall motion was graded as follows: normal, normal motion at rest, with normal or increased wall motion (hyperkinesia) after dipyridamole (score=1); hypokinetic, marked reduction of endocardial motion (score=2); akinetic, virtual absence of inward motion (score=3); and dyskinetic, paradoxical wall motion away from the center of the left ventricle in systole (score=4). The wall motion score index was derived by summation of individual segment scores divided by the number of interpreted segments. Inadequately visualized segments were not scored.

For each test, a dipyridamole time (i.e., the interval from the onset of infusion to development of obvious dyssynergy) was also obtained. For instance, a DET positive at the first minute after the end of the infusion of the second dose had a dipyridamole time of 11 minutes. The dipyridamole time of a negative test was arbitrarily assumed to be 15 minutes.

**Exercise Stress Test**

Patients performed a multistage bicycle ergometer test, with an initial load of 25 W and increments of 25 W every 2 minutes. A 12-lead electrocardiogram and systolic and diastolic pressures, measured using a cuff sphygmomanometer, were recorded basally and each minute. End points of the test were moderately severe chest pain, diagnostic ST segment shift, maximal age-related heart rate, or limiting dyspnea or fatigue in the absence of ischemia.

Rate-pressure product (heart rate×systolic blood pressure) was used as an index of heart work and was measured at the onset of ischemia (arbitrarily fixed at 0.10 mV of horizontal or downsloping ST segment shift 0.08 second after the J point compared with the baseline tracing) or, in patients with negative responses, at peak exercise.

**Coronary Angiography**

Left-sided heart catheterization and coronary angiography were performed in a standard manner by the Judkins or Sones technique. Significant coronary artery stenosis was defined as greater than 70% reduction in the luminal diameter of any of the three coronary arteries or their primary branches or more than 50% reduction of the luminal diameter of the left main coronary artery. Angiograms were reviewed by two angiographers who were unaware of the results of DET.
TABLE 1. Hemodynamic Findings During Dipyridamole Stress Without and With Anti-ischemic Therapy in 57 Patients

<table>
<thead>
<tr>
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<th>Without therapy</th>
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<th>With therapy</th>
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<tbody>
<tr>
<td></td>
<td>DET−(n=5)</td>
<td>DET+(n=52)</td>
<td>DET−(n=20)</td>
<td>DET+(n=37)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>Basal 77±5</td>
<td>Peak 99±8*</td>
<td>Basal 70±8</td>
<td>Peak 93±12*</td>
</tr>
<tr>
<td></td>
<td>DET+(n=20)</td>
<td>DET+(n=37)</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>Basal 133±8</td>
<td>Peak 128±8†</td>
<td>Basal 132±10</td>
<td>Peak 129±9*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>83±4</td>
<td>81±3†</td>
<td>82±6</td>
<td>82±5</td>
</tr>
<tr>
<td>Rate-pressure product (beats/min×mm Hg×1/100)</td>
<td>103±10</td>
<td>127±16*</td>
<td>97±18</td>
<td>130±27*</td>
</tr>
</tbody>
</table>

Data are mean±SD.

n, Number of patients; DET, dipyridamole echocardiography test; +, positive result; −, negative result; peak, soon before aminophylline administration (in positive cases) or 7 minutes after the end of dipyridamole infusion (in negative cases).

*p<0.01; †p<0.05.

Drug Protocol

For each study patient, two DETs were performed with a time lag ranging from 4 to 7 days. One DET was performed with the patient on placebo, the other on active antianginal treatment, in random order. If one patient performed the test first on active treatment and then on placebo, the minimal wash-out time was 48 hours for calcium antagonists or nitrates and 72 hours for β-blockers. Both the patient and the physician interpreting the stress test were unaware of the given therapy. The active treatment was independently decided by the physician in charge and consisted of monotherapy in 37 patients: β-blockers in 24 (propranolol 120–240 mg/day in 16 and atenolol 100 mg/day in eight); calcium antagonists in 13 (nifedipine 30–40 mg/day in four, verapamil 240–320 mg/day in five, and diltiazem 180–360 mg/day in four patients). The remaining 20 patients received combination therapy: nitrates (isosorbide-5-mononitrate 80–120 mg/day) plus calcium antagonists (nifedipine 30 mg/day in three, verapamil 240 mg/day in eight, and diltiazem 180–360 mg/day in six) in 17; nifedipine 30–40 mg/day plus propranolol 120 mg/day in three.

All patients performed also an EET on a different day in random order and within 24 hours since DET: one EET off therapy and the other on active treatment. Four patients did not perform EET because of inability to exercise.

Statistical Analysis

Data are reported as mean±SD. Difference between values are tested for significance by means of χ² and paired and unpaired Student’s t tests. Linear regression analysis was used to correlate DET and EET findings. A probability value less than 0.05 was considered statistically significant.

Results

Coronary Arteriography

By selection, all studied patients showed a significant stenosis in at least one major coronary artery. In particular, 28 patients had one-vessel, 20 had two-vessel, and nine had three-vessel disease.

Two-dimensional Echocardiography

Baseline left ventricular dyssynergy of contraction was found in 23 patients. Twenty-two of these patients had a history of previous myocardial infarction; in each, dyssynergy was present in the region involved by previous myocardial infarction.

Dipyridamole Echocardiography Test

Hemodynamic behavior of study patients during the dipyridamole tests are displayed in Table 1. Echocardiographic images were suitable for analysis in all studies. Side effects due to dipyridamole were always minor and well tolerated by the patients; in particular, no symptomatic arterial hypotension (>30 mm Hg from baseline value) was observed, even when using the full dosage.

After dipyridamole, a transient dyssynergy occurred in 52 patients off and in 37 on therapy (91% versus 65%, p<0.01). In the 28 patients with on-vessel disease, transient dyssynergy occurred in 24 off and 16 on therapy (86% versus 57%, p<0.05); in the 29 patients with multivessel disease, transient dyssynergy occurred in 28 off and 21 on therapy (97% versus 72%, p<0.05). The transient ventricular dyssynergy always involved a region fed by a stenotic vessel. In resting conditions, the wall motion score index was similar in the DET studies performed off and on therapy (1.09±0.13 versus 1.10±0.14, p=NS). At peak dipyridamole, the wall motion score index was significantly higher in DET studies performed off therapy (1.36±0.13 versus 1.31±0.14, p<0.01). Furthermore, therapy induced an increase in dipyridamole time (6.8±2.5 versus 8.4±2.6 minutes, p<0.01). A diagnostic ST segment depression occurred in 40 patients off and in 29 on therapy (70% versus 51%, p<0.01). Chest pain occurred in 39 patients off and in 28 on therapy (68% versus 49%, p<0.01) (Figure 1). None of the five patients with negative DET without therapy had a positive response to DET with therapy.
The therapy-induced decrease in DET sensitivity was found for each of the tested antianginal drug regimens (Table 2).

In the 37 patients with positive DET both off and on therapy, the dyssynergy involved the same ventricular region. Wall motion score index was 1.38±0.14 off and 1.31±0.14 on therapy (p<0.01), and the dipyridamole time was 6.7±2.5 minutes off and 8.4±2.6 on therapy (p<0.01).

Exercise Stress Test
All patients in the study performed two EETs without and with therapy, within 1 day of the corresponding DET. Hemodynamic findings of these patients during exercise are displayed in Table 3.

After exercise, a transient diagnostic ST segment depression occurred in 40 patients off and in 27 on therapy (70% versus 47%, p<0.01). None of the 17 patients with negative EET without therapy had a positive response to EET with therapy. In the 27 patients with the two positive EETs, the rate–pressure product changed from 214±59 to 216±61 (p=NS); the duration of effort (i.e., time from beginning of effort to the development of diagnostic ST segment depression or to the end of the test, in negative cases) significantly increased from 6.0±2.1 to 7.4±1.8 minutes (p<0.01).

Comparison of Dipyridamole Echocardiography and Exercise Electrocardiography Tests
Of the 16 patients with negative DET after therapy introduction, 10 (63%) had a negative response also at EET on treatment. EET and DET yielded concordant (positive versus negative) results in 41 of 57 patients (off treatment) and in 35 of 57 (on therapy; 71% versus 61%, p=NS; Figure 2).

In the subgroup of 38 patients with both positive DET and EET without treatment, the therapy-induced variations in exercise time (evaluated at the end of exercise in the patients with a negative test on treatment) were significantly correlated with the therapy-induced variations in dipyridamole time (r=0.5, p<0.01; Figure 3), whereas they were not significantly correlated to variations in wall motion score index (r=0.3, p=NS; Figure 4).

Discussion
The results of this study show that antianginal therapy can protect from dipyridamole-induced ischemia and that the therapy-induced changes in DET response tend to parallel variations in exercise tolerance. The objective evaluation of the response to therapy during DET is better achieved based on the timing rather than the extent and severity of the
dipyridamole-induced dyssynergy. The presence of a correlation between therapy-induced changes in exercise and dipyridamole time can be considered consistent with a previous study, documenting the presence of a relation between these two parameters in patients off therapy.8 The absence of correlation between the wall motion score index and therapy-induced changes in exercise tolerance may be due, at least in part, to test protocol that we adopted.

According to our approach, the development of a new wall motion abnormality is an absolute end point of the test, chosen to prevent potential complications from severe and prolonged ischemia. The wall motion score index might have been more meaningful if a more aggressive protocol were used, implying the full dose administration in all patients. However, we believe that this would have very likely lowered the safety of the test.

Effects of Therapy on Dipyridamole-Induced Ischemia

We are accustomed to think of myocardial ischemia within the familiar framework of “supply–demand mismatch.” The mechanism of action of anti-ischemic drugs is also usually easily fitted within this framework. In particular, β-blockers are credited with reducing exercise-induced ischemia by decreasing myocardial oxygen demand and possibly by increasing supply through a reduction in extravascular compressive forces.9 However, this straightforward explanation seems inadequate in justifying the protective effects of β-blockers on dipyridamole-induced ischemia. Experimental data show that β-blockers do not affect the dipyridamole-induced increase in flow,10 and this is in good agreement with the clinical experience that this class of drugs affects little, if any, the results of nuclear myocardial perfusion imaging with dipyridamole.1 On the other hand, the increase in myocardial oxygen consumption does not play any significant role in the induction of dipyridamole-induced ischemia, which is due to an absolute reduction in subendocardial flow (tightly linked to regional wall thickening) mostly for “vertical” and “horizontal” steal phenomena.5 However, experimental studies on the model of the exercising dog have shown that β-blockers protect myocardium from stress-induced myocardial dysfunction also by improving the regional myocardial blood flow–function relation: for a given transmural flow, there is a rise of subendocardial and a fall of subepicardial flow, with an improved

**FIGURE 2.** Chart of dipyridamole echocardiography test (DET) and exercise electrocardiography test (EET) results in the study population off and on antianginal treatment. +, Positive result; –, negative result.

**FIGURE 3.** Correlation between the therapy-induced variations in dipyridamole and exercise time in the 38 patients with positivity of both tests off treatment. Δ, Variations.

**FIGURE 4.** Correlation between the therapy-induced wall motion score index (WMSI) (during dipyridamole) and exercise time variations in the 38 patients with positivity of both tests off treatment. Δ, Variations.
regional performance. This same mechanism has also been documented with some calcium antagonists, such as diltiazem, and may explain, in part, the beneficial effects of this class of drugs on dipyridamole-induced ischemia.

Calcium antagonists can effectively prevent ischemia provoked by dipyridamole also through other mechanisms, which they share with nitrates, and they tend to increase the coronary flow supply during stress. In this case, the prevention of steal phenomena may be due to the increase in collateral flow (which has been shown with nitrates and, to a much lower extent, with some calcium antagonists) and to the dilation of epicardial coronary lumen size. The pronounced increase in collateral flow can prevent horizontal steal phenomena due to dipyridamole, whereas even a small increase of the coronary diameter can dramatically reduce the blood pressure drop across the stenosis (which is proportional to the fourth power of the vessel radius), therefore preventing vertical steal phenomena, which are linked to a critical decrease in poststenotic perfusion pressure.

Comparison With Previous Studies

Since 1976, dipyridamole infusion had been combined with the 12-lead electrocardiogram for the diagnosis of myocardial ischemia. With the dipyridamole electrocardiographic test, the only objective marker of myocardial ischemia is ST segment shift. Previous investigators have convincingly shown that antianginal therapy can suppress electrocardiographic signs of myocardial ischemia induced by dipyridamole. Kubota et al. repeated the dipyridamole electrocardiographic test (at the dose of 0.56 mg/kg during 4 minutes) after premedication in 12 patients who had developed ST segment depression, detected by 87-lead electrocardiographic mapping, during the first test. After oral administration of nitrates (four patients) or diltiazem (eight patients), ST segment depression after dipyridamole infusion was completely suppressed in 11 patients. Osterspey et al. showed suppression of signs of ischemia (detected by 12-lead electrocardiography after dipyridamole infusion up to 0.75 mg/kg during 10 minutes) in 11 of 47 patients with a positive test and coronary artery disease who repeated the test under antianginal therapy.

Exercise and Dipyridamole Stress: Similarities and Differences

EET and DET results tended to be symmetrically affected by therapy. However, the two tests have different pathogenetic mechanisms of provocation of ischemia. In particular, exercise can induce ischemia by transient coronary constriction or by fixed reduction of coronary reserve due to structural coronary stenosis, whereas the prerequisite of dipyridamole test positivity is a reduction of coronary flow reserve due to organic factors.

However, the overall good concordance of the two stress tests suggest that in the selected study population (stable angina patients with documented coronary disease) EET and DET mostly explored the "organic" side of coronary disease, and effort-induced coronary hypertone modulation, which would have certainly made this correlation worse, played a relatively minor role, although modulation certainly increased the scatter of the correlation between EET and DET results.

Limitations of the Study

In the present study, the correlation between the two stress tests was made with two different markers of ischemia: ST segment changes for EET and transient dyssynergy for DET. Electrocardiographic changes are obviously less specific and less sensitive markers of ischemia, although less operator dependent. The correlation might have been more meaningful if the transient dyssynergy would have been taken as a marker of ischemia also during exercise. However, despite the recognized limitations of the electrocardiographic marker, EET still remains the standard diagnostic procedure to assess the efficacy of therapeutic interventions.

Echocardiographic analysis was semiquantitative and subjective. Although this method is simple, reliable, and reproducible with experienced operators, the accuracy of the temporal allocation of a dyssynergy can be negatively affected by the qualitative nature of the assessment.

Last, the study gives no information on the underlying mechanisms of the protective effects of therapy. To substantiate the hypothesized mechanisms, it should be necessary to monitor not only the left ventricular function but also the regional coronary flow and its transmural distribution in resting conditions and during stress. Further studies are therefore needed to specifically address this point.

Clinical Implications

Antianginal pharmacological therapy reduces the sensitivity of DET as a screening test for coronary artery disease. It suppresses or delays the appearance of the transient dyssynergy, thus obscuring the diagnostic interpretation of DET. Even in patients receiving antianginal medications, a positive DET will have the usual implications for management. Similarly to EET or radionuclide ventriculography, a negative DET in patients on antianginal drugs does not exclude significant and possibly threatening myocardial ischemia.

Another important practical point stems from the documented significant correlation between changes in exercise tolerance and dipyridamole time induced by therapy. In addition, the binary results (positive versus negative) of the two tests tended to change concordantly after therapy. The response to therapy may therefore provide a clue to the objective assessment of efficacy of antianginal therapy in patients unable to exercise. These data can be considered consistent with those obtained in anginal patients undergoing coronary angioplasty, in whom the anatomic improvement in the
treated coronary lesion was correlated with the change in the presence, timing, and extent of dipyridamole-induced dyssynergy.20

Therefore, if the purpose of DET is to diagnose ischemia, it should be performed in the absence of antianginal medications. If the purpose of the test is to assess the protective effects of antianginal therapy, the test should be repeated while the patient is on medications.

In conclusion, the prevalence of dipyridamole-induced ischemia can be dramatically reduced by anti-ischemic therapy, and DET appears to be suitable for an exercise-independent assessment of the potential beneficial effects of pharmacological therapeutic interventions.

References

KEY WORDS • echocardiography • myocardial ischemia • dipyridamole • antianginal therapy
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