Low-Dose Dipyridamole Infusion Acutely Increases Exercise Capacity in Angina Pectoris
A Double-Blind, Placebo Controlled Crossover Stress Echocardiographic Study

Stefano Tommasi, MD, Erberto Carluccio, MD, Maurizio Bentivoglio, MD, Luigi Corea, MD, FESC, FACC, Eugenio Picano, MD, PhD
Perugia and Pisa, Italy

OBJECTIVES
The aim of this study was to assess whether endogenous accumulation of adenosine, induced by low-dose dipyridamole infusion, protects from exercise-induced ischemia.

BACKGROUND
Adenosine is a recognized mediator of ischemic preconditioning in experimental settings.

METHODS
Ten patients (all men: mean age 63.4 ± 7.3 years) with chronic stable angina, angiographically assessed coronary artery disease (n = 7) or previous myocardial infarction (n = 3) and exercise-induced ischemia underwent on different days two exercise-stress echo tests after premedication with placebo or dipyridamole (15 mg in 30 min, stopped 5 min before testing) in a double-blind, placebo controlled, randomized crossover design.

RESULTS
In comparison with placebo, dipyridamole less frequently induced chest pain (20% vs. 100%, p = 0.001) and >0.1 mV ST segment depression (50% vs. 100%, p < 0.05). Wall motion abnormalities during exercise-stress test were less frequent (placebo = 100% vs. dipyridamole = 70%, p = ns) and significantly less severe (wall motion score index at peak stress: placebo = 1.55 ± 0.17 vs. dipyridamole = 1.27 ± 0.2, p < 0.01) following dipyridamole, which also determined an increase in exercise time up to echocardiographic positivity (placebo = 385.9 ± 51.4 vs. dipyridamole = 594.4 ± 156.9 s, p < 0.01).

CONCLUSIONS
Low-dose dipyridamole infusion increases exercise tolerance in chronic stable angina, possibly by endogenous adenosine accumulation acting on high affinity A1 myocardial receptors involved in preconditioning or positively modulating coronary flow through collaterals. (J Am Coll Cardiol 2000;35:83–8) © 1999 by the American College of Cardiology

Adenosine is a recognized mediator of myocardial preconditioning (1,2). It acts on high affinity subtype A1 of adenosine myocardial receptors which enhances the inhibitory G protein responsiveness, determining a protection against ischemia by promoting the protein-kinase C activation (3,4) and opening of the ATP-dependent K+ channel (5). However, clinical experience has shown that adenosine accumulation is a double-edged sword for ischemic myocardium, with definite dose-dependent ischemic potential (6,7). At high doses, adenosine stimulates low affinity A2 coronary receptors, which are thought to mediate arteriolar relaxation, and thereby malignant coronary vasodilation and eventually myocardial ischemia in the presence of steal-prone coronary anatomy (8,9). Dipyridamole determines endogenous adenosine accumulation via inhibition of cellular uptake (6). High intravenous doses determine a four-fold increase in plasma adenosine (10) and have a clear pro-ischemic effect—exploited for diagnostic testing with functional imaging (11). On the contrary, very low doses and prolonged infusion of intravenous dipyridamole induce only a mild increase in plasma adenosine concentration (12). We hypothesized that this mild stimulation by adenosine achieved with low dose dipyridamole infusion might exert an anti-ischemic effect in patients with exercise-induced ischemia, conceivably through a predominant stimulation of high affinity A1 myocardial receptors (2,13). We therefore evaluated the effects of low-dose dipyridamole premedication in 10 patients with stable angina, exercise-induced ischemia and angiographically assessed coronary artery disease (CAD) (or previous myocardial infarction [MI]), in a randomized, double-blind, placebo controlled, crossover study design. Exercise-induced ischemia was evaluated by assessing effort-induced chest pain as a tertiary end point, electrocardiographic changes as a secondary end point and regional wall motion abnormalities by two-dimensional echocardiography as a primary end point.

From the Department of Clinical and Experimental Medicine, Cardiology Unit, University of Perugia, Perugia, Italy, and Institute of Clinical Physiology, CNR, Pisa, Italy.
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Abbreviations and Acronyms

- CAD = coronary artery disease
- MI = myocardial infarction
- WMSI = wall motion score index

METHODS

Patients. Ten men (63.4 ± 7.3 years) with chronic stable angina and abnormal exercise test limited by angina with clear-cut horizontal or downsloping ST segment depression (≥0.15 mV) and obvious echocardiographic positivity (akinesthesia of ≥2 adjacent segments that were normally contracting in resting condition) were selected. Patient characteristics are reported in Table 1. All patients had CAD proved by angiography with visually assessed ≥75% luminal diameter narrowing in at least one major artery. Six patients had one vessel and four patients had two-vessel disease; none had three-vessel disease or significant left main narrowing. Patients were excluded if they had collateral vessels at the coronary angiography, MI within three months, unstable angina, chronic left or right bundle branch block, symptomatic congestive heart failure, complex ventricular arrhythmias, nonsinus rhythm, valvular heart disease or technically poor acoustic window. An additional inclusion criteria required all patients to be off calcium antagonists and beta-adrenergic blocking agents (stopped 3 days before testing) and have at least two reproducible (<15% variability in exercise time) positive exercise stress tests in the previous week (14). All patients gave written, informed consent for the study.

Study design. Patients were studied in the morning in the fasting state. They performed two exercise stress tests on two nonconsecutive days with a 48 h interval between the two tests. Before each exercise stress test, they received in a double blind fashion, dipyridamole (15 mg in 30 min, administered in microboluses of 1 mg every 2 min) or corresponding placebo, which were randomly allocated in a crossover study design.

Exercise stress test. All patients performed two multistage bicycle ergometer tests, with an initial load of 25 W and subsequent increments of 25 W every 2 min (14). Electrocardiographic leads showing the most obvious ischemic changes during the previous exercise stress tests were continuously monitored during exercise. Twelve-lead electrocardiogram and systolic and diastolic pressures, obtained by a cuff sphygmomanometer, were recorded at baseline and each minute thereafter. Criteria for interrupting the test were moderately severe chest pain, 0.2 mV of ST segment depression 0.08 after the J point or maximal age-related heart rate and muscular exhaustion in the absence of ischemia (14). In this study, the heart rate-pressure product (heart rate × systolic blood pressure × 1/100) was used as an index of heart work and measured at the onset of ischemia (arbitrarily fixed at 0.10 mV of ST segment depression) or at peak exercise in negative tests. Two-dimensional echocardiographic monitoring was also performed during exercise stress test with a commercially available imaging system (ATL UltraMark 9, Bothell, Washington). At baseline, peak stress and recovery phase (3 min after stopping exercise with patient in the supine position) the wall motion score index (WMSI) was calculated by using a 16 segment model of the left ventricle, each segment scored from 1 = normal to 4 = dyskinetic according to the recommendations of the American Society of Echocardiography (15). To avoid the bias of the interobserver variability in stress echo reading (16,17), the same experienced observer reviewed and scored each and every stress stress study being blinded to the study condition (placebo vs. dipyridamole). The intra- and interobserver reproducibility of the stress echo reading in our lab is >90%. For each study, the following data were analyzed: 1) WMSI at rest, peak and recovery, and 2) exercise-time as the interval (seconds) between starting of exercise and appearance of obvious dysynchrony (change in wall motion score >0.20 from baseline).

Statistical analysis. Data are expressed as mean ± 1 standard deviation. Continuous variables before and immediately after infusion of placebo or dipyridamole were compared using a paired Student t test and Wilcoxon test for nonparametric data. Analysis of echocardiographic, ergonomic and hemodynamic variables during exercise-stress echo after pretreatment with placebo or dipyridamole was performed using a two-way repeated measures analysis of variance. Post hoc comparisons between groups at various time points were performed with Student t test for unpaired data with Bonferroni correction (18). Categorical variables were compared with chi-square test and Fisher exact test when appropriate. We considered as significant a two-tailed p value <0.05.

RESULTS

Resting conditions. Table 1 summarizes the clinical characteristics of the study population. Hemodynamic, echocar-

Table 1. Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>63.4 ± 7.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.6 ± 13.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.2 ± 4.7</td>
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<tr>
<td>BSA (m²)</td>
<td>1.93 ± 0.13</td>
</tr>
<tr>
<td>Hypertension (number)</td>
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</tr>
<tr>
<td>Previous AMI (number)</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes (number)</td>
<td>2</td>
</tr>
<tr>
<td>Dyslipidemia (number)</td>
<td>9</td>
</tr>
<tr>
<td>Smokers (number)</td>
<td>5</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; BSA = body surface area.
Table 2. Effects of Placebo and Dipyridamole (15 mg in 30 min) on Hemodynamic, Echocardiographic and Electrocardiographic Parameters

<table>
<thead>
<tr>
<th>Test 1</th>
<th>Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>Placebo</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>139.5 ± 14.2</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>86.5 ± 9.4</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>81.5 ± 8.3</td>
</tr>
<tr>
<td>RPP</td>
<td>11370 ± 1690.9</td>
</tr>
<tr>
<td>QTc</td>
<td>0.41 ± 0.02</td>
</tr>
<tr>
<td>WMSI</td>
<td>1.07 ± 0.07</td>
</tr>
</tbody>
</table>

HR = heart rate; RPP = rate pressure product; QTc = heart rate-corrected QT interval (ms); SBP = systolic blood pressure; WMSI = wall motion score index.

Exercise testing. All patients had technically adequate resting, effort and recovery ECG tracing as well as echocardiographic images. At peak effort, after pretreatment with placebo, all patients exhibited a score of ST segment depression (defined as sum, in mm, of the ST segment depression in all the leads with a positive electrocardiographic response) of 4.8 ± 1.3 mm at a mean load of 90 ± 12 W, associated with the appearance of anginal chest pain.
Wall motion abnormalities appeared in all patients, involving $6.4 \pm 2.7$ myocardial segments with a mean WMSI of $1.55 \pm 0.17$. In comparison with placebo, pretreatment with dipyridamole demonstrated a significant increase in seconds of exercise until 0.1 mV of ST segment depression ($612.4 \pm 168.6$ vs. $405.8 \pm 58.2$ s, $p < 0.01$) or until echocardiographic positivity ($594.4 \pm 156.9$ vs. $385.9 \pm 51.4$ s, $p < 0.01$) (Table 3 and Fig. 1). Watts to positivity were also significantly higher after dipyridamole than placebo ($135 \pm 29$ vs. $90 \pm 12$, $p < 0.001$) as well as the rate-pressure product ($26,284 \pm 4,703$ vs. $21,966 \pm 3,190$, $p < 0.01$) expressing a higher heart work necessary to reach an ischemic threshold. During exercise-stress echo performed after pretreatment with dipyridamole, angina appeared in only two patients ($p < 0.001$ vs. pretreatment with placebo) and was also less severe. The exercise stress test was, moreover, completely negative in three patients who reached the 85% of predicted heart rate without appearance of angina, ST segment depression or wall motion abnormalities at the echocardiographic monitoring. Considering the primary end point of exercise-stress echo, exercise induced wall motion abnormalities were less severe after dipyridamole when compared with placebo, with a mean WMSI of $1.27 \pm 0.17$ (vs. $1.55 \pm 0.17$ of placebo, $p < 0.01$) and more rapidly recovering ($162 \pm 178$ vs. $384 \pm 94$ s, $p < 0.01$) (Fig. 2).

**DISCUSSION**

Low dose, prolonged dipyridamole infusion, at a dose known to increase plasma adenosine levels only modestly, increases work tolerance and ischemic threshold in patients with stable effort angina and angiographically assessed CAD.

**Pathophysiological mechanisms.** At least in theory, several mechanisms might concur to the beneficial effect of dipyridamole, including preconditioning, increase in coronary collateral blood flow and metabolic cardioprotection. The principal receptor target of low dose dipyridamole infusion is A1 receptor present on the myocardium and known to mediate preconditioning. The high affinity for adenosine can explain why it can be activated also by a dipyridamole dose known to increase plasma adenosine only modestly over resting level (12). With higher and faster dipyridamole infusion rates, as those used for stress testing purposes, plasma adenosine concentration increases more substantially, with values three- to four-fold higher than those present at rest (10). Such adenosine concentration is effective in stimulating low affinity A2 receptors present in coronary vessels. In particular, stimulation of A2a receptors produces marked dilation of coronary resistance vessels, determining arteriolar vasodilation and frequent occurrence of steal phenomena in the presence of significant CAD. This heterogeneity of populations of adenosine receptors may explain why a beneficial anti-ischemic effect of the drug is detectable at low doses and a clear detrimental pro-ischemic effect appears at high doses in unselected
patients (6,7). Adenosine is known to increase coronary blood flow in patients with spontaneously visible collaterals, as a result of a reduction in the coronary collateral vascular resistance and peripheral vascular resistance of the recipient vessel (19,20). With high dipyridamole doses, angiographically assessed coronary collateral circulation represents a steal-prone coronary anatomy favoring the induction of ischemia during vasodilator stress testing (21). In our study, we excluded patients with collateral vessels at the coronary angiography, but this selection criterion does not rule out the anatomic presence and functional relevance of coronary collaterals. In fact, Cohen and Rentrop (22) showed that coronary collaterals could be demonstrated during coronary occlusion even if they were not evident during routine baseline coronary angiography. It is conceivable that low dose dipyridamole might increase coronary flow through collaterals (19,20). An additional possibility is a metabolic effect of adenosine. In fact, adenosine increases glucose uptake independent of its vasodilatory effect and stimulates glycolytic flux in anoxic myocardium (23,24). Which, if any, of the three pathways (preconditioning, coronary hemodynamic, cardiometabolic effect) is more relevant in determining the beneficial effects of dipyridamole cannot be established from this study.

Comparison with previous studies. Several studies have shown the protective effects of dipyridamole or exogenous adenosine in human models of myocardial ischemia, mostly with intracoronary injection during coronary angioplasty (25–27). Bamiphyline is an A1 adenosine receptor blocker that abolishes preconditioning due to repeated episodes of ischemia, again suggesting that adenosine A1 receptor stimulation may be important to prevent ischemia (28). Laghi-Pasini et al. (12) convincingly showed that peripheral infusion of low-dose dipyridamole prevents dipyridamole-induced ischemia detected during pharmacological stress echo, clearly demonstrating the two faces of dipyridamole in the very same patient in the same setting: dipyridamole is anti-ischemic and protective at very low dose and pro-ischemic and detrimental at high doses. Our study moves along the same line, since we used a “therapeutic” dosage and infusion schedule similar to the one proposed by Laghi-Pasini et al. (12). However, our study is also basically different, since we evaluated the “therapeutic” effect of dipyridamole on a physiological model of exercise-induced ischemia.

The integrated anti-ischemic adenosine strategy. Adenosine has been named a “retaliatory metabolite” (29) acting to protect from ischemia the very same cells that produce it. A1 receptors are a first line, short-acting, functional line of defense of adenosine accumulation against acute ischemia. This response temporally overlaps with an A1–A2 receptors mediated second line, long-acting, structural line of defense exerted by adenosine accumulation against chronic ischemia via coronary angiogenesis (30). Such a “cardiovascular” anti-ischemic system might be important not only in the cardiac, but possibly also at the cerebrovascular level (31). Further studies are needed to explore the far reaching implications of this hypothesis.

Study limitations. The main limitation of our study was the small number of patients studied. However, although only 10 subjects were studied, the power of the investigation was substantially increased by using each subject as his own control in a double-blind crossover design in which dipyridamole was compared with placebo. Another limitation was the lack of determination of plasma adenosine levels. The absence of electrocardiographic signs of ischemia after infusion with dipyridamole showed the absence of clear-cut ischemic effect of the drug, so that the plasma and interstitial adenosine levels reached in our patients by low dose, prolonged dipyridamole infusion were likely unable to induce a steal phenomena in the coronary circulation. On the other hand, Laghi-Pasini et al. (12), using a lower dose of intravenous dipyridamole (2 mg every 30 min for five consecutive times) have recently demonstrated a pulsed increase in plasma adenosine levels to determine a cardio-protective effect during a subsequent dipyridamole stress test. The design of our study does not allow clarification of the underlying mechanism of the anti-ischemic effect observed with low dose dipyridamole. A1 receptor-mediated preconditioning, increase in coronary blood flow (through collaterals?) and metabolic cardioprotection through potentiation of the glycolytic pathway are all reasonable but unproven candidates.

Reprint requests and correspondence: Dr. Erberto Carlucci, Via dell’Allodola, 1, 06100 Ponte S. Giovanni, Perugia, Italy.

REFERENCES


