Bamiphylline Improves Exercise-Induced Myocardial Ischemia Through a Novel Mechanism of Action

Achille Gaspardone, MD, FESC; Filippo Crea, MD, FACC, FESC; Maria Iamele, MD; Fabrizio Tomai, MD; Francesco Versaci, MD; Antonio Pellegrino, MD; Luigi Chiarilippo, MD, FACC; and Pier Agostino Gioffré, MD, FESC

Background. In patients with stable angina pectoris, aminophylline, a nonselective antagonist of adenosine receptors, markedly improves exercise capacity. To establish the role played by A₁ adenosine receptors in the anti-ischemic action of aminophylline, the effects of bamiphylline, a selective A₁ antagonist, on exercise-induced ischemia were investigated in patients with stable angina pectoris.

Methods and Results. In a single-blind, placebo-controlled, randomized cross-over trial in 18 patients, oral administration of 1200 mg bamiphylline increased both the time to 1-mm ST segment depression (from 524±177 to 664±192 seconds, P<.01) and the rate-pressure product at 1-mm ST segment depression (from 159±31 to 190±34 beats per minute per mm Hg/10² (P<.001). End-diastolic and end-systolic left ventricular volumes, left ventricular ejection fraction, and systolic septal and posterior wall thickening investigated by two-dimensional echocardiography in 12 of the 18 patients were not affected by oral administration of bamiphylline (124±22 versus 125±20 mL, P=NS; 49±12 versus 50±13 mL, P=NS; 60±8% versus 58±7%, P=NS; 35±6% versus 36±7%, P=NS; 32±6% versus 33±6%, P=NS, respectively). In 7 of the 18 patients, the intravenous infusion of bamiphylline (5 mg/kg in 15 minutes) during cardiac catheterization did not produce any significant change of heart rate (76±10 versus 75±13 beats per minute, P=NS), mean right atrial pressure (3.8±1.7 versus 3.7±1.7 mm Hg, P=NS), mean aortic pressure (102±12 versus 99±10 mm Hg, P=NS), or left ventricular end-diastolic pressure (14±3 versus 14±4 mm Hg, P=NS) compared with baseline. Furthermore, after intravenous infusion of bamiphylline, the diameter of seven proximal and distal normal segments and of seven stenotic segments were similar to those measured at baseline (3.1±0.5 versus 3.1±0.5 mm, P=NS; 1.6±0.5 versus 1.6±0.5 mm, P=NS, respectively).

Conclusions. In patients with stable angina pectoris, oral administration of bamiphylline improves exercise capacity. Its anti-ischemic action does not appear to be mediated by systemic hemodynamic effects or by stenosis dilation. Therefore, the improvement of myocardial ischemia caused by bamiphylline is probably due to redistribution of coronary blood flow toward the underperfused subendocardium. This novel anti-ischemic action would appear to be mediated by antagonism of A₁ receptors. (Circulation 1993;88:502-508)

KEY WORDS • adenosine • receptors • angina • bamiphylline • ischemia

In patients with stable angina pectoris, aminophylline (theophylline ethylenediamine), a nonselective antagonist of adenosine receptors, improves exercise capacity and reduces the severity of exercise-induced angina.⁴ The most important pharmacological effect of aminophylline, at therapeutic concentrations, is blockade of adenosine receptors.⁵-⁷ The effects of adenosine are due to the stimulation of two classes of extracellular receptors, subtypes A₁ and A₂.⁸-¹⁰ The stimulation of A₁ receptors, present in cardiomyocytes and perivascular sympathetic nerves,¹³ causes electrophysiological effects and inhibits the neuronal release of catecholamines.¹³-¹⁵ The stimulation of A₂ receptors, present in endothelial and vascular smooth muscle cells,¹⁶ causes coronary vasodilation.¹⁰,¹⁷,¹⁸ The xanthine derivative bamiphylline is the most selective antagonist of A₁ adenosine receptors¹⁹ available for clinical use. To establish the role played by A₁ adenosine receptors in the anti-ischemic and antiangiinal effects of aminophylline, we investigated the effects of bamiphylline on exercise-induced ischemia and on anginal pain in patients with stable angina pectoris.

Methods

Patients

Eighteen patients (15 men and 3 women; age, 47 to 71 years; mean age, 61 years) with chronic stable angina...
pectoris (symptom duration ranging from 6 to 48 months), participated in this study. Six patients had suffered a previous myocardial infarction more than 12 months before the study (four non-Q wave myocardial infarction and two inferior). All patients had reproducible positive exercise tests for myocardial ischemia with horizontal or downsloping ST segment depression of 2.0 mm or more and anginal pain. All patients had at least one critical stenosis (internal diameter reduction of more than 70% by visual assessment) in the proximal two thirds of one major epicardial coronary artery. Coronary angiography showed one-vessel disease in 4 patients, two-vessel disease in 12 patients, and three-vessel disease in 2 patients. All patients were normotensive, in sinus rhythm, and without evidence of heart failure, cardiomyopathy, or valvular disease. No patient had evidence of left ventricular hypertrophy or conduction defects that could interfere with the interpretation of ST segment changes, and no patient was taking digitalis. All patients gave written informed consent for participation in the study, which was approved by the ethics committee.

**Exercise Test**

All 18 patients were enrolled. Nitrate preparations other than sublingual nitroglycerin and calcium entry-blocking agents were withdrawn 4 days before the study, and β-blocking agents were withdrawn 5 days before the study. Only sublingual nitroglycerin was used during the latter period, and a minimum of 12 hours were allowed to elapse before testing was begun if this drug was used. Patients were also requested to abstain from xanthine-containing drugs, food, and drinks for at least 48 hours before the study. Before entering the study, each patient underwent at least two exercise tests according to the modified Bruce protocol to familiarize them with the procedure and with the staff. A single-blind, placebo-controlled, randomized cross-over design was used. Patients were randomized to two groups of nine patients. One group underwent a symptom-limited, computer-assisted treadmill exercise test using the modified Bruce protocol 60 to 90 minutes after 1200 mg oral bamiphylline (Chiesi Farmaceutici, Parma, Italy) on day 1 and after placebo on day 2. The other group received placebo on day 1 and bamiphylline on day 2. A 12-lead ECG and arterial blood pressure (cuff sphygmomanometer) was obtained with patients in standing position immediately before the administration of bamiphylline, immediately before exercise testing (60 to 90 minutes after bamiphylline administration), at 1-minute intervals during exercise, and each minute up to 15 minutes after exercise. Three ECG leads were continuously monitored before, during, and after exercise. All exercise tests were performed on two consecutive days between 9:00 AM and 12:00 noon with the laboratory temperature at 22 to 24°C. The level of the ST segment, 60 ms after the J point was calculated after signal averaging by means of a computer-assisted system (CASE Marquette 12) in all 12 leads. The calculated values were printed out, along with the heart rate, against time in trend format. This provided measurement of the ST segment level with an accuracy of 0.1 mm. The lead showing the greatest ST segment depression was selected for analysis. Before each test, patients were urged to indicate the onset of angina. Criteria for interrupting the test were more than 1.0-mm ST segment depression 60 ms after the J point or maximal age-related heart rate, severe chest pain, or muscular exhaustion in the absence of ischemia. The following parameters were measured: resting heart rate and blood pressure; time, in seconds, to the onset of 1-mm ST segment depression; heart rate, blood pressure, and rate-pressure product at the onset of 1-mm ST segment depression; time to pain onset, in seconds; maximal ST segment depression; exercise duration, in seconds; and maximal anginal pain normalized for maximal ST segment depression. In negative tests, all of the parameters were measured at peak exercise. Immediately before each exercise test, venous blood samples were obtained to measure serum levels of bamiphylline. Samples were centrifuged at 1000 rpm for 15 minutes, and serum was frozen at −60°C until analyzed. Serum levels of bamiphylline were assessed by high-performance liquid chromatography.²⁰ At the beginning of each exercise test, patients were instructed to promptly report the onset of anginal pain. Immediately after the test, the severity of maximal exercise-induced angina was assessed using a visual-analog scale.²¹ The 100-mm scale was marked from no symptom to severe symptom. The scale was measured from 0 to the subject’s mark in millimeters. All patients were asked to mark the scale to express the severity of exercise-induced pain and the severity of the anginal pain during daily life for which they used to take nitroglycerin.

**Echocardiographic Study**

In 12 of the 18 patients (10 men and 2 women), the effects of bamiphylline on left ventricular volumes and function were assessed using two-dimensional echocardiography. After the patient was placed in the left lateral decubitus position, two-dimensional echocardiograms were obtained using a commercially available phased-array imaging system with 2.5-MHz transducers (Hewlett Packard, Sonos 1000). Studies were recorded on VHS videotape. Four views (parasternal long-axis, parasternal short-axis at the mitral, papillary muscle and apical level, apical four-chamber, and two-chamber) were obtained at rest and after administration of bamiphylline or placebo. To this purpose, patients were randomized to two groups of six patients. One group underwent two-dimensional echocardiographic examination 60 to 90 minutes after oral bamiphylline (1200 mg) on day 1 and after placebo on day 2. The other group received placebo on day 1 and bamiphylline on day 2. All studies were performed by one experienced operator blind to the treatment. The echocardiograms were read at baseline and after placebo or bamiphylline administration. The following parameters were analyzed: left ventricular end-diastolic and end-systolic volumes, left ventricular ejection fraction, wall thickening (systolic thickening of the interventricular septum or posterior wall minus diastolic thickening of the interventricular septum or posterior wall/systolic thickening of the interventricular septum or posterior wall) and segmental wall motion. For wall motion analysis, the left ventricle was divided into 11 segments, which were graded as hyperkinetic, normal, hypokinetic, akinetic, or dyskinetic. Ventricular volumes were calculated using single-plan Simpson’s rule.²² All parameters were calculated independently in a blinded-to-treatment fashion.
by two expert echocardiographers who had no knowledge of the patient's history or results of the stress ECGs or coronary angiograms. A third investigator reviewed the echocardiograms in blinded manner if the first two investigators were not in agreement.

**Hemodynamic and Angiographic Study**

In 7 of the 18 patients (all men), the effects of the infusion of bamiphylline were assessed hemodynamically and angiographically. Fifteen minutes after completion of the diagnostic catheterization, a model 7F Swan-Ganz catheter was positioned in the right atrium to measure baseline right atrial pressure and then advanced to the pulmonary artery to allow pressure monitoring and collection of venous blood samples. Similarly, a model 7F pigtail catheter was positioned in the left ventricle to measure baseline end-diastolic pressure and then pulled back in the aortic root to allow pressure monitoring and arterial blood sampling. Blood samples for cardiac output determinations were obtained in triplicate. The intravenous infusion of bamiphylline injectable (5 mg/kg in 15 minutes) (bamifyllini hydrochloridum 300 mg/5 mL dissolved in 0.9% NaCl; Christiaens sa, Brussels, Belgium) was then started. Heart rate, pulmonary artery, and aortic pressures were recorded continuously throughout the infusion period. Cardiac output determinations were recorded before and at the end of the infusion period when right atrial pressure was also measured during the pull back of the Swan-Ganz catheter and the pigtail catheter was repositioned in the left ventricle to measure end-diastolic pressure. Immediately after hemodynamic assessment, coronary angiography was repeated in the most suitable view of the left coronary artery, selected during diagnostic arteriography. Hemodynamic data were displayed on an oscilloscope and recorded on a multichannel tape recorder throughout the study and then played back on a direct-writing oscillograph. Pressures were measured through the heparin-filled catheters connected via stiff polyvinyl tubes to strain-gauge manometers. Electronic resistance-capacitance filters with 2-second time constant were used to derive mean right atrial pressure. Cardiac output was calculated by the Fick technique. Total pulmonary resistance was calculated dividing mean pulmonary arterial pressure by the cardiac output; systemic vascular resistance was calculated by dividing mean aortic pressure minus mean right atrial pressure by the cardiac output. The luminal diameter of the coronary arteries was measured by an automated edge contour detection computer analysis system (ELK Cine-Angio System CAP-35E, Medis ELK, Neunen, The Netherlands). The size of the stem of the Judkins coronary catheter was used for calibration purposes to obtain measurements in millimeters. All major coronary arteries were divided into thirds using the American Heart Association classification. For the purpose of the study, normal and diseased segments located in proximal and distal locations were analyzed. The arteriograms were analyzed by two independent expert observers blind to the treatment.

**Statistical Analysis**

Statistical analysis of the ECG, echocardiographic, hemodynamic, and angiographic data was performed using Student's t test for paired data. Pain severity and the derived parameters were analyzed using the Wilcoxon signed-rank test, as these parameters do not have a normal distribution. The degree of ST segment depression is expressed in millimeters (1 mm=0.1 mV). Data are presented as mean±1 SD. Visual-analog scale data are expressed as median and range values. For the purposes of this study, a value of P<.05 was considered significant.

**Results**

**Exercise Test**

The mean serum bamiphylline concentration normalized for body surface area was 1.6±0.3 µg/mL. One patient complained of transient dizziness after oral administration of bamiphylline. No patient reported any symptom with placebo. The values of resting heart rate and systolic and diastolic blood pressures on bamiphylline were similar to those on placebo (79±12 versus 78±12 beats per minute, P=NS; 124±12 versus 124±12 mm Hg, P=NS; 76±12 versus 75±13 mm Hg, P=NS). Bamiphylline, compared with placebo, increased the time to 1-mm ST segment depression from 52±177 to 664±192 seconds (P<.01), the heart rate at 1-mm ST segment depression from 104±8 to 117±12 beats per minute (P<0.01), the rate-pressure product at 1-mm ST segment depression from 159±31 to 190±34 beats per minute · mm Hg · 10² (P<.001), and total exercise duration from 614±186 to 714±164 seconds (P<.01) (Figs 1 and 2). In two patients, exercise test was negative for ST segment changes after bamiphylline.
ment depression was similar after placebo or bamiphylline (1.4±0.4 versus 1.5±0.5 mm, P=NS). Furthermore, oral bamiphylline increased the time to pain onset from 438±190 to 564±191 seconds (P<.02) (Fig 1) and decreased the severity of maximal anginal pain normalized for maximal ST segment depression from 38 (range, 11 to 84) to 17 (range, 0 to 65) (P<.05) (Fig 3). Three patients did not experience any pain at all after bamiphylline. Finally, bamiphylline did not affect the degree of ST segment depression at the onset of pain (0.9±0.4 versus 0.9±0.6 mm, P=NS).

Echocardiographic Findings

Image quality after placebo or bamiphylline administration was unchanged in all subjects. The values of left ventricular end-diastolic volume, left ventricular end-systolic volume, left ventricular ejection fraction, and interventricular septal and posterior wall thickening following oral administration of bamiphylline were similar to those observed following placebo (124±22 versus 125±20 mL, P=NS; 49±12 versus 50±13 mL, P=NS; 60±8% versus 58±7%, P=NS; 35±6% versus 36±7%, P=NS; 32±6% versus 33±6%, P=NS, respectively). Four patients had regional akinesia at baseline, involving one segment in two patients, two segments in one patient, and three in one. After bamiphylline administration, segmental wall motion was similar to those observed after placebo administration.

Hemodynamic and Angiographic Findings

During intravenous infusion of bamiphylline, two patients complained of transient dizziness and diplopia, which quickly disappeared by reducing the infusion rate. Compared with baseline values, intravenous infusion of bamiphylline did not produce any significant change of heart rate (76±10 versus 75±13 beats per minute, P=NS), mean aortic pressure (102±12 versus 99±10 mm Hg, P=NS), left ventricular end-diastolic pressure (14±3 versus 14±4 mm Hg, P=NS), mean right atrial pressure (3.8±1.7 versus 3.7±1.7 mm Hg, P=NS), mean pulmonary arterial pressure (12.7±2.4 versus 12.2±1.5 mm Hg, P=NS), cardiac output (5.2±0.8 versus 5.4±0.9 L/min, P=NS), systemic vascular resistance (999±367 versus 953±361 dyn·s·cm⁻⁵, P=NS), and total pulmonary resistance (198±44 versus 177±48 dyn·s·cm⁻⁵, P=NS) (Table 1).

A total of seven proximal and seven distal normal coronary segments of the left anterior coronary artery or circumflex artery were analyzed. Seven stenotic segments were also analyzed. None of the analyzed vessels was filled by angiographically visible collaterals. After intravenous infusion of bamiphylline, the diameters of the normal segments of the proximal and distal third of the coronary artery were similar to those measured at baseline arteriography (3.1±0.5 versus 3.1±0.5 mm and 1.6±0.2 versus 1.7±0.2 mm, respectively; P=NS). Also, the internal diameter of the stenotic segments was not affected by bamiphylline (1.6±0.5 versus 1.6±0.5 mm, P=NS) (Table 1).

Discussion

This study shows that in patients with stable angina pectoris bamiphylline, the most selective antagonist of 8,7,8-bisubstituted of aminophylline, has been successfully used to treat bronchial asthma and lung anaphylaxis in young children and infants and chronic obstructive pulmonary disease in adults with an efficacy comparable to that of aminophylline but with substantially fewer side effects. The therapeutic threshold of bamiphylline is almost 50 times lower than that of aminophylline (0.2 μg/mL versus 10 μg/mL), whereas the tolerance range is almost 100 times wider. In crude synaptic membranes prepared from rat brain, bamiphylline displaces radioligands from A₁ adenosine receptors with a potency similar to that of 8-phenil-theophylline, whereas it showed a much lower potency on A₂ adenosine receptors. This resulted in a
high degree of A<sub>1</sub> receptor selectivity indicated by a A<sub>2</sub>/A<sub>1</sub> K<sub>r</sub> ratio of 596.19 A critical issue in our study was the choice of an appropriate dose of bamiphylline. In vitro studies have shown that bamiphylline, at the mean plasma concentration obtained in the present study (&lt;0.5 &middot; 10<sup>-7</sup> M), displaces 80% of <sup>3</sup>H-DPX (an antagonist of A<sub>1</sub> adenosine receptors), 50% of <sup>3</sup>H-CHA (an agonist of A<sub>1</sub> adenosine receptors), but 5% only of <sup>3</sup>H-NECA (an agonist of A<sub>2</sub> adenosine receptors). Thus, at the dose used in this study, bamiphylline administration resulted in a rather selective blockade of A<sub>1</sub> adenosine receptors.

Anti-Ischemic Effects of Bamiphylline

The mechanism of the anti-ischemic effect of bamiphylline does not appear to be mediated by coronary artery dilation. In fact, in this study, intravenous administration of bamiphylline had no significant effect on the luminal diameter of normal or stenotic segments of large epicardial coronary arteries. Furthermore, the anti-ischemic action of bamiphylline does not seem to be related to a reduction of myocardial oxygen consumption. Indeed, bamiphylline administration did not change resting left ventricular volumes or hemodynamic parameters. Our findings are in agreement with previous in vitro and in vivo experimental studies showing that bamiphylline is devoided of cardiostimulant effects.29 Lack of cardiostimulatory effects has also been confirmed in healthy volunteers and in patients with obstructive lung disease.30

As bamiphylline does not dilate large epicardial vessels like nitrates and calcium antagonists, does not reduce myocardial oxygen consumption like &beta;-blockers and calcium antagonists, and does not reduce left ventricular load like nitrates, its anti-ischemic effect must be due to a different mechanism. The latter is likely to be a transmural redistribution of coronary blood flow toward the subendocardium as previously proposed to explain the anti-ischemic effect of aminophylline.31 and confirmed by preliminary experimental studies.32 In fact, on the assumption that during exercise, luxury subepicardial perfusion occurs distal to a critical coronary stenosis, a selective subepicardial vasoconstriction might limit subendocardial underperfusion, thus delaying the onset of ischemia.34-37 We have previously hypothesized that this beneficial transmural redistribution of coronary blood flow, which we labeled the “Robin Hood” effect,31 might also explain the anti-ischemic effect of theophylline,1,4 a nonspecific antagonist of adenosine receptors. As the vascular effects of adenosine are mediated by A<sub>1</sub> receptors, it would have been reasonable to assume that the constriction of subepicardial vessels was due to blockade of this subtype of adenosine receptors. Yet, as bamiphylline is a rather selective A<sub>1</sub> adenosine receptor antagonist, the anti-ischemic effect observed in this study is unlikely to be mediated by antagonism of adenosine A<sub>1</sub> receptors.10,17,18 A<sub>1</sub> adenosine receptors are mainly localized in the atria, ventricles, and sympathetic perivascular nerves.10,12 At neural sites, these receptors cause prejunctional inhibition of catecholamine release from perivascular sympathetic nerves.10 Therefore, both bamiphylline and theophylline might improve myocardial ischemia by an enhancement of the catecholamine-mediated antitransmural steal effect proposed by Feigl,38 who suggested that the apparent paradox of the sympathetic coronary vasoconstriction during exercise might improve subendocardial perfusion through a selective constriction of subepicardial vessels. The hypothesis that the vasoconstrictor effect of methylxanthines involves catecholamines is supported by the observation that the increase of vascular resistance caused by aminophylline in the conscious dog is attenuated by &alpha;-adrenergic blockade.39 Of note, in our study, bamiphylline did not affect heart rate or arterial blood pressure under resting conditions, suggesting that prejunctional A<sub>1</sub> adenosine receptors are not active at rest. Another potential mechanism by which bamiphylline can limit subepicardial perfusion might be inhibition of ATP-sensitive potassium channels. In fact, recent preliminary data suggest that the activation of these channels that provokes coronary vasodilation is due, in part, to the activation of A<sub>1</sub> adenosine receptors.40

Effects of Bamiphylline on the Anginal Pain

In our study, the improvement of exercise-induced anginal pain obtained with bamiphylline was greater than that predicted on the basis of the improvement of myocardial ischemia. Indeed, the severity of pain at peak exercise normalized for maximal ST segment depression was significantly less after bamiphylline than after placebo. These findings suggest that the improvement of the anginal pain produced by bamiphylline is likely to be due also to the direct inhibition of the algogenic effects of adenosine. Adenosine is a mediator of the ischemic pain,41,42 and its algogenic effects are, at least partially, mediated by A<sub>1</sub> receptors.43,44 Preliminary observations demonstrated that bamiphylline significantly reduces the pain produced by intra-arterial infusion of adenosine45 and that the intradermal preinjection of bamiphylline in healthy volunteers completely prevents the pain induced by intradermal injection of adenosine.44 The present study supports and expands these previous observations, suggesting also that the algogenic effects caused by endogenous adenosine released during exercise-induced myocardial ischemia are partially mediated by A<sub>1</sub> adenosine receptors. However, the observation that the degree of ST segment depression at the onset of pain was not affected by bamiphylline indicates that other algogenic substances are involved in the genesis of the anginal pain.

Study Limitations

A limitation of this study is the use of a single-blind design. However, the selection of objective end points (as time to and rate-product at 1-mm ST segment depression during exercise testing), the computerized assessment of coronary angiograms and ECGs and the analysis of the results blind to the treatment should substantially overcome the drawbacks of the single-blind design. A critical issue in this study is the A<sub>1</sub> receptor selectivity of bamiphylline that was assessed in vitro in 1987.19 To our knowledge, the A<sub>1</sub> bamiphylline selectivity has never been directly compared with that of some of the newest xanthine A<sub>1</sub> antagonists such as 8-cyclopentyltheophylline or 8-cyclopentyl-1,3-dipropylxanthine, which have been developed in recent years.45 However, the recent clinical observation that bamiphylline does not suppress the adenosine-induced cutaneous vasodilation that is known to
be mediated by vascular A₂ receptors suggests that the A₁ receptors selectivity of bamiphylline is substantially preserved in humans. Finally, the lack of significant vasoactive effects of bamiphylline on coronary stenosis diameter found at rest during diagnostic catheterization does not exclude the possibility of vasoactive effects during exercise.

**Conclusions**

In conclusion, in patients with stable angina pectoris, oral administration of bamiphylline, a rather selective antagonist of A₁ adenosine receptors, increases the ischemic threshold, prolongs the exercise duration, delays the onset of anginal pain, and reduces its severity for a similar degree of ST segment depression. The anti-ischemic action of bamiphylline is not mediated by a reduction of myocardial oxygen consumption, left ventricular unloading, or coronary stenosis dilation, but it is probably due to redistribution of coronary blood flow toward the subendocardium. The antianginal action of bamiphylline appears to be due also to direct blockade of cardiac sensory receptors sensitive to adenosine. Finally, the results of our study indicate that both the anti-ischemic and the antianginal action of aminophylline, a nonselective adenosine antagonist, observed in earlier studies are partially mediated by the inhibition of A₁ receptors. Because of the lack of cardiostimulant effects and the absence of major undesirable side effects, bamiphylline more than aminophylline might represent a complementary drug in the treatment of patients with coronary artery disease.

**Acknowledgments**

We wish to thank Dr. Maria Pia Abbracchio from the Institute of Pharmacological Sciences, University of Milan, Italy, and Dr. Annalisa Rubino from the Department of Anatomy and Developmental Biology, University College, London, UK, for helpful suggestions and fruitful discussion. We also wish to thank Chiesi Farmaceutici, Parma, Italy, for the generous supply of bamiphylline. We are grateful to Miss Emma Tomsett and Mrs. Teresa Palumbo for invaluable technical assistance.

**References**

Bamiphylline improves exercise-induced myocardial ischemia through a novel mechanism of action.
A Gaspardone, F Crea, M Iamele, F Tomai, F Versaci, A Pellegrino, L Chiariello and P A Gioffré

Circulation. 1993;88:502-508
doi: 10.1161/01.CIR.88.2.502
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/88/2/502

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/