Cessation of Platelet-Mediated Cyclic Canine Coronary Occlusion After Thrombolysis by Combining Nitric Oxide Inhalation With Phosphodiesterase-5 Inhibition

Ulrich Schmidt, MD, PtD, Richard O. Han, MD, Thomas G. DiSalvo, MD, FACC, J. Luis Guerrero, BA, Herman K. Gold, MD, PtD, FACC, Warren M. Zapol, MD, Kenneth D. Bloch, MD, Marc J. Semigran, MD

Boston, Massachusetts

OBJECTIVES
We sought to evaluate the ability of type 5 phosphodiesterase (PDE5) inhibitors to augment the antithrombotic effects of inhaled nitric oxide (NO) in a canine model of platelet-mediated coronary thrombosis after thrombolysis.

BACKGROUND
Type 5 phosphodiesterase inhibitors potentiate the ability of NO to inhibit platelet aggregation in vitro by preventing platelet cyclic guanosine monophosphate catabolism. We previously reported that breathing low concentrations of NO gas attenuated, but did not prevent, cyclic flow reductions (CFRs) in a canine model of coronary thrombosis after thrombolysis.

METHODS
Cyclic flow reductions were induced after creation of a left anterior descending coronary artery stenosis, endothelial injury, thrombus formation and thrombolysis. Dogs were either untreated or treated with inhaled NO (20 ppm by volume), intravenous zaprinast, intravenous dipyridamole or the combination of inhaled NO with either PDE5 inhibitor (n = 4 per group).

RESULTS
Cyclic flow reductions ceased, and complete coronary patency was achieved in all dogs after they breathed NO combined with zaprinast (by 12.0 ± 4.7 min [mean ± SEM]) or dipyridamole (by 9.8 ± 4.7 min). The frequency of CFRs was unaffected by NO, dipyridamole or zaprinast alone. Systemic arterial blood pressure and bleeding time were unchanged with any treatment. Ex vivo thrombin-induced platelet aggregation in dogs breathing NO and receiving dipyridamole was reduced by 75 ± 7% (p < 0.05).

CONCLUSIONS
The PDE5 inhibitors potentiated the antithrombotic properties of inhaled NO in a canine model of platelet-mediated coronary artery thrombosis after thrombolysis, without prolonging the bleeding time or causing systemic hypotension. (J Am Coll Cardiol 2001;37:1981–8) © 2001 by the American College of Cardiology

Platelets play a fundamental role in the pathogenesis of acute ischemic coronary syndromes, including unstable angina and myocardial infarction (MI) (1). Platelet-mediated thrombosis can limit the efficacy of thrombolytic therapy for acute MI (2). Aspirin, an irreversible platelet cyclo-oxygenase inhibitor, and ticlopidine, an inhibitor of adenine diphosphate-induced activation of the platelet glycoprotein (GP) IIb/IIIa receptor, are effective in the prevention and treatment of acute coronary syndromes (1). However, these agents are relatively weak inhibitors of platelet function, and coronary occlusion can occur despite their administration. More potent GP IIb/IIIa receptor antagonists inhibit platelet-mediated thrombosis and reduce the frequency of MI, death and urgent revascularization in patients presenting with acute coronary syndromes (3,4).

The therapeutic use of these agents is associated with a marked prolongation of the bleeding time and occasional thrombocytopenia, both of which contribute to an increased risk of hemorrhage (3–6). Thus, improving the efficacy and safety of platelet inhibitors used to treat acute ischemic coronary syndromes remains an important goal of research.

Nitric oxide (NO) stimulates soluble guanylate cyclase, thereby increasing intracellular cyclic guanosine monophosphate (cGMP) concentrations. Increased cGMP levels relax vascular smooth muscle and inhibit platelet adhesion, aggregation and granule release (reviewed in [7]). Cyclic GMP is metabolized to inactive GMP by phosphodiesterase (PDE) isoenzymes. Eleven PDE classes have been described, with some classes having multiple isoenzymes (8). Most PDE isoenzymes metabolize cyclic adenosine 3’:5’-cyclic phosphate (cAMP) or both cAMP and cGMP. Type 5 PDE (PDE5) hydrolyzes cGMP specifically and is abundant in vascular smooth muscle and platelets (9,10).

Nitrovasodilators, such as nitroglycerin and sodium nitroprusside (SNP), possess platelet inhibitory properties owing to their ability to release NO (11). In a canine model of platelet-mediated coronary occlusion, SNP inhibited thrombosis, but its antithrombotic effect was limited by
systemic vasodilation and hypotension, which occur at the doses required to inhibit platelet aggregation (12). The PDE5 inhibitors potentiate the platelet inhibitory properties of NO in vitro (9,10,13,14), but they also augment the vasodilator effects of NO donor compounds in vivo (13,15,16).

Inhaled NO is a selective pulmonary vasodilator in adults and children with pulmonary hypertension (reviewed in [17]). It has recently become appreciated that the biologic effects of inhaled NO can extend beyond the lungs, either by exposure of circulating blood cells as they transit the lungs (18) or by the release of NO from hemoglobin (19) or nitrosoylated plasma proteins (20). We previously reported that breathing low concentrations of NO improves coronary artery patency and reduces cyclic flow reductions (CFRs) in a canine model of platelet-mediated coronary artery thrombosis after thrombolysis (21). However, cyclic coronary artery occlusion persisted despite breathing high concentrations of inhaled NO. In the current study, we tested the hypothesis that systemic treatment with PDE5 inhibitors—zaprinast or dipyridamole—would potentiate the anti-thrombotic effects of inhaled NO in this canine model of a platelet-mediated acute coronary syndrome.

**METHODS**

**Canine model of coronary artery occlusion after thrombolysis.** Thirty adult mongrel dogs (weight 20 to 25 kg) of either gender were anesthetized with 30 mg/kg body weight of intravenous pentobarbital, tracheally intubated and mechanically ventilated. The fraction of inspired oxygen was adjusted between 0.21 and 0.35 with the use of an oxygen blender (Bird Blender, Palm Springs, California) to maintain the arterial blood oxygen tension between 80 and 100 mm Hg, as determined by periodic arterial blood gas measurements, or oxygen saturation ≥94% as determined by a pulse oximeter (Nellcor, Pleasanton, California) placed on a shaved area of the ear. Supplemental pentobarbital (10 to 15 mg/kg) was given every 20 min, as required, to maintain general anesthesia. A left thoracotomy was performed in the fifth intercostal space, the pericardium was opened and the heart was suspended in a pericardial cradle. The dogs were then instrumented for intracoronary infusion, electrocardiographic monitoring and measurement of systemic blood pressure and left anterior descending coronary artery (LAD) coronary flow (T106 Flowmeter, Transonic Systems, Ithaca, New York), as described previously (21). In brief, after a 2.5-cm segment of the LAD was isolated, a 2-mm-wide plastic wire tie (Massachusetts Gas and Electric Supply, Boston, Massachusetts) was progressively constricted around the distal end of the segment to reduce blood flow to 50 ± 10% of baseline. A previous angiographic study has shown that this constriction decreases the lumen diameter by >90% (22). The isolated LAD was traumatized by external compressions to damage the endothelium and promote thrombus adherence. Snare occluders distal to the probe and proximal to the constriction site were applied, and a mixture of 0.1 ml thrombin (100 U/ml; Thrombinar, Armour Pharmaceutical, Kankakee, Illinois) with 0.3 ml of previously sampled blood was injected through a catheter in a diagonal branch into the emptied coronary artery segment to induce thrombus formation. The proximal snare was released after 10 min of arterial occlusion, and the distal snare was released 2 min later. After 10 min, a 75-U/kg bolus of heparin was administered intravenously, followed by a continuous infusion of 50 U/kg per h. After a 30-min period of stable occlusion, a 0.45-mg/kg bolus of TPA (Genentech, South San Francisco, California) was administered intravenously at 15-min intervals until patency (flow >25% of baseline flow) of the thrombosed coronary artery was achieved or until a maximum of four boluses had been administered. The dogs were excluded from further study in the event of 1) failure to reperfuse; 2) reperfusion without re-occlusion; 3) <3 cycles occurring during the first 45-min observation period; or 4) death before the end of the first observation period. The coronary artery patency ratio (CAPR) was defined as the fraction of a 45-min observation period during which the coronary artery was patent. Cyclic flow reduction was defined as re-occlusion of the artery after a spontaneous increase to >25% of baseline flow.

These investigations were approved by the Subcommittee on Research Animal Care of the Massachusetts General Hospital and were in compliance with the “Position of the American Heart Association on Research Animal Use,” adopted by the Association in November 1984.

**Experimental protocol.** A 45-min observation period (pre-treatment period) was initiated when re-flow was first achieved after thrombolysis. During a subsequent 45-min observation period (treatment period), the dogs were randomly assigned to one of six groups (n = 4 each): 1) to receive no additional therapy; 2) to breathe 20 ppm NO through inhalation; 3) to receive zaprinast (1.0 mg/kg in saline intravenously over 4 min, followed by a continuous infusion of 0.05 mg/kg per min; Rhone-Poulenc Rorer, Dagenham, Essex, United Kingdom); 4) to receive dipyridamole (0.15 mg/kg in saline intravenously over 4 min, followed by a continuous infusion of 0.004 mg/kg per min;
Sigma, St. Louis, Missouri); or 5) and 6) to receive these doses of zaprinast or dipyridamole, respectively, while breathing 20 ppm NO. Nitric oxide gas was introduced into the ventilator circuit as previously described (21), and the inspired NO level was continuously monitored by an electrochemical NO-NOx analyzer (NOx-Box, Bedfont Scientific, Kent, United Kingdom). After the treatment period, all animals were monitored for an additional 45 min, during which neither NO nor a PDE inhibitor was administered (post-treatment period).

**Bleeding time and platelet count measurements.** Temple bleeding times were measured using an automated, spring-loaded device (Simplate-II, Organon Teknika, Durham, North Carolina) on the ventral aspect of the tongue at the mid-point of the pre-treatment, treatment and post-treatment periods in all groups of animals. Platelet counts were measured simultaneously with bleeding time determinations.

**Ex vivo whole-blood aggregation.** Thrombin-induced ex vivo whole-blood platelet aggregation was measured during the pre-treatment and treatment periods in control animals and in the groups of dogs receiving NO, dipyridamole and the combination of NO and dipyridamole. Blood (1.8 ml) was collected in tubes containing 3.13% (wt/vol) sodium citrate. Citrated blood (500 μl) was immediately transferred to cuvettes containing an equal volume of saline. The solution was incubated at 37°C with magnetic stirring (1,000 rpm) in an impedance aggregometer (Model 440, Chronolog, Havertown, Pennsylvania). After reaching a stable baseline (~5 min), the aggregometer was calibrated (20 ohms · min set to 80% of full scale). Aggregation was induced by the addition of thrombin (5 U/ml). Thrombin-induced ex vivo whole-blood aggregation was indicated by increased impedance and was quantitated as the area under the impedance versus time curve for the first 30 s after aggregation began. The effect of a treatment strategy on platelet aggregability in an individual experiment is reported as the ratio of the area under the impedance versus time curve during the treatment period to that obtained in the pre-treatment period.

**Ultrasound measurements in a pharmacologic model of coronary artery vasoconstriction.** In an additional four dogs, the LAD cross-sectional area and blood flow velocity were measured using an ultrasonic flow probe and a 30-MHz intravascular ultrasound transducer (Endosonics, San Jose, California) sutured in place adjacent to the artery under a flap of pericardial tissue. Mean aortic and left atrial pressures were measured concurrently. The coronary artery was not injured, nor was a stenosis created. After baseline measurements were obtained, an intracoronary infusion of U46619 (9,11-dideoxy-9-epoxymethano-prostaglandin F2α) was administered at 10 nmol/min to induce coronary vasoconstriction. Measurements were then made during U46619 infusion and after breathing 20 ppm NO for 10 min, 10 min after NO breathing ceased, during infusion of zaprinast (1.0 mg/kg intravenously over 4 min, followed by a continuous infusion of 0.05 mg/kg per min) and after breathing 20 ppm NO for 10 min during zaprinast infusion. Zaprinast and NO were then discontinued, and after 30 min, SNP (2 μg/kg per min) was administered intravenously.

**Statistical analysis.** All data are reported as the mean value ± SEM. The significance of differences in the CAPR, CFR frequency, bleeding times, thrombin-induced whole-blood aggregation and hemodynamic variables between treatment groups was determined by one-way analysis of variance (ANOVA), with a Neuman-Keuls test for comparison of control and treated dogs, and by a two-way ANOVA, with a Neuman-Keuls test within groups of dogs. A value p < 0.05 was considered significant.

**RESULTS**

**Characteristics of the canine coronary artery model of re-occlusion after thrombolysis.** Based on predetermined criteria, 6 of the 30 dogs were excluded from consideration because of a lack of reperfusion (n = 3), because <3 cycles occurred during the pre-treatment period (n = 2) or because death occurred before the end of the first observation period (n = 1). The external constrictor reduced LAD blood flow by 51 ± 3% from a baseline of 24 ± 5 ml/min. The activated clotting time 2 h after beginning the heparin infusion was 225 ± 30 s. There were no significant differences in the number of tissue plasminogen activator (t-PA) boluses required to achieve reperfusion, activated clotting time, LAD blood flow, CFR frequency or CAPR during the pre-treatment period, among any of the experimental groups (Table 1). Ventricular fibrillation occurred in three dogs (one each in the control, dipyridamole and zaprinast plus NO treatment groups) before the pre-treatment period and in two dogs during the pre-treatment period (one each in the control, zaprinast and NO treatment groups). One dog in the dipyridamole group died of intractable ventricular arrhythmias at the beginning of the post-treatment period.

**Effects of inhaled NO and PDE inhibitors on cyclic flow variation frequency and coronary artery patency.** Blood flow in the LAD of each dog is schematically represented in Figure 1, with black areas indicating intervals of relative coronary occlusion (blood flow <25% of post-constriction flow), and white areas indicating intervals of patency. The CFRs persisted despite the inhalation of 20 ppm NO or the administration of intravenous zaprinast or intravenous dipyridamole alone. However, in dogs receiving a combination of 20 ppm NO and zaprinast, cycling ceased 12.0 ± 4.7 min after the initiation of combined treatment (Fig. 1). The complete inhibition of coronary occlusion persisted during the post-treatment period in three of the four dogs; in the other dog, the CFRs resumed 34 min after treatment was stopped.

In all of the dogs receiving a combination of inhaled NO and dipyridamole, cycling ceased 9.8 ± 4.9 min after the
initiation of the treatment period (Fig. 1). The CFRs recurred in three of the four dogs 6.7 ± 1.0 min after treatment was stopped; in the other dog, complete inhibition of cycling persisted throughout the post-treatment period.

The effects of treatment with inhaled NO and intravenous PDE5 inhibitors, as well as their combination on coronary artery patency, were quantitated by measuring the CAPR (Fig. 2) and the frequency of CFR. In untreated animals and in animals treated with only intravenous zaprinast or dipyridamole, the CAPR and CFR frequency did not change during the treatment period versus the pre-treatment period. In dogs breathing 20 ppm NO alone, neither the change in CAPR (51 ± 4% to 61 ± 5%, p = 0.07) (Fig. 2) nor the change in CFR frequency (6.9 ± 0.6 to 4.5 ± 0.5 cycles/h, p = 0.08) was statistically significant.

In dogs breathing 20 ppm NO during zaprinast infusion, the CAPR increased from 46 ± 9% to 89 ± 2% (p < 0.05) (Fig. 2), and the CFR frequency decreased from 6.7 ± 0.1 to 1.0 ± 0.5 cycles/h (p < 0.05).

In dogs breathing 20 ppm NO during an infusion of dipyridamole, the CAPR increased from 41 ± 7% to 87 ± 5% (p < 0.05) (Fig. 2), and the CFR frequency decreased from 6.0 ± 0.9 to 1.3 ± 0.5 cycles/h (p < 0.05). Although cycling did resume in three dogs after NO and dipyridamole were stopped, the CAPR was higher (79 ± 10%) and the CFR frequency was lower (3.3 ± 1.4 cycles/h) during the post-treatment period versus the pre-treatment period (p < 0.05).

Systemic arterial pressure, left atrial pressure and heart rate did not differ at the mid-point of the three study periods in untreated animals or in dogs treated with inhaled 20 ppm NO, intravenous zaprinast or dipyridamole, or with the combination of inhaled 20 ppm NO with intravenous zaprinast or dipyridamole.

**Effects of inhaled NO and PDE inhibitors on coronary flow and cross-sectional area in a pharmacologic model of coronary artery vasoconstriction.** In four additional dogs, the LAD cross-sectional area and blood flow were measured simultaneously, without injuring the vessel or creating a stenosis. After intracoronary administration of 10 nmol/min of U-46619, peak diastolic coronary blood flow was decreased by 30 ± 2% (p < 0.05) (Fig. 3A), and the coronary cross-sectional area was decreased by 12 ± 3% (p < 0.05) (Fig. 3B). Inhalation of 20 ppm NO, intravenous administration of zaprinast or the combination of inhaled 20 ppm NO and intravenous zaprinast did not dilate the LAD or alter blood flow. Administration of intravenous SNP increased peak diastolic coronary flow by 63 ± 14% (p < 0.05) (Fig. 3A) and increased the coronary artery cross-sectional area by 22 ± 5% (p < 0.05) (Fig. 3B), despite a 15 ± 2% decrease in mean arterial pressure (p < 0.05).

**Effects of inhaled NO and PDE inhibitors on bleeding time and ex vivo whole-blood aggregation.** The blood platelet concentration was unchanged during the three treatment periods in all six groups. The bleeding time did not change in any of the experimental groups (data not shown). Ex vivo thrombin-induced platelet aggregation in whole blood did not change during the treatment period in control dogs or in dogs treated with either inhaled NO alone or intravenous dipyridamole alone (Fig. 4). The combination of inhaled NO and intravenous dipyridamole decreased platelet aggregation to 25 ± 7% of that measured during the pre-treatment period (p < 0.05) (Fig. 4).

**DISCUSSION**

The major finding of this study is that simultaneous administration of a PDE5 inhibitor potentiated the antithrombotic effect of inhaled NO in a canine model of platelet-mediated coronary artery thrombosis after thrombolysis. Intravenous administration of either zaprinast or dipyridamole, alone, did not alter the frequency of cyclic coronary artery occlusion in this model. However, the CFRs ceased soon after combining inhalation of 20 ppm NO with intravenous administration of either PDE5 inhibitor.

Although the vasodilator effects of breathing low concentrations of NO appear to be limited to the lungs, studies...
have suggested that inhaled NO can have systemic effects. In animal models with (23) and without (18) pulmonary injury, as well as in critically ill newborns (24,25) and adults (26), breathing NO has been observed to prolong the bleeding time or prolong ex vivo platelet aggregation, or both. We previously reported that breathing 20 or 80 ppm NO decreased platelet-mediated coronary thrombosis after thrombolysis (21); however, breathing NO up to 200 ppm did not abrogate the CFRs. Therefore, we sought to augment the antithrombotic efficacy of inhaled NO.

Figure 1. Schematic representation of the coronary artery patency status in each of four dogs during three sequential 45-min observation periods (pre-treatment, intra-treatment and post-treatment). During the treatment period, the dogs were either untreated (control), breathed 20 ppm nitric oxide (NO), received zaprinast (1.0 mg/kg intravenously over 4 min, followed by a continuous infusion of 0.05 mg/kg per min), received dipyridamole (0.15 mg/kg intravenously over 4 min, followed by a continuous infusion of 0.004 mg/kg per min), received NO plus zaprinast or received NO plus dipyridamole. White areas of bars represent coronary patency (flow >25% of immediate post-constriction flow), and black areas represent occlusion.
Rationale for combining PDE5 inhibitors with inhaled NO as antithrombotic therapy. Cyclic GMP mediates many of the antithrombotic effects of NO (11). Increased platelet cGMP concentrations inhibit phosphatidylinositol metabolism, decrease intracellular calcium levels and inhibit the function and expression of the platelet GP IIb/IIIa and P-selectin receptors, respectively (reviewed in [7]). Inhibitors of cGMP metabolism by PDE5 augment the ability of NO donor compounds to decrease platelet aggregation in vitro (9,13,14). The use of PDE5 inhibitors to increase the effects of NO donor compounds is limited by the systemic hypotension associated with concomitant administration of NO donor compounds and PDE5 inhibitors (13,15,16). Systemic vasodilatation is often undesirable in the treatment of acute coronary artery syndromes.

We tested the hypothesis that systemic administration of PDE5 inhibitors would augment the ability of inhaled NO to prevent coronary artery thrombosis after thrombolysis in our model, without causing hypotension. The PDE5 inhibitors studied included zaprinast, because it is relatively PDE5-selective (10), and dipyridamole, because it has been extensively used in patients with cardiovascular disease (27). Neither zaprinast nor dipyridamole, when used alone had a significant impact on coronary artery patency in our model. Of note, dipyridamole did not prevent thrombosis in a similar canine model of coronary artery stenosis and injury (7). In the current study, inhalation of 20 ppm NO alone did not alter platelet-mediated cyclic occlusion in a statistically significant manner. However, breathing 20 ppm NO simultaneously with intravenous administration of either PDE5 inhibitor led to rapid inhibition of platelet-mediated coronary artery thrombosis. The addition of either zaprinast or dipyridamole to 20 ppm of inhaled NO produced a greater antithrombotic effect than was previously observed with 80 ppm of inhaled NO (21). Although both PDE5 inhibitors abrogated the CFRs during NO inhalation, the greater PDE5 specificity of zaprinast may confer additional benefit, as it maintained coronary patency for a longer period after treatment was stopped, as compared with dipyridamole.

Mechanism of inhibition of cyclic coronary occlusion. To characterize the mechanisms responsible for the antithrombotic effects of inhaled NO and a PDE5 inhibitor, thrombin-induced platelet aggregation was measured ex vivo in dogs receiving inhaled NO, dipyridamole and their combination. Although neither inhaled NO nor dipyridamole alone inhibited thrombin-induced platelet aggrega-
tion, their combination did. The observation that the antithrombotic effect of inhaled NO was potentiated by the addition of a PDE5 inhibitor suggests that this antithrombotic effect is mediated by alterations in platelet cGMP metabolism. Alternatively, NO may inhibit platelet function through cGMP-independent mechanisms (28,29), and dipyridamole could augment the effect of inhaled NO through its antioxidant activity (30). Evidence against the importance of an antioxidant effect is the observation that zaprinast, which shares dipyridamole’s PDE5 inhibitory effects but is not an antioxidant, potentiated the antithrombotic effects of inhaled NO.

After cessation of NO breathing and PDE5 administration, the improvement in arterial patency persisted for at least 45 min. The prolonged coronary artery patency after discontinuation of PDE5 inhibitors and NO inhalation may be attributable to persistent increases in platelet cGMP concentrations or to the time required to re-accumulate activated platelets at the site of coronary injury.

We considered the possibility that combining PDE5 inhibitors with inhaled NO improved coronary patency by reversing coronary artery vasoconstriction. However, direct measurement of the coronary artery cross-sectional area during infusion of a vasoconstrictor (U46619) demonstrated that NO inhalation with or without zaprinast did not increase the coronary artery diameter or coronary blood flow. Although these observations suggest that the effects of inhaled NO with PDE5 inhibitors on coronary patency are not due to a local effect on coronary vascular tone, it remains possible that the antithrombotic effects of inhaled NO are mediated by the delivery of NO adducts to the site of vascular injury.

Study limitations. Ventricular arrhythmias (in one case intractable) occurred in several animals during the study. Except for the one intractable case, these events occurred before the initiation of therapy and, therefore, do not represent an effect of NO, PDE5 inhibition or their combination. The doses of NO used in this study were chosen on the basis of our previous investigation (21), in which 20 ppm produced a submaximal antithrombotic effect, and the doses of PDE5 inhibitors were selected on the basis of previous investigations, to avoid systemic hypotension (27). Further studies to determine the optimal coronary antithrombotic doses of inhaled NO and PDE5 inhibitors are necessary.

Clinical implications. The development of effective inhibitors of platelet-mediated thrombosis that do not induce hemorrhagic complications remains an important goal in the treatment of acute ischemic coronary syndromes (1), as well as in the prevention of thrombosis and restenosis after percutaneous coronary revascularization (5). Our observation—that combining inhaled NO with PDE5 inhibitors was effective in eliminating CFRs but did not prolong the bleeding time—suggests that beneficial coronary antithrombotic effects may be achieved, whereas the hemorrhagic complications associated with the use of other antithrombotic therapies (5) may be avoided. In contrast to the combination with NO donor compounds, the combination of a PDE5 inhibitor with inhaled NO was not associated with potentially deleterious systemic hypotension. The clinical implications of our observations in a barbiturate-anesthetized canine model remain to be established; however, agents effective in this model, such as the GP IIb/IIIa antagonists abciximab and tirofiban (22), are effective for the treatment of acute ischemic coronary artery syndromes (4,5). Further investigation of the ability of NO and PDE5 inhibitor therapy to improve coronary patency and decrease adverse events in patients with platelet-mediated acute ischemic coronary syndromes is warranted.

Reprint requests and correspondence: Dr. Marc J. Semigran, Bigelow 626, Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts 02114. E-mail: semigran.marc@mgh.harvard.edu.

REFERENCES


6. The Sibrafiban Versus Aspirin to Yield Maximum Protection from


