

# Sildenafil Improves Coronary Artery Patency in a Canine Model of Platelet-Mediated Cyclic Coronary Occlusion After Thrombolysis

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<b>OBJECTIVES</b>	We sought to assess the effect of sildenafil, a highly-specific type 5 phosphodiesterase (PDE5) inhibitor, on platelet-mediated cyclic coronary flow reductions occurring in a canine model of coronary thrombosis despite aspirin therapy.
<b>BACKGROUND</b>	The PDE5 inhibitors augment the antithrombotic effects of nitric oxide in vitro and in vivo, but it has been proposed that the PDE5 inhibitor sildenafil is prothrombotic.
<b>METHODS</b>	Cyclic coronary flow reductions were induced in the left anterior descending coronary artery by creation of a stenosis, endothelial injury, and thrombus formation followed by treatment with aspirin, heparin, and tissue plasminogen activator. After an initial observation period, dogs were treated with or without sildenafil (100 $\mu$ g/kg bolus followed by 4 $\mu$ g/kg/min infusion).
<b>RESULTS</b>	Cyclic coronary flow reductions ceased in five of six animals 18 $\pm$ 5 min after initiation of sildenafil but continued in all six control animals. The portion of the observation period during which the coronary artery was patent increased from 52 $\pm$ 9% to 83 $\pm$ 5% after sildenafil administration ( $p = 0.008$ ) but did not differ between the first and second observation periods in untreated dogs (49 $\pm$ 11% vs. 44 $\pm$ 11%, respectively). Among animals with plasma free sildenafil levels $\geq$ 20 nmol/l, cyclic coronary flow reductions were 73 $\pm$ 12% less frequent and the time to cessation of cycling 72 $\pm$ 14% shorter than in animals with levels <20 nmol/l ( $p < 0.05$ for both). Sildenafil transiently decreased blood pressure 7 $\pm$ 1% but did not change heart rate. Sildenafil treatment reduced ex vivo thrombin-induced platelet aggregation by 39 $\pm$ 3% ( $p < 0.005$ ).
<b>CONCLUSIONS</b>	Sildenafil improves coronary patency in a canine model of platelet-mediated coronary artery thrombosis, likely via inhibition of platelet aggregation. (J Am Coll Cardiol 2006;47:1471-7) © 2006 by the American College of Cardiology Foundation

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Platelet-mediated thrombosis has a fundamental role in the pathogenesis of acute coronary syndromes (ACS) (1). Several randomized clinical trials have demonstrated the efficacy of antiplatelet agents such as aspirin, thienopyridines, and glycoprotein (GP) IIb/IIIa receptor antagonists in the treatment of ACS. However, aspirin may not eliminate platelet-mediated reocclusion after thrombolysis (2). Furthermore, patients with ST-segment elevation myocardial infarction resistant to the antithrombotic effects of clopidogrel have recurrent cardiovascular events more frequently than those in whom platelet aggregation is suppressed (3). The more potent GP IIb/IIIa receptor antagonists improve cardiovascular outcomes of patients with ACS and those undergoing percutaneous coronary interventions (4-6). Unfortunately, GP IIb/IIIa receptor antagonists markedly prolong bleeding time and occasionally cause thrombocytopenia, resulting in a greater risk of clinical hemorrhage

(4-6). Hence, the exploration of other agents that alter signaling pathways for platelet activation is needed to improve the safety and efficacy of antiplatelet therapy.

The effect of altering the intracellular concentration of the second messenger cyclic guanosine monophosphate (cGMP) on platelet activation appears to vary depending on the specific activators or inhibitors of cGMP synthesis studied. Nitric oxide (NO) donor compounds increase intracellular cGMP and inhibit platelet adhesion and aggregation (7,8). However, several agents that stimulate platelet aggregation, including thrombin, collagen, epinephrine, and adenosine monophosphate, also have been shown to increase platelet cGMP (reviewed in 9). Furthermore, different cGMP analogs appear to either promote (10,11) or inhibit platelet aggregation (12,13).

Type 5 phosphodiesterase (PDE5) hydrolyzes cGMP to relatively inactive GMP and is present in numerous cell types, including platelets and vascular smooth muscle cells (14). We previously used a canine model of coronary artery thrombosis superimposed on endothelial damage and high-grade stenosis to demonstrate that two PDE5 inhibitors, zaprinast and dipyridamole, did not inhibit platelet-mediated thrombosis after thrombolysis when administered alone but were able to markedly augment the antithrom-

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#### Abbreviations and Acronyms

ACS	= acute coronary syndromes
CAPR	= coronary artery patency ratio
CFR	= cyclic coronary flow reductions
cGMP	= cyclic guanosine monophosphate
GP	= glycoprotein
LAD	= left anterior descending coronary artery
MAP	= mean systemic arterial blood pressure
NO	= nitric oxide
PDE5	= type 5 phosphodiesterase

botic effects of inhaled NO (15). Sildenafil is a clinically available PDE5 inhibitor with greater specificity and potency than either dipyridamole or zaprinast (16). Thus, we sought to determine the effect of sildenafil on coronary artery patency in a canine model of platelet-mediated thrombosis despite aspirin therapy.

## METHODS

**Canine model of coronary artery occlusion after thrombolysis.** 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 in 1984.

Adult mongrel dogs (weight 18 to 22 kg) were anesthetized with intravenous pentobarbital (30 mg/kg), tracheally intubated, and mechanically ventilated. Supplemental pentobarbital was given as needed to maintain general anesthesia. The fraction of inspired oxygen (FiO<sub>2</sub>) was adjusted to maintain P<sub>a</sub>O<sub>2</sub> >80 mm Hg, as determined by periodic arterial blood gas measurements. A left thoracotomy was performed in the fifth intercostal space, and dogs were instrumented for intracoronary infusion, electrocardiographic monitoring, and measurement of systemic blood pressure as previously described (17). A 2.5-cm segment of the proximal left anterior descending coronary artery (LAD) was isolated. A 0.7-mm internal diameter catheter was then inserted into a side-branch of the isolated LAD segment, and an ultrasonic flow probe (T106 Flowmeter, Transonic Systems, Ithaca, New York) was placed on the proximal portion of the artery for continuous blood flow monitoring. A 2-mm wide plastic wire tie (Massachusetts Gas and Electric Supply, Boston, Massachusetts) was progressively constricted around the distal end of the segment until the hyperemic response to mechanical occlusion was eliminated and an approximately 50% reduction in initial blood flow was achieved. Angiographic study has shown that this degree of constriction decreases luminal diameter by >90% (18). The rate of coronary blood flow after LAD constriction was considered "baseline" flow.

The isolated segment of the LAD was traumatized by external compressions to damage the endothelium and promote thrombus adherence. Thrombus was formed within the LAD segment by adding 0.1 ml of thrombin

to 0.3 ml of previously sampled blood through the diagonal branch catheter after applying snares proximal to the constriction site and distal to the probe. Snares were released after 10 min of arterial occlusion and, in all cases, the presence of thrombus was confirmed by lack of arterial blood flow through the segment and by visual inspection. Ten minutes later, heparin (40 U/kg) and aspirin (2.5 mg/kg) were administered intravenously. Additional heparin (5 to 20 U/kg) was administered every 20 min as needed to maintain an ACT of 150 to 200 s. After 30 min of stable occlusion, a 0.45-mg/kg bolus of tissue plasminogen activator (Genentech, South San Francisco, California) was administered intravenously at 15-min intervals until coronary artery patency (>25% of baseline flow) was achieved.

**Experimental protocol.** Achievement of coronary patency marked the starting point for the first of two 60-min observation periods. The first 60-min observation period served as a pretreatment period for all 12 animals. For the second 60-min observation period, dogs were assigned randomly to receive no additional therapy (n = 6) or to receive sildenafil (100 µg/kg in normal saline over the course of 2 min followed by a continuous infusion of 4 µg/kg/min, n = 6). This dose of sildenafil was chosen in an effort to mimic peak plasma concentrations of sildenafil produced after the administration of a 50-mg oral dose to a 70-kg human being (19).

Systemic arterial pressure and coronary artery blood flow were measured continuously. A cyclic coronary flow reduction (CFR) was defined as reocclusion of the coronary artery after a spontaneous increase to >25% of baseline flow. Coronary artery patency ratio (CAPR) was the fraction of an observation period during which the coronary artery was patent.

**Activated clotting time (ACT), hemoglobin, and platelet count measurements.** Activated clotting time measurements were performed using an Hemochron 800 dual-well coagulation timer and FTCA 510 reaction tubes (International Technidyne, Edison, New Jersey) every 20 min, and 5 to 20 U/kg boluses of heparin were administered to maintain ACT between 150 and 200 s. Hemoglobin and platelet counts were measured from samples taken at the midpoints of periods one and two.

**Measurement of ex vivo whole-blood aggregation and plasma sildenafil levels.** In the group of dogs treated with sildenafil, thrombin-induced ex vivo platelet aggregation was measured before any arterial manipulation or pharmacotherapy (baseline) and at the midpoints of periods one and two. Blood (3 ml) was collected in tubes containing a final concentration of 3.13% (weight/volume) sodium citrate. Citrated blood (500 µl) was then transferred into cuvettes containing 490 µl of saline and maintained at 37°C with magnetic stirring (1,000 rpm) in an impedance aggregometer (Model 440, Chronolog, Havertown, Pennsylvania). After reaching a stable baseline, the aggregometer was calibrated such that full-scale deflection was 40 Ohms.

**Table 1.** Characteristics of the Canine Coronary Artery Model of Reocclusion After Thrombosis and Thrombolysis

Parameter	Control (n = 6)	Sildenafil (n = 6)
Initial coronary blood flow (ml/min)	17.0 ± 1.7	14.4 ± 1.7
Coronary blood flow after application of constrictor (ml/min)	9.4 ± 1	7.4 ± 1
Number of tPA boluses before reperfusion	1.3 ± 0.2	1 ± 0
CFRs during period 1, cycles/h	5.3 ± 0.6	4.2 ± 1.0
CAPR during period 1, %	49 ± 11	52 ± 9

Data are presented as the mean value ± SEM. There was no difference in any of these variables between the two groups.

CAPR = fraction of the pre-treatment period during which the coronary artery was patent; CFRs = frequency of cycle flow reductions; tPA = tissue plasminogen activator.

Aggregation was induced by the addition of 10 μl of 200 U/ml thrombin solution. The extent of whole blood aggregation was assessed as the maximum impedance reached during a 6-min observation period after exposure to thrombin. Thrombin was used as the agonist for assessment of ex vivo whole blood platelet aggregation in this model because pilot studies using thrombin (2 U/ml), ADP (10 μmol/l), or collagen (5 μg/ml) led to the observation that thrombin produced the most consistent platelet aggregation.

Plasma samples were collected after 30 min of sildenafil infusion and stored at -70°C. Plasma free sildenafil concentrations were measured by high-performance liquid chromatography as described previously (20).

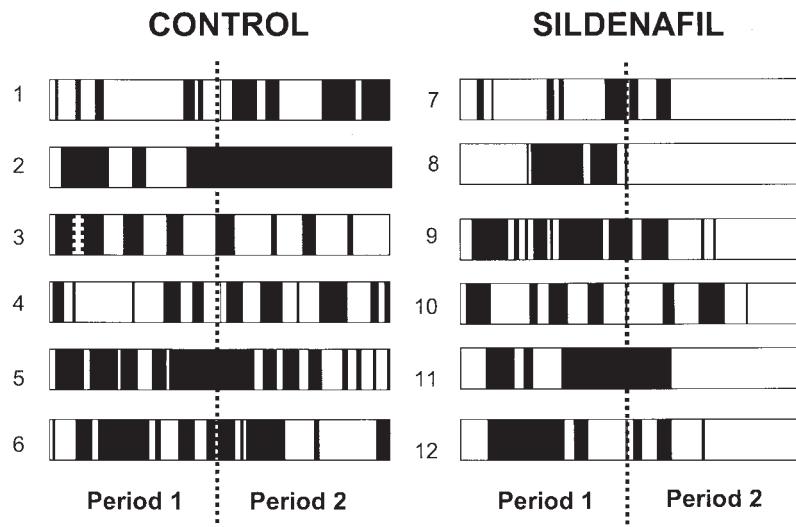
**Statistical analysis.** All data are reported as the mean value ± SEM. The significance of changes in CAPR and CFR, as well as hemodynamic and hematologic variables from period 1 to period 2, was determined by a paired Student *t* test. The significance of the changes in platelet aggregability at baseline and during periods one and two was determined using a repeated-measures analysis of variance

followed by the Neuman-Keuls procedure. A value of *p* < 0.05 was considered significant.

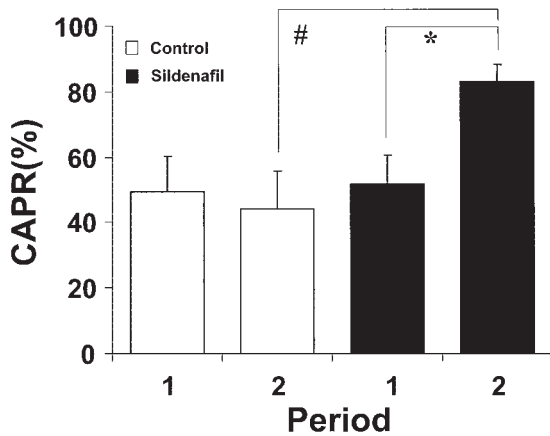
## RESULTS

**Characteristics of the canine model of platelet-mediated cyclic coronary occlusion after thrombolysis.** The characteristics of the canine model before treatment with or without sildenafil (period 1), including the frequency of CFRs and the CAPR, are summarized in Table 1. Application of the external constrictor reduced LAD blood flow by 49 ± 5% in the sildenafil group and by 44 ± 6% in the control group. There were no significant differences between the two experimental groups in the LAD blood flow after application of the constrictor, the number of tissue plasminogen activator boluses required to establish coronary patency (Table 1), or in the ACT (data not shown). Cyclic coronary flow reduction frequency and CAPR during period 1 also did not differ between the two experimental groups.

**Effects of sildenafil on coronary artery patency.** Left anterior descending coronary artery patency after thrombolysis during periods 1 and 2 is represented schematically for individual animals in Figure 1. Black areas indicate intervals of coronary occlusion (blood flow <25% of post-constriction baseline), and white areas indicate intervals of patency. In dogs that did not receive sildenafil, CFR frequency during periods 1 and 2 did not differ (5.3 ± 0.8 cycles/h and 4.2 ± 1.0 cycles/h, respectively). In contrast, CFRs ceased in five of six animals 18 ± 5 min after the initiation of sildenafil. The number of CFRs in period 2 tended to be fewer in sildenafil-treated animals than in control animals (2.4 ± 0.8 vs. 4.2 ± 1.0, *p* = 0.06). In dogs that did not receive sildenafil, the CAPR did not differ from period 1 to period 2 (49 ± 11% vs. 44 ± 11%). However, after the administration of sildenafil, CAPR increased from 52 ± 9% during



**Figure 1.** Schematic representation of the coronary artery patency status of 12 dogs during two sequential observation periods. All dogs were observed during an initial 60-min period (period 1). During the second period (period 2), six animals received sildenafil (50 μg/kg bolus followed by 4 μg/kg/min), whereas six control animals received no further treatment. White areas represent coronary patency (flow >25% of baseline), and black areas represent occlusion.



**Figure 2.** Coronary artery patency ratio (CAPR; fraction of an observed observation period during which the coronary flow was >25% of immediate postconstriction flow). Dogs in the control group (n = 6) were given no additional treatment in period 2. Dogs in the sildenafil group were given 100  $\mu\text{g}/\text{kg}$  sildenafil bolus followed by an infusion of 4  $\mu\text{g}/\text{kg}/\text{min}$  during period 2. \*p = 0.008; #p = 0.007.

period 1 to  $83 \pm 5\%$  during period 2 (p < 0.01) after the initiation of sildenafil (Fig. 2). CAPR during period 2 was greater in sildenafil-treated dogs than in control dogs (p < 0.008).

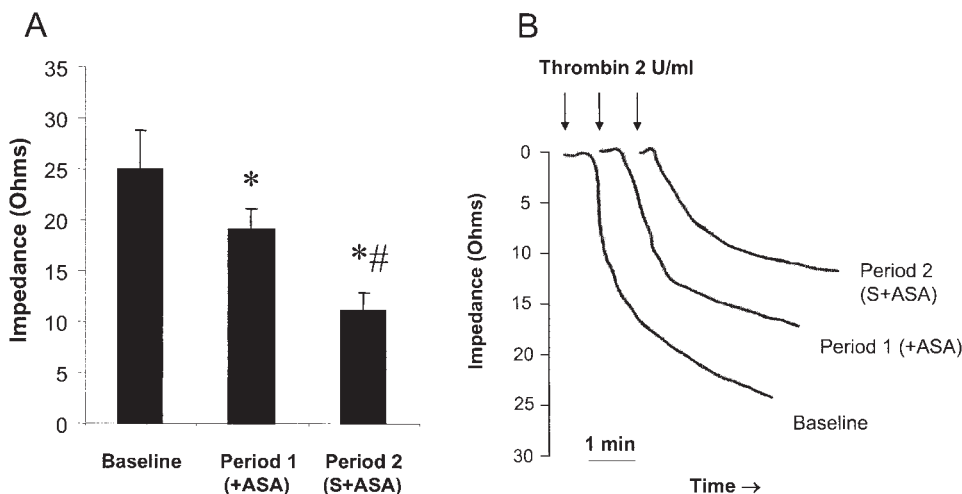
The average free plasma sildenafil levels attained 30 min after administration of the bolus and initiation of the infusion were  $30.3 \pm 6.6$  nmol/l. Among dogs treated with sildenafil, CFRs were less frequent in the three dogs with free plasma sildenafil levels >20 nmol/l (Fig. 1, dog #7, #8, and #11) than in those dogs with sildenafil levels less than 20 nmol/l ( $1.0 \pm 0.4$  vs.  $3.7 \pm 0.5$ , respectively, p < 0.05). In addition, the time to cessation of cycling was shorter in the dogs with free plasma sildenafil levels >20 nmol/l ( $9.8 \pm 3.5$  min) than in those with levels <20 nmol/l ( $32.3 \pm 2.3$  min, p < 0.05).

**Effects of sildenafil on ex vivo whole-blood aggregation.** In the group of dogs which were to be treated with sildenafil, ex vivo thrombin-induced platelet activation was  $24 \pm 2\%$  lower at the midpoint of period 1 than at baseline (p = 0.007), which likely was attributable to treatment with aspirin. Administration of sildenafil decreased ex vivo platelet activation by an additional  $39 \pm 5\%$  as measured at the midpoint of period 2, compared with that observed at the midpoint of period 1 (p < 0.05) (Fig. 3A). Representative platelet aggregation curves (dog #9) are shown in Fig 3B. In dogs that were not treated with sildenafil, ex vivo thrombin-induced platelet activation at the midpoints of period 1 and period 2 did not differ. The blood platelet and hemoglobin concentrations were unchanged during the two observation periods in both groups of dogs (Table 2).

**Effects of sildenafil on arterial blood pressure and heart rate.** One minute after bolus administration of sildenafil, a transient decrease in mean systemic arterial blood pressure (MAP) from  $97 \pm 6$  mm Hg to  $91 \pm 5$  mm Hg was observed (Fig. 4, p < 0.05). By 5 min after the initiation of sildenafil, MAP had returned to pre-sildenafil levels, and there was no further change in MAP during the remainder of the 60-min sildenafil infusion period (Table 2). Heart rate did not change following treatment with sildenafil.

**DISCUSSION**

This study was conducted to determine the effects of sildenafil on platelet-mediated thrombosis in a well-characterized canine model of coronary artery thrombosis after thrombolysis (18). Our study demonstrates that intravenous sildenafil increased coronary artery patency, reduced ex vivo platelet aggregability, and stopped cyclic flow reduction in the majority of animals. We observed that dogs with free sildenafil levels >20 nmol/l (the average peak concentration observed in patients after administration of a 50-mg



**Figure 3.** Effects of aspirin and sildenafil on platelet aggregation. (A) Thrombin-induced platelet aggregation during the treatment period (+ aspirin [ASA], at 30 min, and +sildenafil and aspirin [S+ASA] at 90 min) relative to baseline aggregation in the pretreatment period, as determined by whole blood aggregometry (n = 6 dogs). \*p < 0.05, ASA versus baseline. \*#p < 0.05, ASA+sildenafil versus each of the other groups. (B) Representative platelet aggregation recordings in dog 9.

**Table 2.** Blood Pressure and Hematologic Values During the Two Observation Periods

	Control (n = 6)		Sildenafil (n = 6)	
	Period 1	Period 2	Period 1	Period 2
Mean arterial pressure (mm Hg)	78 ± 5	78 ± 5	98 ± 6	93 ± 4
Hemoglobin (g/100 ml)	7.8 ± 0.4	7.4 ± 0.8	7.9 ± 0.3	7.8 ± 0.3
Platelet count (thousands/mm <sup>3</sup> )	252 ± 11	249 ± 9	310 ± 24	285 ± 19

Data are presented as the mean value ± SEM. There was no difference in any of these variables between the two groups.

oral dose of sildenafil) had fewer CFRs and a more rapid cessation of cyclic occlusion than did dogs with free sildenafil levels <20 nmol/l.

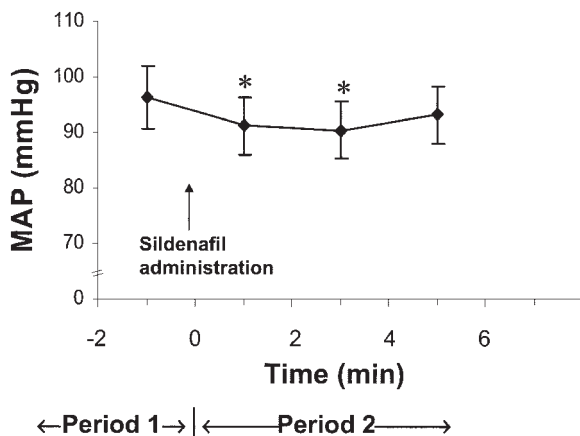
Sildenafil is a specific inhibitor of PDE5, which is present in a variety of cell types that contribute to vascular homeostasis, including platelets and vascular smooth muscle cells (21). Previous histologic studies in this canine model have demonstrated the presence of intracoronary platelet-rich thrombus during cyclic occlusion (22), and other studies using this model have shown that cyclic occlusion is reduced only by antithrombotic agents that inhibit platelet function (23). These results, as well as the current observations that sildenafil administration inhibited ex vivo platelet aggregation, are supportive of inhibition of platelet function as the mechanism for the improvement in coronary patency observed during sildenafil administration. We cannot exclude the possibility that coronary vasodilation contributed to our observation that sildenafil improved coronary patency; however, in patients with coronary disease undergoing PCI, sildenafil did not change coronary cross-sectional area or blood flow (24).

Nitric oxide-donor compounds and inhaled NO increase platelet cGMP concentrations, decrease platelet aggregation in vitro, and inhibit thrombosis in vivo. Other agents that activate cGMP synthesis by soluble guanylate cyclase also inhibit platelet aggregation in vitro and thrombosis in vivo, including YC-1 (25), BAY 41-8543 (26), and BAY 41-2272 (27). It is probable that the antithrombotic effects of

sildenafil are attributable to its ability to increase cGMP concentrations in platelets by inhibiting PDE5.

The PDE5 inhibitors have been shown to reduce platelet aggregation in an animal model of endothelial injury (28), and reduce human ex vivo platelet aggregability (29). PDE5 inhibitors also augment the ability of NO-donor compounds to decrease platelet aggregation in vitro (17) and platelet-mediated thrombosis in vivo (29). The clinical utility of the concomitant administration of PDE5 inhibitors and NO donor compounds to prevent thrombosis is limited by severe systemic arterial hypotension (30). We recently reported that although two PDE5 inhibitors, dipyridamole and zaprinast, did not inhibit coronary thrombosis and thrombolysis when administered alone, they markedly augmented the anti-thrombotic effects of inhaled NO (15) without systemic hypotension. The ability of sildenafil to inhibit coronary thrombosis in the absence of exogenous NO is most likely because it is a more specific and potent inhibitor of PDE5 than either dipyridamole or zaprinast. The dose of sildenafil that was administered in this study produced a plasma concentration that exceeded the IC<sub>50</sub> for PDE5 (3.5 nmol/l), whereas the doses of dipyridamole and zaprinast administered in the previous study (15) would not be expected to achieve the IC<sub>50</sub> of these agents for PDE5, which are 500- (31) and 250-fold (13) greater than sildenafil, respectively. It is probable that doses of dipyridamole sufficient to achieve a level of PDE5 inhibition similar to that achieved by sildenafil would block adenosine reuptake, potentially leading to hypotension (32). Because concentrations of zaprinast necessary to block PDE5 activity are likely to inhibit type 1 phosphodiesterase (16), it is probable that doses of zaprinast sufficient to inhibit thrombosis would increase intracellular cAMP in cardiac and vascular smooth muscle, leading to tachycardia and vasodilation.

It has previously been reported that sildenafil did not improve coronary patency in a canine model of coronary thrombosis (33). In an effort to mimic the thrombogenic environment of clinical ACS, our model differs from that previously used (33) because aspirin was administered to the animals at the beginning of the study. Thus, the platelet inhibitory effects observed in the current study may be the result of a greater inhibitory role for cGMP in platelets no longer subject to activation through the arachadonic acid pathway. Further study of the role of cGMP signaling on platelet aggregability in the presence of cyclooxygenase



**Figure 4.** Effect of the bolus administration of sildenafil on mean arterial blood pressure (MAP). There was a transient fall in MAP within 1 min of the bolus administration of sildenafil that persisted for 3 min. The MAP 5 min after sildenafil administration did not differ from that at the end of period 1. \*p < 0.05.

inhibition may clarify the reason for the differing results in the two studies.

Li et al. (11) have reported that concurrent addition of cGMP analogs and sildenafil potentiated ristocetin- or thrombin-induced platelet aggregation *in vitro* when the proaggregatory stimulus was administered within 10 min of sildenafil exposure. These investigators proposed that the platelet responses to cGMP are biphasic, initially promoting aggregation and subsequently limiting thrombus formation. In the present study, we observed an inhibitory effect of sildenafil on *ex vivo* platelet aggregation 30 min after its administration. Furthermore, cessation of *in vivo* cyclic occlusion did not occur until  $18 \pm 5$  min after sildenafil was given. Although we did not measure platelet aggregability early after sildenafil administration, we did not observe an early increase in CFR or a reduction in CAPR during the initial 30 min after sildenafil administration. Our observations are consistent with the antiaggregatory effect of increased platelet cGMP concentration observed *in vitro* (13), and in other models of cyclic coronary occlusion causing myocardial ischemia (7).

**Clinical implications.** Cases of acute myocardial infarction after the use of sildenafil have been reported (34,35). The results of this study suggest that these events are unlikely to be attributable to a prothrombotic effect of this drug and are in agreement with a recent case-control study of Mittleman et al (36) and a recent report from the U.S. Food and Drug Administration (37) that did not find a higher incidence of myocardial infarction or other thrombotic events with sildenafil use when compared with expected rates in a similar patient population. Our observation of an antiplatelet effect of sildenafil also is consistent with that of Halcox et al. (38), who observed that sildenafil decreased platelet aggregation in patients with CAD.

In the animal model we used, aspirin reduced *ex vivo* platelet aggregation by 24%; however, cyclic coronary occlusion continued, which likely is attributable to the presence of a potent thrombotic stimulus of a partially lysed thrombus at the site of a severe fixed coronary stenosis that may be caused by thrombin (2). In this study, the addition of sildenafil to aspirin resulted in the cessation of cyclic coronary occlusion and a 39% further reduction in *ex vivo* platelet aggregation. Furthermore, agents that have previously been shown to be effective in this model, such as abciximab and tirofiban, have proven effective for the treatment of ACS (23). Our results suggest that agents that augment intracellular cGMP, such as PDE5 inhibitors, merit further exploration as adjunctive therapy in ACS and other syndromes associated with platelet-mediated thrombosis.

**Study limitations.** Our observations of the benefits of sildenafil administration in a canine model of platelet-mediated thrombosis after thrombolysis may not be applicable to the risk of initial thrombotic coronary occlusion occurring in patients at risk for ACS. Furthermore, the potential application of our observations to the treatment of ACS is limited by the current use of nitrate therapy for these patients. The use of PDE5

inhibitors concomitantly with nitrates is contraindicated because of the propensity of this combination to cause profound hypotension. Although we observed coronary patency in our study for 60 mins after the initiation of administration of sildenafil, the duration of action of this effect was not assessed and may be limited by the 4-h half-life of sildenafil. Although tachyphylaxis to the hemodynamic effects of sildenafil has not been reported in patients with pulmonary hypertension (39), the possibility that this will limit its use as an antiplatelet therapy remains to be explored.

**Conclusions.** Sildenafil improves coronary patency in an *in vivo* model of platelet-mediated thrombosis and inhibits *ex vivo* platelet aggregation despite aspirin therapy. These results suggest that blockade of cGMP hydrolysis may represent a novel target for antiplatelet therapy.

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