Is Measurement of Cyclic Guanosine Monophosphate in Plasma or Urine Suitable for Assessing In Vivo Nitric Oxide Production?

To the Editor:

In their recently published article on nitric oxide (NO) synthesis in patients with peripheral arterial occlusive disease Böger et al.1 based their conclusions among others on urinary excretion of cyclic guanosine monophosphate (cGMP). The increasing use of urinary and plasma cGMP as a marker of NO production prompts us to critically comment on the basis of doing this. NO stimulates soluble guanylate cyclase and elevates intracellular cGMP.2 The other isozyme of guanylate cyclase, particulate guanylate cyclase, is stimulated by natriuretic peptides, which also leads to an increase in intracellular cGMP.3 The induction of cGMP either by natriuretic peptides, NO, or nitrates in target tissues may cause an egression of cGMP into the supernatant.4,5 We observed a release of cGMP into the medium after stimulation of human internal mammary artery grafts with either atrial natriuretic peptide (ANP) or SIN-1 (unpublished results). However, much higher concentrations of SIN-1 were necessary to achieve comparably high cGMP concentrations in the medium.

In humans, ANP injections cause a rapid and pronounced increase in plasma and urinary cGMP,6,7 whereas nitroglycerol infusions or molsidomine injections lead to a nonsignificant increase or no increase in peripheral venous plasma cGMP concentrations.6,8 cGMP is only partly eliminated from plasma by glomerular filtration, and most of plasma cGMP is eliminated by extrarenal clearance. Urinary cGMP is primarily of renal cellular origin and correlated with the natriuresis induced by ANP.8 Therefore urinary cGMP has been proposed as a biologic marker for the renal activities of natriuretic peptides in vivo.8 We found no correlation between plasma and urinary cGMP concentrations in humans.9 Urinary and plasma cGMP concentrations are influenced by renal function. Urinary cGMP per gram of creatinine was significantly lower and plasma cGMP of patients with renal diseases was significantly higher than that of control subjects.6,9 Therefore urinary cGMP is mainly influenced by the biologic activities of natriuretic peptides and also by renal function. As a consequence, urinary cGMP does not appear to be a reliable marker for the in vivo NO production in humans.

However, Tsutamoto et al.10 could demonstrate that the arteriovenous cGMP difference may be useful for assessing the local stimulation of the soluble guanylate cyclase in humans. Although venous cGMP concentrations did not change, the decrease in arterial cGMP during nitroglycerol infusion indicated a local cGMP production by stimulation of the soluble guanylate cyclase. A decrease in ANP plasma concentrations during nitroglycerol infusion excluded natriuretic peptides as a cause of the observed cGMP production. cGMP production correlated with hemodynamics and did not occur after captopril administration.

In conclusion, most of the plasma cGMP is derived from the endogenous natriuretic peptides and only a minor part from other pathways, such as soluble guanylate cyclase. The change of plasma cGMP concentrations by nitrates is much smaller than that by ANP, with the same hemodynamic effect.10 In contrast to urinary cGMP, the arteriovenous cGMP production may allow assessment of the activation of soluble guanylatecyclase in vivo. However, it is mandatory to measure natriuretic peptide concentrations simultaneously to exclude changes in natriuretic peptides as the underlying cause of cGMP production.

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Response

The letter by Drs Mair and Puschendorf gives us an opportunity to comment on the use of plasma and urinary nitrate and cGMP as indicators of in vivo nitric oxide formation.

Nitric oxide is formed in the vascular endothelium and in other tissues. One of its major targets is the soluble guanylyl cyclase (sGC), which leads to the formation of cGMP. NO is rapidly inactivated through oxidation to nitrite and nitrate; under pathophysiologic conditions, oxidative inactivation may occur even before the sGC has been stimulated.1 Both cGMP and nitrite/nitrate can be found in conditioned endothelial cell media, in plasma, and in urine. Because the chemical half-life of NO is in the range of seconds, NO itself can hardly be measured in vivo. Two main strategies have therefore been followed to assess NO activity in vivo. One is to determine NO-dependent vasodilation and the other is to measure the metabolites and/or second messenger of NO, nitrite/nitrate and cGMP, as biochemical surrogates for NO. However, both of these strategies may be limited by some constraints:
NO-dependent vasodilation allows one to assess the biologic activity of NO irrespective of whether decreased elaboration of NO or enhanced oxidative inactivation may underlie this disorder. On the other hand, the simultaneous quantitation of nitrite/nitrate and cGMP allows differentiation between impaired NO synthesis (in which case nitrite/nitrate levels and cGMP levels are expected to be low) and oxidative inactivation (in which case cGMP levels are expected to be low, but nitrite/nitrate levels should be normal or elevated). This approach is curtailed by the potential influence of dietary nitrate intake and by cGMP formation by the particulate guanylyl cyclase as discussed by Drs Mair and Puschendorf. However, because dietary nitrate would only affect nitrate levels but not those of cGMP, and activation of the particulate GC would only affect cGMP levels but not those of nitrate, we have repeatedly advocated the parallel use of both indicators to estimate NO elaboration. Furthermore, plasma levels of these index molecules may only reflect a momentary situation in a localized area of the circulation, whereas urinary levels reflect systemic NO production rates but may be affected by renal excretory function. We have addressed this latter question in an experimental study and found that correction of urinary nitrate and cGMP concentrations by urinary creatinine concentration (ie, urinary excretion rates of these metabolites instead of urinary concentrations) eliminates the dependency on renal excretory function. Using this approach, we and others have adopted nitrate and cGMP measurements as reliable indicators of NO elaboration during physiologic (eg, physical exercise) and pharmacologic stimulation. In our recent study to which Drs Mair and Puschendorf refer, we have analyzed basal urinary nitrate and cGMP excretion rates in patients with peripheral arterial occlusive disease of the legs. Twenty-three of these patients had impaired renal function as judged by creatinine clearance. We have reanalyzed urinary nitrate and cGMP excretion rates in the subgroups of patients with normal or impaired renal function and found no statistically significant differences in these parameters despite a 50% reduction of creatinine clearance in the patients with impaired renal function (Figure). This demonstrates again that urinary nitrate and cGMP excretion rates are independent of renal excretory function.

The in vitro studies cited by Drs Mair and Puschendorf confirm that cGMP levels are influenced both by ANP and NO donors. However, it is difficult to us to extrapolate results obtained with pharmacologic concentrations of ANP and NO donors in isolated arteries in vitro to physiologic situations in vivo. Indeed, Arnal and coworkers found that the in vivo basal aortic cGMP levels in rats were mainly dependent on NO synthase:soluble guanylyl cyclase activity. During chronic NO synthase inhibition, aortic cGMP levels significantly decreased; in this setting cGMP levels were correlated with ANP levels. The reduction of aortic cGMP levels during NO synthase inhibition was reversed by L-NAME, they were not paralleled by increased plasma ANP levels. These authors also showed a correlation between the changes in urinary cGMP excretion and the acetylcholine-induced decrease in systemic blood pressure. We have shown that changes in urinary cGMP excretion rates could not be explained by differences in ANP levels in healthy humans at baseline and even after intravenous volume loading. This may be different in patients in whom the ANP system is activated, as in chronic heart failure. The usefulness of urinary nitrate and cGMP as markers for systemic NO elaboration in vivo should therefore be evaluated in any patient group separately.

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Effects of Ischemic Preconditioning

To the Editor:

The clinical existence and relevance of ischemic preconditioning will remain difficult to prove because patients cannot be subjected to the rigorous protocols performed in laboratory animals and because of our inability to accurately determine infarct size and its determinants in humans. Furthermore, the presence of atherosclerotic lesions in coronary arteries can result in intermittent/chronic ischemia that could result in tolerance to the ischemic stimulus. Consequently, investigating the phenomenon of ischemic preconditioning in animal models that mimic the clinical situation is important. It was therefore with great interest that we read the article by Kapadia et al in which they describe that the protective effect of ischemic preconditioning is not abolished in the presence of a critical stenosis. Although this study in a closed chest swine model is another major step forward in bridging the gap between the laboratory and the clinical setting, there are a number of issues that deserve comment.

The authors did not find a protective effect of the stenosis alone, which reduced blood flow by approximately 35% (P = NS), and indicated that this finding is at variance with the results of a study from our laboratory in which we showed that 30-minute 70% flow reduction resulted in a reduction of infarct size produced by 60 minutes of coronary artery occlusion. However, in a subsequent study we demonstrated that when flow was reduced by only 30% for up to 90 minutes immediately preceding the 60 minutes of total coronary occlusion, cardioprotection was absent. Furthermore, Ovize et al reported that 25 minutes of 50% flow reduction immediately preceding the total coronary occlusion failed to limit infarct size, suggesting that the flow reduction in the study by Kapadia et al was not severe enough to produce cardioprotection.

Although the stenosis did not abolish ischemic preconditioning, the authors concluded that the presence of a critical stenosis might limit preconditioning despite a nonsignificant trend (versus P = 0.60) toward a difference in infarct size in the preconditioning + stenosis group (PC/S) and the preconditioning group (PC). Such a conclusion appears premature in view of a number of methodologic considerations. First, collateral myocardial blood flow tended to be higher in the PC than in the PC/S group. Second, the relation between area of necrosis (AN) and the area at risk (AAR) is linear but not proportional because of a positive intercept on the AR-axis, so that at an AAR that comprises 5% of the left ventricle, no infarction occurs. Consequently the ratio of AN/AAR depends on the AAR, so that AN/AAR decreases at smaller AAR. In the present study there was a trend toward a smaller AAR in PC versus PC/S, which could have contributed to the trend toward a larger infarct size in PC/S than in PC. Finally, body temperature may have varied considerably despite the closed chest, particularly during recovery from anesthesia, when the animals exhibited tremulousness. Because temperature is an important determinant of infarct size in swine, this could have further added to differences between experimental groups.

In contrast to the obvious advantages of this closed chest swine model, the very high dropout rates caused by refractory fibrillation and technical problems pose a serious disadvantage, making such studies laborious and expensive. Nonetheless we may have to rely on such models for assessment of clinical relevance of the ischemic preconditioning phenomenon. Development of a chronically instrumented animal model in which myocardial function, perfusion, and metabolism can be monitored and the effects of the presence of a chronic (days to weeks) stenosis possibly resulting in repetitive stunning and/or hibernation will be a next step in the assessment of the clinical relevance of ischemic preconditioning.

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Response

We appreciate the comments of Drs Duncker and Verdouw. Their 1995 publication was inadvertently overlooked in our search of the literature. They found no cardioprotection as a result of a 30% reduction in coronary blood flow before coronary occlusion. This is consistent with our finding and antedates our report. In that report, 15 minutes (not 25 minutes) of an approximately 50% flow reduction failed to produce a preconditioning effect when there was no intervening period of full reperfusion after the partial flow restriction. The difference in severity of ischemia, the added effect of full reperfusion after the period of total occlusion, and the use of dogs rather than swine render that study considerably different from the one we reported. Nevertheless, it is another negative study with respect to a partial coronary artery occlusion as a preconditioning agent.

Our results with the stenosis group that received the preconditioning occlusion (PC/S) left us with a seemingly intermediate result in terms of infarct as a percentage of area at risk, although statistically, the preconditioned (PC) and PC/S groups did not differ significantly. We wanted to recognize this difference and used tentative language to describe it. In the last paragraph of our article, the wording was less tentative than intended. We agree that there is no clear evidence that the stenosis attenuated the preconditioning effect of brief occlusions.

We agree with Drs Duncker and Verdouw that in our study there was “a trend toward a smaller AAR in PC versus PC/S, which could have contributed to the trend toward a larger infarct size in PC/S than in PC.” As noted, the differences in AAR/LV were not significant, albeit working with small sample sizes (30 ± 3.0% in PC/S and 25.9 ± 3.0% in PC).

Regarding the temperature of the animals during the study, there was no significant difference between mean temperature of PC and PC/S animals after the first preconditioning occlusion (PC = 36.8 ± 1.26°C; PC/S = 36.5 ± 1.08°C; x ± SD).

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Studies such as these are handicapped by the very high mortality of animals and numerous technical problems. Nevertheless, efforts to closely approximate the human condition are needed. We agree that a reliable chronic animal model is needed and would be a significant step forward in studies of preconditioning.

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**Effects of Exercise During Long-term Support With a Left Ventricular Assist Device**

To the Editor:

Jaski et al,1 in their article in *Circulation*, provide important information regarding exercise physiology during long-term TCI Heartmate left ventricular assist device (LVAD) support. They indicate that the native left ventricle contributes directly to systemic cardiac output during exercise yet do not attempt to quantify left ventricular contribution.

In our institution, of more than 660 patients referred for cardiac transplantation between 1990 and 1997, 50 patients had to receive LVAD support, 39 by the Novacor,2 7 by the TCI Heartmate, and 4 by the Medos system. We have reported a protocol for the Novacor LVAD that allows for quantification of native left ventricular function.3 A similar protocol was developed for the TCI Heartmate LVAD with the purpose of (a) quantifying left ventricular contribution and (b) assessing left ventricular functional reserve. A 7.5F thermodilution Swan-Ganz catheter was placed in the pulmonary artery. Cardiac output, pulmonary capillary wedge pressure, pulmonary artery pressure, and right atrial pressure as well as arterial pressure (by cuff inflation) were recorded at rest, during upright bicycle exercise after 5 minutes on the 25-, 50-, and 75-W levels as well as 3 and 10 minutes after exercise. Simultaneously, TCI Heartmate LVAD hemodynamic data (pump rate, pump stroke volume, pump output) were automatically recorded. Data were compared by subtraction. Two different LVAD settings were chosen. In setting I (“fill-to-empty”), we achieved maximal pump washout in conjunction with optimal pump output, as did Jaski et al.1 In this setting, the aortic valve remained largely closed as assessed by simultaneous transthoracic echocardiography. The LVAD acted as a series pump. The left ventricle was unloaded. Setting 2 (“fixed rate mode”) consisted of a fixed pump rate of 50/min so that synchronization of pump and native left ventricular action was no longer possible. In this situation, incomplete emptying of the left ventricle into the pump was encountered with a resultant rise in left ventricular load. Thus the pump rate reduction actually led to an afterload and preload challenge for the native left ventricle. In this situation, total cardiac output even at rest was substantially supported by the recipient’s own heart as documented by aortic valve opening. The LVAD acted as a parallel pump.

This protocol was, as a pilot test with institutional review board approval and patient informed consent, applied in the last 3 of our 7 TCI Heartmate recipients (all men; mean age, 50 ± 12 years; 1 idiopathic, 2 ischemic cardiomyopathy) after recovery (117 ± 20 days after surgery) and informed consent. At the time of the study, all patients were receiving vasodilators, aspirin, and dipyridamole. Results are summarized in the Table. The main finding was the quantification of the percentage left ventricular stroke volume across the aortic valve (between zero and 53% of total = right ventricular stroke volume) and a higher percent left ventricular stroke volume (53 ± 14% versus 15 ± 12%; P = 0.024) on the 75-W level in setting 2 compared with setting 1. The difference may be considered as left ventricular functional reserve.

It has been shown that exercise testing in LVAD recipients can be safely performed.4 Patients with the TCI left ventricular assist device walked up to 6 miles and were in New York Heart Association class II. Functional benefit with increase of peak O2 to 15 mL/kg per minute and normalization of neurohormones has been reported.5 In the Pittsburgh series, in 31 Novacor patients, mean peak O2 increased from 10 to 15 mL/kg per minute.6 All of these LVAD exercise protocols have assessed the combined function of the left heart–left ventricular assist device complex without quantifying the specific contribution of the native left ventricle.

**TCI Heartmate Settings 1 and 2 and Associated Changes Before, During, and After Exercise in 3 Patients**

<table>
<thead>
<tr>
<th></th>
<th>Before Exercise</th>
<th>75 W</th>
<th>3 Minutes After Exercise</th>
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<tbody>
<tr>
<td></td>
<td>S1</td>
<td>S2</td>
<td>S1</td>
</tr>
<tr>
<td>PR</td>
<td>77 ± 28</td>
<td>50 ± 0</td>
<td>120 ± 1</td>
</tr>
<tr>
<td>HR</td>
<td>90 ± 9</td>
<td>104 ± 6</td>
<td>137 ± 11</td>
</tr>
<tr>
<td>PCWP</td>
<td>2 ± 2</td>
<td>4 ± 2</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>SVR</td>
<td>1459 ± 397</td>
<td>1633 ± 201</td>
<td>724 ± 145</td>
</tr>
<tr>
<td>PO</td>
<td>5.7 ± 1.9</td>
<td>4.2 ± 0.1</td>
<td>9.6 ± 0.5</td>
</tr>
<tr>
<td>TCO</td>
<td>5.7 ± 2.4</td>
<td>4.9 ± 1.0</td>
<td>11.4 ± 2.1</td>
</tr>
<tr>
<td>LVO</td>
<td>0.0 ± 0.6</td>
<td>0.7 ± 1.1</td>
<td>1.8 ± 1.8</td>
</tr>
<tr>
<td>%LVSV</td>
<td>3 ± 5</td>
<td>15 ± 6</td>
<td>15 ± 12</td>
</tr>
</tbody>
</table>

S1 indicates setting 1 (“fill-to-empty”); S2, setting 2 (“fixed rate mode”); PR, pump rate (L/min); HR, heart rate; PCWP, pulmonary capillary wedge pressure (mm Hg); SVR, systemic vascular resistance (dyne·s·cm⁻⁵); PO, pump output (L/min); TCO, total cardiac output (L/min); LVO, native left ventricular output (L/min); and %LVSV, left ventricular stroke volume/right ventricular stroke volume × 100.

Values are given as mean ± SD.

*P < .05 according to *t* test.
With the proposed protocol, the relative contribution of the native left ventricle to total stroke volume and cardiac output may be quantified. Furthermore, left ventricular functional reserve can be safely and reliably assessed in clinically stable TCI Heartmate patients. Thus this protocol may facilitate prediction of left ventricular recovery and the potential for weaning, the potential for chronic LVAD support, as well as estimation of the risk associated with device dysfunction.

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Response

We appreciate Dr Deng and his coworkers for acknowledging the findings of the EVADE pilot trial and for providing additional data in their carefully studied three patients. We also found that from rest to peak exercise, Fick systemic blood flow increased significantly more than left ventricular assist device (LVAD) output (2.8±1.9 versus 1.6±1.1, P<.05), implying parallel ejection of blood through the native aortic valve in the fill-to-empty mode used for our study. The fixed-rate protocol used by Dr Deng and coworkers for quantifying LV contribution may serve as a valuable tool either for predicting LV recovery before LVAD explant or for evaluating patient safety during chronic LVAD support. Both of our studies address the need for additional data from larger prospective studies to help understand the unique physiology of the LV-LVAD complex as well as to further define the role of the LVAD in long-term implantation.

We disagree with the calculation of percent LVSV through an LSVS/RVSV ratio, because it implies that LVAD filling occurs only during LV systole. Because LVAD filling also occurs during LV diastole in response to the negative pressure induced by the LVAD during its filling phase, the actual percent LVSV ejected through the native aortic valve during LV systole should be, in fact, higher than the values reported in their study.

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A Fast and Accurate Method for Genotyping the Angiotensin-Converting Enzyme I/D Polymorphism

To the Editor:

The association of the insertion/deletion (I/D) polymorphism of the ACE gene with ischemic vascular disease is disputed.1 Mistyping as DD of 4% to 5% of ID subjects may contribute to conflicting findings.2,3 The original method4 preferentially extends allele D. The addition of 5% DMSO, or the use of an allele-specific oligonucleotide (ASO), reduces mistyping.5,6 Although the ASO technique is the method of choice,7,8 it is time consuming because a second nested PCR must be performed on the DD samples obtained with the original method. We have devised a one-step multiplex PCR, which we tested on 520 individuals and compared the results with those obtained with other methods.

An insertion-specific primer pair (hace5a, hace5c) and a sense primer flanking the Alu-type sequence4 are used simultaneously. One hundred micrograms of genomic DNA are amplified on a PTC100 thermal cycler (MJ Research) in a total volume of 20 μL containing 10, 2.5, and 15 picomoles of the Alu-flanking sense primer, the insertion-specific primer, and the antisense primer, respectively. 1.5 mmol/L MgCl2, 50 μmol/L of each dNTP and 0.5 U of Taq polymerase (Promega). After 40-second denaturation at 94°C, we ran 32 cycles of 30 seconds at 94°C, 45 seconds at 68°C, and 90 seconds at 72°C, followed by 3 minutes at 72°C. The products are identified according to standard procedures.7 The D allele generates a 234-bp band; allele I produces two bands of 522 and 335 bp, respectively. Similar to the ASO-PCR protocol, the multiplex PCR detected 7 samples out of 274 ID individuals that were mistyped as DD with the original procedure (2.6%). The DMSO protocol showed only three misclassifications (1.1%) in this setting. Thus this fast, reliable new PCR procedure is an improvement in the detection of the ACE gene I/D polymorphism.

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Response

Dr Mancini and coworkers describe a new, multiplex PCR procedure for fast detection of the ACE gene insertion/deletion (I/D) polymorphism but do not come to a decision as to the possible application of ACE I/D genotyping. Although mistyping of 4% to 5% of ID subjects as DD may have contributed to conflicting results of the ACE gene polymorphism on risk of ischemic heart disease in some of the early studies that did not correct for mistyping, this is unlikely for the three largest studies because they all corrected for mistyping by reanalyzing all DD individuals in a PCR with an insertion-specific primer. In these studies that comprised approximately 3600 men and more than 10,000 women and men and included prospective, retrospective, cross-sectional, and case-referent/case-control designs, the ACE I/D polymorphism was not associated with risk of ischemic heart disease, coronary artery stenosis, myocardial infarction, ischemic cerebrovascular disease, or longevity. Furthermore, a recent meta-analysis including 15 studies comprising almost 9000 individuals suggested publication bias toward positive results for the smaller studies. In our view, therefore, the ACE I/D polymorphism is not suitable as a marker for ischemic heart disease, coronary artery stenosis, myocardial infarction, ischemic cerebrovascular disease, or related diagnoses and should not be used as such. However, the ACE polymorphism D-allele has consistently been associated with elevated plasma ACE levels and activity in a codominant pattern in most studies and may therefore be a marker for some other disease manifestation associated with plasma ACE levels.

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Delayed Profound Thrombocytopenia After c7E3 Fab (Abciximab) Therapy

To the Editor:

We read with interest the article “Acute Profound Thrombocytopenia After c7E3 Fab (Abciximab) Therapy” by Berkowitz et al.1 The thrombocytopenia so caused usually occurs within 24 hours of infusion, and it underscores the importance of the close monitoring of platelet count after infusion. We describe a case of profound thrombocytopenia that developed 6 days after infusion.

A 62-year-old white man was admitted with acute anterior myocardial infarction on April 27, 1997. The patient had a history of intravenous dye allergy, and 125 mg methylprednisolone and diphenhydramine was given. Coronary angiography revealed total occlusion of the left anterior descending coronary artery, and primary percutaneous transluminal coronary angioplasty was performed with resultant TIMI 3 flow and a small dissection. Intraprocedure ACT was maintained from 300 to 400 seconds. Bolus abciximab of 0.25 mg/kg followed by 10 mg/min infusion for 12 hours was given. Heparin was continued until April 29. Coumadin, captopril, metoprolol, ASA, and insulin were started April 28. Platelet count was monitored closely after abciximab therapy and was stable at 175 to 180 000/mL. On May 3, the platelets acutely decreased to 7000/mL, confirmed by repeat testing. The patient had a witnessed diaphoretic attack with transient apnea lasting for 40 seconds, which recovered spontaneously without residual neurologic deficit. Peripheral blood smear was normal. Serum creatinine was 0.8 mg/dL. Disseminated intravascular coagulation panel was negative. With possible intracranial bleeding, one unit of single-donor pheresis platelets was given. Intravenous immunoglobulin of 1 g/kg was also given. Because of possible drug-induced thrombocytopenia, metoprolol and captopril were discontinued. Urgent computed tomography and subsequent magnetic resonance imaging of the brain showed ischemic changes. Heparin-dependent platelet antibody with platelet aggregation study was negative.2 The platelet count increased to 34 000/mL after transfusion. Benazapril and metoprolol were reinitiated. The platelets increased steadily to 201 000/mL at discharge on May 10. The patient was readmitted on May 11 with acute inferior myocardial infarction. Coronary angiography revealed total occlusion of the right coronary artery, and primary percutaneous transluminal coronary angioplasty was performed with a 20% residual lesion. The patient recovered uneventfully. Because of recurrent thrombosis of the heart and brain, the following
tests were performed: activated protein C resistance assay, Factor V Leiden analysis, protein C, protein S, homocysteine level, and anticardiolipin antibody. The results were all normal. The patient has remained asymptomatic to date.

The cause of thrombocytopenia associated with cerebral infarct is intriguing. Heparin-induced thrombocytopenia is unlikely because the heparin was discontinued 4 days before onset of thrombocytopenia and the negative heparin-dependent platelet antibody.3 Thrombotic thrombocytopenic purpura is also unlikely with normal renal function, absence of schistocytes, and resolution without appropriate intervention. Drug-induced thrombocytopenia is unlikely because metoprolol and benazepril were successfully restarted.

The prompt recovery in this case is consistent with abciximab-induced thrombocytopenia; however, delayed occurrence is unusual. We speculate that the methylprednisolone given before the first procedure may have delayed the onset of thrombocytopenia. In conclusion, we describe a case of profound thrombocytopenia occurring 6 days after abciximab therapy, possibly related to the therapy. The concomitant cerebral infarct may be incidental.

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Is Measurement of Cyclic Guanosine Monophosphate in Plasma or Urine Suitable for Assessing In Vivo Nitric Oxide Production?
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