Role of Nitric Oxide and Adenosine in Control of Coronary 
Blood Flow in Exercising Dogs

Johnathan D. Tune, PhD; Keith Neu Richmond, PhD; Mark W. Gorman, PhD; Eric O. Feigl, MD

Background—Inhibition of nitric oxide (NO) synthesis results in very little change in coronary blood flow, but this is thought to be because cardiac adenosine concentration increases to compensate for the loss of NO vasodilation. Accordingly, in the present study, adenosine measurements were made before and during NO synthesis inhibition during exercise.

Methods and Results—Experiments were performed in chronically instrumented dogs at rest and during graded treadmill exercise before and during inhibition of NO synthesis with Nω-nitro-L-arginine (L-NNA, 35 mg/kg IV). Before inhibition of NO synthesis, myocardial oxygen consumption increased 3.7-fold, and coronary blood flow increased 3.2-fold from rest to the highest level of exercise, and this was not changed by NO synthesis inhibition. Coronary venous oxygen tension was modestly reduced by L-NNA at all levels of myocardial oxygen consumption. However, the slope of the relationship between myocardial oxygen consumption and coronary venous oxygen tension was not altered by L-NNA. Inhibition of NO synthesis did not increase coronary venous plasma or estimated interstitial adenosine concentration. During exercise, estimated interstitial adenosine remained well below the threshold concentration necessary for coronary vasodilation before or after L-NNA.

Conclusions—NO causes a modest coronary vasodilation at rest and during exercise but does not act as a local metabolic vasodilator. Adenosine does not mediate a compensatory local metabolic coronary vasodilation when NO synthesis is inhibited. (Circulation. 2000;101:2942-2948.)

Key Words: nitric oxide n adenosine n coronary disease n exercise

Although nitric oxide (NO) is thought to be one of the factors controlling coronary blood flow, the inhibition of NO synthesis with arginine analogues results in either no change1–11 or a small decrease12–16 in coronary blood flow at rest or when myocardial oxygen consumption is elevated. Previous studies have also shown that coronary venous oxygen tension, a sensitive indicator of the match between coronary blood flow and myocardial metabolism, is only modestly decreased when NO synthesis is inhibited.1,2,6 A proposed explanation for the modest decrease in coronary flow and coronary venous oxygen tension is that there is an increase in adenosine levels that compensates for the loss of NO-mediated coronary vasodilation. This explanation is supported by experiments in which either coronary venous adenosine concentration and/or adenosine release was augmented after inhibition of NO synthesis.15,17

Adenosine receptor blockade has also been used in combination with NO synthesis inhibition in this context. A decrease in coronary blood flow after adenosine receptor blockade was interpreted as a compensatory adenosine coronary vasodilation after NO synthesis inhibition.15,18 However, this was not observed in all studies.6,14,17

The present study was designed to examine the role of adenosine in local metabolic control of coronary blood flow when NO synthesis is inhibited. Experiments were performed in chronically instrumented dogs at rest and during graded treadmill exercise with and without inhibition of NO synthesis with Nω-nitro-L-arginine (L-NNA). Interstitial adenosine concentration was estimated from arterial and coronary venous measurements by using a previously described, axially distributed, mathematical model.19,20 The present results indicate that NO contributes modestly to matching coronary blood flow with myocardial oxygen consumption at rest and during exercise but that adenosine does not increase to mediate coronary vasodilation when NO synthesis is inhibited.

Methods

General Preparation
Experiments were performed on 10 adult male mongrel dogs (weighing 23 to 37 kg) taught to run on a treadmill. The surgical procedures performed in the present study were previously described by Tune et al.21 Briefly, a splenectomy was performed, and a catheter was placed in the descending thoracic aorta to measure aortic blood pressure and to obtain arterial blood samples. A second catheter was placed in the coronary sinus via the right atrial appendage for coronary venous blood sampling. A flow transducer was placed around the circumflex artery.
At the time of the experiment, a catheter-tip pressure transducer (Millar Instruments) was inserted into the aortic catheter to measure blood pressure.21 Coronary blood flow was measured with an ultrasonic flow transducer (Transonic) and normalized per gram of perfused myocardium.21 Blood gas values were determined with an Instrumentation Laboratories 1306 analyzer. Oxygen content was determined by using the fuel-cell method (Total O₂X, Hospex), and lactate concentration was determined with a YSI model 1500 lactate analyzer.

**Plasma Adenosine Measurement and Estimation of Cardiac Interstitial Adenosine Concentration**

Adenosine measurements were made as previously described.21 Briefly, blood samples were immediately mixed with an ice-cold enzymatic stop solution. After immediate centrifugation, the supernatant was deproteinized and purified on C-18 Sep-Pak cartridges. Each sample was divided into 2 aliquots, and adenosine deaminase (0.1 U, Boehringer) was added to 1 of the aliquots, which was used as a paired blank for high-performance liquid chromatography (Hewlett Packard 1100).

Cardiac interstitial adenosine concentration was estimated by use of a 4-region (plasma, endothelial cell, interstitial space, and parenchymal cell) axially distributed mathematical model as previously described.19,20,22

**Exercise Protocol**

The hypothesis that adenosine increases to mediate coronary vasodilation when NO synthesis is inhibited was examined at rest and during graded treadmill exercise with 2 treatments: (1) control vehicle (n = 10) and (2) L-NNA (n = 10). Each animal served as its own control, and the animals were allowed at least 2 days of recovery between experiments. The dose of L-NNA (35 mg/kg IV) used in this investigation was previously found to reduce vasodilation to acetylcholine by >60% in conscious dogs.2,9,11 The L-NNA was dissolved in 120 mL of 0.9% saline and was infused intravenously over 10 minutes

**Statistical Analyses**

Data are presented as mean±SEM. Multiple linear regression was used to compare slopes for the 2 treatments when a response variable was plotted versus myocardial oxygen consumption (SAS). ANCOVA was used to adjust a response variable for linear dependence on myocardial oxygen consumption after testing for parallel regression lines (SAS). The Table presents means by exercise level and does not include probability values because the probability values pertain to the overall treatment effects, as shown in the figures.

**Results**

Hemodynamic and metabolic data for the 10 dogs are given in the Table. Resting values before drug or vehicle administration are presented in the Table but were not included in the statistical analysis of drug and exercise effects. In the control group, myocardial oxygen consumption increased ≈3.7-fold, and coronary blood flow increased ≈3.2-fold from rest to the highest level of exercise (Figure 1A). Blockade of NO synthesis with L-NNA did not attenuate the coronary flow response to exercise, but the slope of the coronary blood flow versus myocardial oxygen consumption relationship was significantly increased (P=0.01). The increased slope with L-NNA treatment was likely due to the lower hematocrit (Table) and does not reflect a potentiation of coronary blood flow when NO synthesis is inhibited. The probable reason that the hematocrit was lower during the L-NNA experiments was that the L-NNA experiments were performed after the control experiments, and blood sampling lowered the hematocrit. Note that if NO had been required for exercise coronary vasodilation, the slope of coronary blood flow versus myocardial oxygen consumption would have been reduced and not increased, as was observed. Systemic administration of L-NNA in the present study resulted in a significant increase in mean aortic pressure (Figure 1C) and a significant decrease in heart rate (Figure 1B), consistent with previous studies.2,9,11

The relationship between myocardial oxygen consumption and coronary venous oxygen tension is shown in Figure 2. The slope of the coronary venous oxygen tension versus myocardial oxygen consumption was not significantly altered by L-NNA, demonstrating that NO is not required for exercise-induced coronary vasodilation. However, the average coronary venous oxygen tension was decreased by L-NNA (P=0.004), indicating that NO contributes to coronary vasodilation at rest and during exercise.

The arterial plasma adenosine concentration was not significantly altered by increased myocardial oxygen consumption or by L-NNA (Figure 3A). During control and L-NNA treatment, coronary venous plasma adenosine and estimated interstitial adenosine concentrations were changed little during exercise (Figures 3B and 4). The slopes of these relationships were not significantly different between control and L-NNA treatment, and the common slope did not differ significantly from zero. The estimated interstitial adenosine concentration remained well below the 117 nmol/L threshold concentration necessary for coronary vasodilation.20 These findings demonstrate that adenosine does not compensate for the loss of vasodilation when NO synthesis is inhibited.

**Discussion**

The present study is the first to measure adenosine levels when NO synthesis is inhibited during exercise. Coronary venous plasma and estimated interstitial adenosine concentrations were unaltered by NO synthesis inhibition at rest and when myocardial oxygen consumption was increased ≈3.7-fold during exercise. Furthermore, the estimated interstitial adenosine concentration remained well below the threshold concentration (117 nmol/L) necessary for coronary vasodilation.20 Therefore, adenosine does not increase to mediate increases in coronary blood flow when NO synthesis is inhibited.

**NO and Coronary Blood Flow Regulation**

Blockade of NO synthesis did not attenuate exercise coronary vasodilation (Figure 1A) or alter the slope of the relationship between coronary venous oxygen tension and myocardial oxygen consumption (Figure 2). These findings are consistent with previous studies using either systemic2,9,11 or intracoronary blockade of NO synthesis1,5 and indicate that NO is not required for exercise coronary vasodilation but does contribute to the control of coronary blood flow at rest and during exercise.

Stamler et al23 recently proposed that nitrosohemoglobin may serve as an NO donor and potentially mediate increases in coronary blood flow. It is unlikely that NO released from nitrosohemoglobin played a significant role in coronary flow regulation in the present study because Bernstein et al2 found...
### Hemodynamic and Metabolic Variables at Rest and During Graded Treadmill Exercise

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<th>Variable</th>
<th>Rest</th>
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<th>Level 2</th>
<th>Level 3</th>
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Values are mean±SEM. n indicates number of dogs.

*n=9.
that NO production in the coronary circulation was significantly impaired by the same dose of L-NNA used in the present study. However, the exact role of nitrosohemoglobin in coronary blood flow control merits further research.

Studies have also shown that NO may have an inhibitory effect on tissue oxygen consumption. Bernstein et al. reported that systemic administration of L-NNA did not significantly alter myocardial oxygen consumption relative to control but did increase myocardial oxygen consumption at a given level of cardiac work. The experimental design of the present study does not test the hypothesis of Bernstein et al. reported that systemic administration of L-NNA did not significantly alter myocardial oxygen consumption relative to control but did increase myocardial oxygen consumption at a given level of cardiac work. The experimental design of the present study does not test the hypothesis of Bernstein et al. reported that systemic administration of L-NNA did not significantly alter myocardial oxygen consumption relative to control but did increase myocardial oxygen consumption at a given level of cardiac work. The experimental design of the present study does not test the hypothesis of Bernstein et al.

**Effect of NO on Epicardial Coronary Diameter**

NO has been shown to contribute to epicardial coronary dilation at rest in dogs and humans and during increases in myocardial oxygen consumption in dogs and humans. This effect of NO is demonstrated by a reduction in epicardial coronary diameter when NO synthesis is inhibited, but with little or no change in coronary blood flow. Jones et al. reported that inhibition of NO synthesis not only resulted in epicardial coronary constriction but also a compensatory arteriolar coronary dilation. The findings of Bernstein et al. suggest that exercise-induced epicardial coronary dilation is mediated by an increase in cardiac NO production. Increased NO production when myocardial oxygen consumption is elevated is probably due to the increases in shear stress that result from the higher coronary flow rates. This is supported by the findings of Van Bibber et al. who found that inhibition of NO synthesis attenuated norepinephrine-induced coronary vasodilation when coronary pressure was held constant but did not affect the coronary vasodilation to norepinephrine when coronary blood flow was held constant.

**Role of Adenosine After Inhibition of NO Synthesis**

There are multiple mechanisms responsible for local metabolic control of coronary blood flow. There is also the suggestion that when one mechanism is inhibited, another may increase in compensation. The present study was
specifically designed to test whether adenosine increases to mediate coronary vasodilation when NO synthesis is inhibited during exercise. Neither coronary venous plasma nor estimated interstitial adenosine concentrations were altered when NO synthesis was inhibited at rest or when oxygen consumption was increased ≈3.7-fold during exercise (Figures 3B and 4). Furthermore, the estimated interstitial adenosine concentration remained well below the 117 nmol/L threshold value necessary for coronary vasodilation. The present results indicate that adenosine does not compensate for the loss of vasodilation by mediating the local metabolic control of coronary blood flow when NO synthesis is inhibited. However, the possibility of compensation by other vasoregulatory agents is not ruled out.

The present findings are also consistent with an earlier study by Tune et al in that coronary venous adenosine concentration was changed little with exercise and the estimated interstitial adenosine concentration remained well below the threshold for coronary vasodilation. These results indicate that adenosine is not responsible for local metabolic control of coronary blood flow.

The methods used in the present investigation are capable of detecting the elevations in coronary venous adenosine concentration that occur during hypoxia, coronary autoregulation, intracoronary norepinephrine infusion, and the release of endogenous adenosine by inhibiting adenosine kinase and adenosine deaminase. Therefore, it is very likely that the present methods are adequate for detecting significant changes in coronary venous plasma adenosine concentration during exercise. Furthermore, the studies cited above demonstrate that increases in cardiac interstitial adenosine concentration are reflected in coronary venous adenosine concentration despite avid uptake of adenosine by coronary vascular endothelium.

In contrast to the present study, Minamino et al reported that coronary venous adenosine concentration increased with time during continuous intracoronary infusion of the NO synthesis inhibitor in open-chest dogs. In the Minamino study, coronary blood flow was unaltered by L-NAME infusion and was also unchanged when the adenosine receptor antagonist
8-sulfophenyltheophylline was combined with L-NAME, which argues against a compensatory adenosine vasodilation. Matsunaga et al.\(^\text{15}\) found that the rate of adenosine release was increased when myocardial oxygen consumption was increased \(\approx 20\%\) by atrial pacing in anesthetized dogs pre-treated with the NO synthesis inhibitor L-NAME. Tayama et al.\(^\text{18}\) observed that chronic 4-week administration of dietary L-NAME resulted in an increase in cardiac adenosine release in a terminal open-chest canine experiment. The release rate is calculated by multiplying coronary flow by the difference in arterial and coronary venous adenosine concentration. A major problem with release rates is that an increase in coronary blood flow or a decrease in arterial adenosine concentration can result in an increase in adenosine release with no change in coronary venous adenosine concentration. The concentration of adenosine in the coronary venous plasma has been shown to be a sensitive indicator of cardiac interstitial adenosine levels.\(^\text{19,20}\) Therefore, reporting only the release rate of adenosine offers little quantitative information on the relationship between interstitial adenosine concentration and coronary blood flow.

Adenosine receptor blockade has also been used in combination with NO synthesis inhibition to determine whether adenosine mediates local metabolic coronary vasodilation when NO synthesis is inhibited. In 3 studies, the results with adenosine receptor blockade after prior inhibition of NO synthesis did not indicate compensation by adenosine.\(^\text{6,14,17}\) In 2 studies, the results were interpreted to mean that adenosine receptor blockade demonstrated a role for adenosine after NO synthesis inhibition.\(^\text{15,18}\) However, a reploting of the data from all 5 of these studies is consistent in that the relation between coronary blood flow and myocardial oxygen consumption is not changed by adenosine blockade after prior NO synthesis inhibition.

**Physiological Role of NO in the Coronary Circulation**

In summary, blockade of NO synthesis decreases coronary venous oxygen tension but does not steepen the relationship between coronary venous oxygen tension and myocardial oxygen consumption. Therefore, NO does not act as a local metabolic vasodilator in the usual sense. Furthermore, when NO synthesis is inhibited, adenosine levels do not increase in compensation. However, NO has meaningful physiological effects within the coronary vascular tree, notably, the upstream dilation of epicardial coronary arteries, which prevents excessive shear stress on the endothelium when flow is increased by downstream vasodilation.

**Acknowledgments**

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**References**


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