Nitric oxide modulates right ventricular flow and oxygen consumption during norepinephrine infusion

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Setty, Srinath, Johnathan D. Tune, and H. Fred Downey. Nitric oxide modulates right ventricular flow and oxygen consumption during norepinephrine infusion. Am J Physiol Heart Circ Physiol 282: H696–H703, 2002.—This study was designed to test if nitric oxide (NO) contributes to norepinephrine-induced right coronary vasodilation and if NO blunts the norepinephrine-induced increase in myocardial oxygen consumption (MV O2) in the right ventricle. In five anesthetized, open-chest dogs, mean aortic pressure, heart rate, right ventricular rate of pressure development over time (dP/dt), right coronary blood flow, and right ventricular MV O2 were measured before and during graded intracoronary infusions of norepinephrine in the absence and presence of a NO synthase blocker, Nω-nitro-L-arginine methyl ester (L-NAME; 150 μg/min ic). During both conditions, right coronary blood flow and right ventricular MV O2 significantly increased with graded infusions of norepinephrine. L-NAME significantly blunted the coronary hyperemic response to norepinephrine, although L-NAME did not alter the relationship between right ventricular MV O2 and norepinephrine dose. However, when right ventricular function was indexed by heart rate × right ventricular maximum dP/dt × peak right ventricular systolic pressure, L-NAME significantly increased the oxygen cost of right ventricular function. These results indicate that NO contributes to norepinephrine-induced right coronary vasodilation and improves right ventricular oxygen utilization efficiency.

right coronary circulation; right ventricular oxygen utilization efficiency; open-chest dogs; Nω-nitro-L-arginine methyl ester

NITRIC OXIDE (NO) formed from L-arginine and released from endothelium causes relaxation of vascular smooth muscle via a cGMP mechanism (17). NO release can be triggered by receptor-mediated mechanisms and by physical stimuli such as endothelial shear stress and mechanical deformation (22, 32). In vitro studies (23, 36, 40, 46) show that NO depresses oxidative metabolism. However, in vivo studies (1, 3, 6, 15, 20, 31, 33, 35, 38, 43) have yielded conflicting results on the effects of NO on myocardial oxygen consumption (MV O2).

NO synthesis inhibition has been frequently used to evaluate NO-mediated mechanisms. In the working left ventricle, NO synthesis inhibition has yielded inconsistent findings regarding NO-mediated control of coronary blood flow (1, 3, 4, 9, 11, 27, 37, 43, 45) and MV O2 (1, 3, 6, 15, 20, 31, 33, 38, 43). In the working right ventricle, NO synthesis inhibition reduces resting right coronary blood flow (2, 10, 39). Furthermore, when changes in right coronary flow are avoided by maximal dilation, NO synthesis inhibition causes an increase in right ventricular MV O2 (35), indicating that NO has a depressive effect on right ventricular oxygen demand. These disparities in right and left ventricular responses to NO may reflect previously demonstrated (16, 21, 34, 42) differences in regulation of left and right coronary flow and in left and right ventricular metabolism. Whether NO might also blunt increases in coronary blood flow and myocardial oxygen demand during positive right ventricular inotropic stimulation is unknown. This question was investigated by treating anesthetized dogs with graded infusions of norepinephrine before and during NO synthesis inhibition.

METHODS

Surgical preparation. This investigation was approved by the Institutional Animal Care and Use Committee and was conducted in accordance with the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised 1996). Five adult dogs of either sex, free of clinically evident disease, were used for this study. The dogs were fasted overnight and then anesthetized with pentobarbital sodium (30 mg/kg iv). Supplemental pentobarbital was administered as needed to maintain stable anesthesia. After intubation, the dogs were ventilated with the use of a respirator (Harvard) with room air supplemented with oxygen to maintain normal arterial blood gases throughout the experiment. A saline-filled vinyl catheter was inserted into the thoracic aorta via a femoral artery to measure aortic pressure. In the other femoral artery, a saline-filled vinyl catheter was placed to withdraw blood to supply an extracorporeal coronary perfusion circuit. A saline-filled vinyl catheter was inserted into a femoral vein for administration of supplementary anesthetic and heparin. The right heart was exposed through a right thoracotomy in the fourth intercostal space and suspended in a pericardial cradle. A Millar catheter-tipped pressure transducer was inserted through the right atrial appendage and advanced across the tricuspid valve to measure
right ventricular pressure and rate of pressure development over time (dP/dt).

The right coronary artery was isolated near its origin, and after heparinization (500 U/kg iv), it was cannulated with a stainless steel cannula (2.1 mm outer diameter, 1.4 mm inner diameter). The right coronary artery was perfused with arterial blood from a pressurized reservoir, which was supplied with blood from a femoral artery. This perfusion tubing was equipped with a heat exchanger to maintain coronary perfusate temperature between 37° and 38°C. To monitor right coronary perfusion pressure, a saline-filled polyethylene-50 catheter was advanced to the orifice of the cannula and connected to a pressure transducer (Telecare, Narco). The right coronary blood flow was measured with an electromagnetic flowmeter (model FM 501; Carolina Medical Electronics) and an in-line flow transducer (model EP 610).

To collect right coronary venous blood samples, a 24 gauge iv catheter was inserted into a superficial vein on the right ventricular epicardial surface. A previous study (25) from this laboratory showed that contamination of this venous blood with blood from sources other than the right coronary artery is < 3% for the right coronary artery perfusion pressure of 100 mmHg used in these experiments. The right coronary venous blood was allowed to drain freely into a beaker and was returned to the dog periodically. Arterial and venous blood samples were collected anaerobically and stored on ice until analysis. Oxygen content of these samples was measured with an oximeter (model 682 CO, Instrumentation Laboratory); PO2, PCO2, and pH were measured with a blood gas analyzer (Synthesis 30, Instrumentation Laboratory); and lactate concentration was measured with an analyzer (STAT model 2300, Yellow Springs Instruments).

Right ventricular MVVo2 and lactate uptake were calculated from the product of coronary blood flow times the respective right coronary arteriovenous difference. Right ventricular mechanical function was estimated from the triple product: heart rate x right ventricular dP/dtmax x peak right ventricular systolic pressure (3). The relationship between right ventricular MVVo2 and the triple product reflects the oxygen cost of right ventricular mechanical function.

**Experimental protocol.** Right coronary perfusion pressure was maintained at 100 mmHg throughout the experimental protocol, so that pressure-induced changes in right ventricular MVVo2 (14) were avoided. Baseline measurements were obtained after allowing 20 min for recovery from surgical procedures and stabilization of the preparation. After recording baseline measurements, graded doses of norepinephrine ranging from 0.01 to 0.20 μg·kg−1·min−1 were infused into the right coronary perfusion line by a Harvard infusion pump. All dogs received norepinephrine infusions of 0.050, 0.075, and 0.100 μg·kg−1·min−1 before and during Nω-nitro-l-arginine methyl ester (l-NAME) treatment. Arterial and right coronary venous blood samples were collected, and hemodynamic and cardiac function variables were recorded when steady-state conditions were achieved (~ 3 min) at each norepinephrine infusion. After the final pretreatment infusion of norepinephrine, the infusion pump was stopped, and 15–20 min were allowed for hemodynamic variables to return to baseline values. Subsequently, l-NAME (150 μg/min) was continuously infused into the right coronary artery perfusion line. Fifteen minutes after initiation of the intracoronary l-NAME infusion, baseline measurements were obtained and the norepinephrine infusion response protocol was repeated. After the final infusion of norepinephrine, the l-NAME infusion was stopped. After stabilization of hemodynamic and cardiac function, Evans blue dye was injected into the right coronary perfusion line. When the right ventricle was visibly dyed, the heart was electrically fibrillated to terminate the experiment. The heart was excised, and the dyed tissue was carefully excised and weighed so that coronary blood flow and MVVo2 could be normalized per gram of tissue mass.

The dose of l-NAME (150 μg/min ic) used to block NO synthesis was previously found to reduce coronary vasodilation to acetylcholine (20 μg ic) by ~65% in the right ventricle (35) and in the left ventricle (6, 26). Complete blockade of acetylcholine-mediated vasodilation was not anticipated because acetylcholine causes vasodilation by additional, non-NO-dependent mechanisms (12).

**Statistical analyses.** All values are presented as means ± SE. Effects of l-NAME at norepinephrine infusions of 0.000, 0.050, 0.075, 0.100, and 0.200 μg·kg−1·min−1 on hemodynamic and right ventricular function variables were evaluated by two-factor analysis of variance. When significance (P < 0.05) was found, Student-Newman-Keuls multiple-comparison tests were performed to identify values different from respective baseline values due to norepinephrine infusion or different from respective untreated values due to l-NAME. Regression analyses were used to examine key variables of oxygen supply-demand balance as functions of norepinephrine dose, right ventricular MVVo2, and right ventricular triple product. For each dose of norepinephrine, mean values were weighted according to the sample size at each dose (each sample was from a different animal). Results of regression analyses were compared by analysis of covariance. The degrees of freedom were equal to 40 for all plots of regression analyses. Statistical computations were performed by GB Statistical Software version 6.5 (Dynamic Microsystems) and interpreted according to the methods of Zar (47).

**RESULTS**

The baseline arterial blood gas variables were the following: pH, 7.41 ± 0.01; PO2, 103 ± 3; PCO2 33 ± 2; and hematocrit, 38 ± 4. None of these variables were significantly affected by graded right coronary infusions of norepinephrine in the absence or presence of NO synthesis inhibition with l-NAME. Right coronary venous pH, PO2, and PCO2 values are reported in the table. Venous pH was reduced by l-NAME, and venous PO2 was reduced by norepinephrine and by l-NAME. Venous PCO2 was increased by l-NAME. Right ventricular uptake of lactate was not significantly affected by either norepinephrine or l-NAME. Hemodynamic and right ventricular function variables are summarized in Table 1. Mean aortic blood pressure was unaffected by norepinephrine or l-NAME. Right ventricular MVVo2, heart rate, right ventricular peak systolic pressure, right ventricular maximum dP/dt (dP/dtmax), and triple product were increased by norepinephrine infusion in the absence and presence of l-NAME treatment. After l-NAME, treatment triple product tended to be lower during all norepinephrine infusions.

Regression analyses demonstrated significant linear effects of norepinephrine dose on right coronary blood flow (R² = 0.95, untreated; R² = 0.81, l-NAME), heart rate (R² = 0.78, untreated; R² = 0.79, l-NAME), right ventricular peak systolic pressure (R² = 0.73, untreated; R² = 0.88, l-NAME), right ventricular dP/dtmax (R² = 0.52, untreated; R² = 0.56, l-NAME), and triple

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Table 1. Hemodynamic and metabolic variables during intracoronary norepinephrine infusion

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Values are means ± SE for all doses of norepinephrine (n = 6 animals) except for the dose 0.200 μg·kg⁻¹·min⁻¹ (n = 3 animals). RCBF, right coronary blood flow; L-NAME, N-nitro-L-arginine methyl ester; mean AoP, mean aortic pressure; HR, heart rate; RVPS, right ventricular peak systolic pressure; RV dP/dtₚ, maximum rate of right ventricular pressure development; triple product, HR × RVPS × RV dP/dtₚ × 10⁻⁶; RCA, right coronary artery; RCV, right coronary vein; LU, lactate uptake; MVo₂, myocardial oxygen consumption. *P < 0.05, different from untreated control, same norepinephrine dose; †P < 0.05, significant effect of norepinephrine infusion; ‡P < 0.05, significant effect of L-NAME.

product (R² = 0.75, untreated; R² = 0.92, L-NAME). No linear trends were evident for mean aortic blood pressure, either untreated or during L-NAME treatment.

Figure 1 illustrates the linear effects of graded norepinephrine infusions on right coronary blood flow in the absence and presence of L-NAME. L-NAME treatment significantly depressed the slope of the relationship between right coronary blood flow and norepinephrine dose, indicating that NO contributes to norepinephrine-induced right coronary hyperemia. L-NAME treatment reduced right coronary blood flow at baseline (13%). There was a further reduction in the right coronary blood flow at the highest dose of norepinephrine (33%), indicating that in the normal right ventricle, NO production is progressively increased with increasing doses of norepinephrine.

By plotting oxygen supply variables as functions of MVo₂, differences in factors affecting oxygen demand, such as heart rate, contractility, and afterload, are normalized (13). Figure 2A shows right coronary blood flow plotted as a function of right ventricular MVo₂ during norepinephrine-induced increases in myocardial oxygen demand in the absence and presence of L-NAME. L-NAME treatment significantly depressed the slope of this relationship (P < 0.0001). Figure 2B shows right coronary venous Po₂ plotted as a function of right ventricular MVo₂ during norepinephrine-induced increases in myocardial oxygen demand in the

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absence and presence of L-NAME. Although the slope of the relationship between mean right coronary venous PO$_2$ and mean right ventricular MV$\dot{O}_2$ was not significantly altered by L-NAME ($P = 0.38$), there was a significant ($P < 0.0001$) decrease in coronary venous PO$_2$ at a given level of MV$\dot{O}_2$. In addition, right coronary venous PO$_2$ was reduced by 12% at baseline and was further reduced by 28% at the highest dose of norepinephrine after L-NAME treatment (see Table 1). These data indicate that the inhibition of NO synthesis at higher levels of MV$\dot{O}_2$ forced the right ventricle to call on its extraction reserve to meet the increase in metabolic demand.

Figure 3 illustrates the linear effects of graded norepinephrine infusions on triple product (heart rate $\times$ right ventricular dP/d$\text{t}_{\text{max}}$ $\times$ peak right ventricular systolic pressure; Fig. 3A) and right ventricular MV$\dot{O}_2$ (Fig. 3B) in the absence and presence of L-NAME. L-NAME treatment significantly depressed the relationship between triple product and norepinephrine dose, indicating that NO improves right ventricular mechanical performance during norepinephrine infusion. However, L-NAME did not significantly alter the relationship between MV$\dot{O}_2$ and norepinephrine. Figure 4 shows right ventricular MV$\dot{O}_2$ plotted as a function of right ventricular triple product, during graded norepinephrine infusions in the absence and presence of L-NAME. L-NAME significantly elevated this relationship. These data demonstrate that NO reduces the oxygen cost of enhanced right ventricular function produced by i.c. norepinephrine. In other words, NO promotes more efficient use of oxygen.

Taken together, these data indicate that during norepinephrine-induced increases in right ventricular myocardial oxygen demand, NO increases right ventricular oxygen delivery by increasing right coronary blood flow and, furthermore, that NO improves right ventricular oxygen utilization efficiency.

**DISCUSSION**

There were two important new findings in this investigation. First, during norepinephrine-induced increases in right ventricular oxygen demand, NO increases myocardial oxygen supply by dilating the right coronary vasculature and elevating right coronary blood flow. Second, during norepinephrine-induced increases in right ventricular mechanical performance, NO reduces right ventricular MV$\dot{O}_2$. Therefore, NO contributes to right ventricular oxygen supply/demand balance by regulating both right coronary blood flow and right ventricular oxygen utilization efficiency.

Effects of NO on right coronary blood flow. As expected, right coronary blood flow increased with graded
norepinephrine infusions. In this investigation, right coronary perfusion pressure was held constant, so changes in coronary blood flow reflect changes in vascular conductance. An important regulatory role for NO in right coronary blood flow control is evident from the decreases in flow caused by NO synthesis inhibition (Fig. 1). Furthermore, NO synthesis inhibition depressed the right coronary blood flow versus right ventricular \( MV_{O2} \) relationship (Fig. 2A). The significantly steeper slope of this relationship before L-NAME indicates that NO production is increased as myocardial oxygen demand is elevated. This increase in NO production is most likely due to increases in coronary vascular shear stress associated with elevated right coronary blood flow at the higher dose of norepinephrine. Thus, for the conditions of these experiments, NO provided a positive feedback mechanism that enhanced oxygen delivery to right ventricular myocardium. Coronary venous \( PO_2 \) is a sensitive index of changes in myocardial oxygen supply/demand balance. The reduction in coronary venous \( PO_2 \) at a given level of \( MV_{O2} \) when NO synthesis was inhibited (Fig. 2B) strengthens the interpretation that NO normally augments right coronary blood flow to match increases in right ventricular myocardial oxygen demand.

Earlier studies (2, 10, 39) have reported reductions in coronary blood flow during NO synthesis inhibition at baseline conditions in the right ventricle. However, this is the first demonstration that NO is an important component of coronary blood flow control during increases in right ventricular oxygen demand. The present findings are consistent with an earlier study of Van Bibber et al. (44), where inhibition of NO synthesis attenuated norepinephrine-induced coronary vasodilation in the left coronary circulation. However, other left ventricular studies (1, 3, 18, 43) have not detected a significant coronary regulatory function of NO when myocardial oxygen demand was increased by exercise. Whether NO mediates right coronary vasodilation during exercise-induced increases in myocardial oxygen demand has not been investigated.

It should be acknowledged that norepinephrine-mediated \( \alpha \)-adrenergic coronary vasoconstriction might have contributed to the decrease in right coronary blood flow when NO synthesis was inhibited in the present investigation (13, 44). This hypothesis is consistent with the findings of Jones et al. (19), who found that NO competes with \( \alpha \)-adrenergic vasoconstriction in the canine left coronary microcirculation. However,
the presence of norepinephrine-mediated α-adrenergic coronary vasoconstriction does not negate the importance of NO in determining the net right coronary response to norepinephrine. The degree to which NO offsets α-adrenergic coronary vasoconstriction in the right coronary circulation merits further investigation.

The mechanism by which norepinephrine stimulates NO production was not examined in the present investigation. However, earlier studies (5, 24, 27, 41) suggest that inotropes such as norepinephrine stimulate coronary β2- and/or α2-adrenoceptors, which augment NO release from coronary endothelial cells. This vasodilator effect is independent of metabolic vasodilation mediated by increases in MV and could be responsible for the significant effect of NO on right coronary blood flow control.

**Effects of NO on right ventricular MV**

As expected, right ventricular MV increased with graded norepinephrine infusions (Fig. 3B). These increases resulted from β-adrenergic receptor-mediated increases in heart rate, right ventricular dP/dt max, and systolic pressure as reflected in the triple product (heart rate × right ventricular peak systolic pressure × right ventricular dP/dt; see Table 1). The increase in right ventricular MV as a function of norepinephrine dose was not altered by NO synthesis inhibition (Fig. 3B).

Reported effects of NO synthesis inhibition on left ventricular MV and mechanical function during inotropic stimulation vary. In agreement with findings of this investigation, Crystal et al. (7, 8) reported that NO synthesis inhibition did not alter left ventricular MV during increased myocardial oxygen demand due to inotropic stimulation in open-chest dogs. In studies of instrumented, exercising dogs, variable effects of NO synthesis inhibition on left ventricular MV have been reported. Bernstein et al. (3) and Tune et al. (43) reported no change in left ventricular MV at rest or during exercise after NO synthesis inhibition; Altman et al. (1) found an increase in left ventricular MV. In these investigations, direct effects of NO synthesis inhibition on MV were obscured by peripheral vasoconstriction, which elevated left ventricular afterload and reflexly reduced heart rate.

**Effects of NO on right ventricular function.** In the present study, both L-NAME and norepinephrine were administered into the right coronary arterial circulation, and systemic hemodynamic perturbations were avoided as demonstrated by stable mean aortic blood pressure. However, heart rate and right ventricular contractility were increased by norepinephrine infusion, so the triple product was used to index mechanical function. NO synthesis inhibition caused a reduction in the triple product at comparable norepinephrine doses (Fig. 3A). This is consistent with the report of Bernstein et al. (3) showing that NO synthesis inhibition caused a reduction in the left ventricular triple product at comparable exercise intensities. These workers offered no explanation for this important mechanical response to NO synthesis inhibition.

In the current study, the blunting of the mechanical response to norepinephrine caused by NO synthesis inhibition might have been related to the concurrent reduction of right coronary blood flow. Because there was no change in right ventricular MV or lactate uptake, the reduction in mechanical function was not due to inadequate blood flow and oxygen supply. A more likely explanation is that factors affecting myocardial contractility were released by coronary endothelium in response to changes in coronary blood flow (28, 29).

Why did MV remain constant in the current study and in that of Bernstein et al. (3) despite a fall in mechanical function after NO synthesis inhibition, which should have reduced myocardial oxygen demand? The absence of a fall in MV might be explained by a change in myocardial substrate selection from glucose to fatty acids, because oxidation of fatty acids requires more oxygen per mole of ATP produced than glucose. However, this seems to be an unlikely explanation. Earlier studies (3, 30) found that blockade of NO synthesis caused a reduction in free fatty acid uptake and an increase in glucose uptake in chronically instrumented dogs (30). In addition, we observed that coronary venous PCO2 was significantly increased after NO synthesis inhibition, consistent with increased glucose oxidation. Because oxidation of glucose requires less oxygen per mol of ATP produced than fatty acids, oxygen utilization efficiency would have been increased by a shift to glucose oxidation after NO synthesis inhibition. We found that myocardial oxygen utilization efficiency was decreased rather than increased after NO synthesis inhibition, so it is unlikely that a shift in the metabolic substrate was responsible for the observed changes in the relationship between MV and the triple product. However, a shift in substrate selection favoring glucose might have mitigated unfavorable effects of NO synthesis inhibition on myocardial oxygen utilization efficiency.

Another explanation involves the depressing effect of NO on oxidative metabolism demonstrated in isolated hepatic cells (40), kidney cells (23), skeletal muscle cells (36), in left ventricular slices (46), and in vivo right ventricle (35). In the present study, after L-NAME treatment, the decrease in oxygen demand due to reduced mechanical function appears to be balanced by an increase in oxygen demand mediated by NO synthesis inhibition. Thus there was no net change in right ventricular MV. However, when right ventricular MV was plotted as a function of triple product (Fig. 4), NO synthesis inhibition increased MV at a given mechanical performance. This finding is consistent with Bernstein et al. (3), who found that NO synthesis inhibition increased left ventricular MV at a given mechanical function. Thus, during norepinephrine infusion in the right ventricle, NO acts to lessen myocardial oxygen demand, thereby increasing oxygen utilization efficiency. This restraining action of NO on right ventricular oxygen demand is consistent with our recent report (35) that NO synthesis inhibition increased right ventricular MV during coronary perfusion pressure-induced increases in right ventricular oxygen demand. Thus, in the normal heart, NO in-
creases blood flow, while a concurrent increase in oxygen utilization efficiency prevents a flow-related increase in mechanical function from increasing myocardial oxygen demand.

Potential limitation of the study. It should be pointed out that NO or its stable metabolites were not measured in this study. Thus the extent to which our dose of L-NAME decreased NO production is unclear. However, Node et al. (26) measured stable metabolites of NO after intracoronary L-NAME (~150–230 µg/min) in the left ventricle and found that L-NAME significantly attenuated the rise in NO production after stimulation of the left ventricle with intracoronary isoproterenol and CaCl₂. In addition, the dose of L-NAME used in this study also decreased the vasodilation to acetylcholine (20 µg ic) by ~65% (35). Therefore, we feel NO synthase was adequately inhibited in this investigation.

In conclusion, this is the first study to show that NO is an important regulator of right coronary blood flow control during norepinephrine-induced cardiac stimulation in the right ventricle. Results also demonstrate that NO improves right ventricular mechanical function with no increase in myocardial oxygen demand. Thus by increasing right ventricular oxygen delivery and oxygen utilization efficiency NO may be particularly important in matching right ventricular oxygen supply with myocardial oxygen demand.

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REFERENCES