ONOMY Science

American Journal of Angiology and Surgery

Research Article Open Access

Nitric Oxide Therapy: Regional Blood Flow are Consistent with Intravascular Nitric Oxidedelivery

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Citation: Nitric Oxide Therapy: Regional Blood Flow are Consistent with Intravascular Nitric Oxidedelivery. Am J Ang and Surg . 2018; 1(1): 001-006.

Submitted: 06 February 2018; **Approved:** 13 February 2018; **Published:** 17 February 2018

Abstract

Nitric oxide (NO) may be stabilized by binding to hemoglobin, by nitrosating thiol-containing plasma molecules, or by conversion to nitrite, all reactions potentially preserving its bioactivity in blood. Here we examined the contribution of blood-transported NO to regional vascular tone in humans before and during NO inhalation. While breathing room air and then room air with NO at 80 parts per million, forearm blood flow was measured in 16 subjects at rest and after blockade of forearm NO synthesis with NG-monomethyl-l-arginine (l-NMMA) followed by forearm exercise stress. l-NMMA reduced blood flow by 25% and increased resistance by 50%, an effect that was blocked by NO inhalation. With NO inhalation, resistance was significantly lower during l-NMMA infusion, both at rest and during repetitive handgrip exercise. S-nitrosohemoglobin and plasma S-nitrosothiols did not change with NO inhalation. Arterial nitrite levels increased by 11% and arterial nitrosyl(heme)hemoglobin levels increased tenfold to the micromolar range, and both measures were consistently higher in the arterial than in venous blood. S-nitrosohemoglobin levels were in the nanomolar range, with no significant artery-to-vein gradients. These results indicate that inhaled NO during blockade of regional NO synthesis can supply intravascular NO to maintain normal vascular function. This effect may have application for the treatment of diseases characterized by endothelial dysfunction.

INTRODUCTION

Nitric oxide (NO) is a soluble gas that is continuously synthesized in endothelial cells from the amino acid l-arginine by the constitutive calcium and calmodulin-dependent enzyme NO synthase and is a critical endogenous vasodilator (1–4). The importance of endothelium-derived NO in the regulation of coronary and systemic vasodilator tone has been demonstrated experimentally by inhibiting its regional synthesis. Thus, NG-monomethyl-l-arginine (l-NMMA), which competes with l-arginine as the substrate for NO synthase but cannot be oxidized to form NO (5), decreases coronary and systemic blood flow when infused intra-arterially into regional vascular beds (6–9). Considerable recent interest and controversy have focused on the role of intravascular NO-derived molecules that conserve and stabilize NO bioactivity and may contribute to blood flow and oxygen delivery. Such molecules include plasma low- and high-molecular-weight S-nitrosothiols and nitrite (10, 11). In addition, NO reacts reversibly with hemoglobin to form an NO-heme adduct, nitrosyl(heme)hemoglobin, and can also nitrosate a surface thiol on cysteine-93 of the β-globin chain to form S-nitrosohemoglobin (SNO-Hb). The role of hemoglobin as an NO transporter is particularly appealing in that delivery of NO may be linked energetically to oxygen binding, promoting the allosteric delivery of oxygen and NO to regions with low oxygen tension (12–15).

The role of intravascular NO species in the regulation of vascular tone is supported by studies of NO breathing. Despite conventional wisdom that NO immediately reacts, with near-diffusion limited kinetics, with oxyhemoglobin to form bioinactive nitrate, animal studies have shown that NO breathing reduces systemic vascular resistance (16), increases kidney filtration rates (17), increases aortic-

cyclic guanosine monophosphate levels (18), and restores blood flow to the intestine after infusion of a NO synthase inhibitor (19, 20). While these observations are consistent with intravascular biostabilization, transport, and delivery of NO, the mechanism of such delivery and the relevance to human physiology and therapeutics is unknown. We therefore sought to determine whether NO inhalation augments NO transport in blood and increases blood flow in a regional vascular bed distant from the lungs. We hypothesized that NO synthesis within the forearm endothelium would be sufficient to maintain resting vascular tone, and thus NO delivery from blood might be more readily appreciated during regional inhibition of NO synthesis, pharmacologically mimicking endothelial dysfunction. To determine how NO is stabilized and delivered to the peripheral vasculature, we measured all known bioactive NO species, including low- and high-molecular-weight plasma S-nitrosothiols, SNO-Hb, nitrosyl(heme)-hemoglobin, and plasma nitrite.

Methods

The protocol was approved by the Institutional Review Board of the National Heart, Lung and Blood Institute, and informed consent was obtained from all volunteer subjects. Eight men and eight women, with an average age of 33 years (range 21–59 years), participated in the study. Volunteers had a normal hemoglobin concentration, and all were in excellent general health without risk factors for endothelial dysfunction (smoking, fasting blood sugar greater than 120 mg/dl, LDL cholesterol greater than 130 mg/dL, blood pressure greater than 140/80 mmHg). Subjects were placed on a nitrate-restricted diet (<15 mg/day) for 3 days before the study and fasted, except for water, after midnight of the study day and during the study (diet described at www.nhlbi.nih.gov/labs/7east/lowNdiet.htm).

Forearm blood flow measurements.

Brachial artery and antecubital vein catheters were placed in the arm, with the intra-arterial catheter connected to a pressure transducer for blood pressure measurements and an infusion pump delivering 5% dextrose in water at 0.5 ml/min. After 20 minutes of rest, baseline arterial and venous blood samples were obtained, and forearm blood flow measurements were made by strain gauge venous-occlusion plethysmography, as reported previously (8). A series of seven blood flow measurements were averaged for each blood flow determination. Forearm vascular resistance was determined by dividing mean blood pressure by forearm blood flow values. Intra-arterial l-NMMA at 8 µmol/min then replaced 5% dextrose in water at the same infusion rate of 0.5 ml/min. This dosage was chosen because of our previous demonstration that vascular effects of l-NMMA in humans are reproducible at this dosage when infusions are separated in time by approximately 1 hour (11). After 5 minutes of intra-arterial l-NMMA, arterial and venous blood samples were obtained and forearm blood flow was measured. Forearm exercise was then initiated during continued l-NMMA infusion, using a hand-grip dynamometer, with one-third of the previously determined maximum grip strength sustained for 10 seconds followed by relaxation for 5 seconds, in repetitive cycles. After 5 minutes of exercise, arterial and venous blood samples were obtained and forearm blood flow was measured during continued exercise. Five percent dextrose in water then replaced l-NMMA infusion into the brachial artery. Inhaled NO was then delivered at 80 ppm by an anesthesia face mask with a reservoir bag (INO Therapeutics Inc., Clinton, New Jersey, USA), with continuous monitoring to assure oxygen delivery of 21%, as reported previously (15, 21). After 1 hour of NO inhalation, arterial and venous samples and blood flow measurements were obtained as described previously for the measurements on room air.

Arterial and venous pH, pO2, and pCO2 were measured at the bedside using the i-STAT system (i-STAT Corp., East Windsor, New Jersey, USA).

Methemoglobin concentration

Methemoglobin concentrations were measured by absorption spectroscopy at 700, 630, 576, and 560 nm using the Winterbourn relationship (22).

Hemoglobin Preparation and Ozone-based chemiluminescent detection of nitrosyl(heme)hemoglobin and S-nitrosohemoglobin

After measurement of methemoglobin concentration, pelleted red cell samples were lysed in distilled water with 0.5 mM EDTA (1:2 dilution), and 200 µl of the hemoglobin lysate was added to 600 µl of 0.2 M KCN/0.2 M K3FeIII(CN)6 with 0.5 mM EDTA in PBS or to 600 µl of PBS with 0.5 mM EDTA and incubated for 35 minutes. Treatment with 100-fold molar excess of KCN and K3Fe(CN)6 selectively removes NO from heme while preserving the S-nitrosothiol bond (15). After the 35-minute incubation, 500 µl of the hemoglobin sample was passed through an extensively washed (2-hour wash with 0.5 mM EDTA HPLC-grade water to remove column preservatives), 9.5-ml bed volume Sephadex G25 column (17-0852-02; Amersham Pharmacia, Uppsala, Sweden) to remove nitrite, small thiols, and the KCN/ K3FeIII(CN)6. The hemoglobin concentration of the Sephadex G25 effluent was measured by conversion to cyanomethemoglobin. Hemoglobin sam-

ples (200 µl) were reacted with I3– to release NO for chemiluminescent detection (15). The method for the measurement of nitrite and S-nitrosothiols by reaction with I3– to release NO gas (21, 23) was applied to hemoglobin that had been treated with and without KCN and K3FeIII(CN)6. In brief, 7 ml of glacial acetic acid and 2 ml of distilled water were mixed with 50 mg of KI. A crystal of I2 was added to yield a concentration of 6–20 mM (23). Helium was bubbled through the reaction mixture, then through 1 N NaOH, and then into the Sievers Model 280 NO analyzer (15, 21). The total amount of SNO-Hb plus nitrosyl(heme)hemoglobin was determined by directly adding hemoglobin samples to the I3– solution without pretreatment with KCN/ K3FeIII(CN)6. The background NO signal from water collected from the washed G25 Sephadex column was subtracted from this signal.

Results

Forearm hemodynamics

l-NMMA infusion during room air breathing significantly reduced forearm blood flow (Figures (Figures1a1a and Figure Figure2a)2a) and increased forearm vascular resistance (Figures (Figures1b1b and Figure Figure2b)2b) from baseline values (both $P < 0.001$). This vasoconstrictor response to l-NMMA was associated with significant increases in the forearm artery-to-vein partial pressure of oxygen (pO2) gradient (from 59 ± 4 to 64 ± 4 mmHg; $P = 0.044$) and artery-to-vein pH gradient (from 0.029 ± 0.008 to 0.051 ± 0.010 units; $P = 0.031$) due to reduction in venous pO2 (from 41 ± 4 to 35 ± 3 mmHg; $P = 0.014$) and pH (from 7.353 ± 0.008 to 7.338 ± 0.008 units; $P = 0.084$) levels from baseline (Figure (Figure3).3). After 5 minutes of repetitive hand-grip exercise during continued l-NMMA infusion, blood flow increased nearly eightfold (Figure (Figure1a1a and Figure Figure2c)2c) and resistance declined (Figure (Figure1b1b and Figure Figure2d)2d) from baseline values (both $P < 0.001$). This response was associated with further widening of the artery-to-vein pO2 gradient (to 79 ± 2 mmHg; $P < 0.001$) and pH gradient (to 0.124 ± 0.012 units; $P < 0.001$) from baseline due to significant reduction in venous pO2 (to 24 ± 1 mmHg; $P < 0.001$) and pH (to 7.263 ± 0.011 units; $P < 0.001$) levels during exercise (Figure (Figure3).

Followed by forearm exercise (c and d). Initial measurements were made on room air (open bars), then repeated during NO breathing at 80 ppm (filled bars). Data are mean ± SEM.

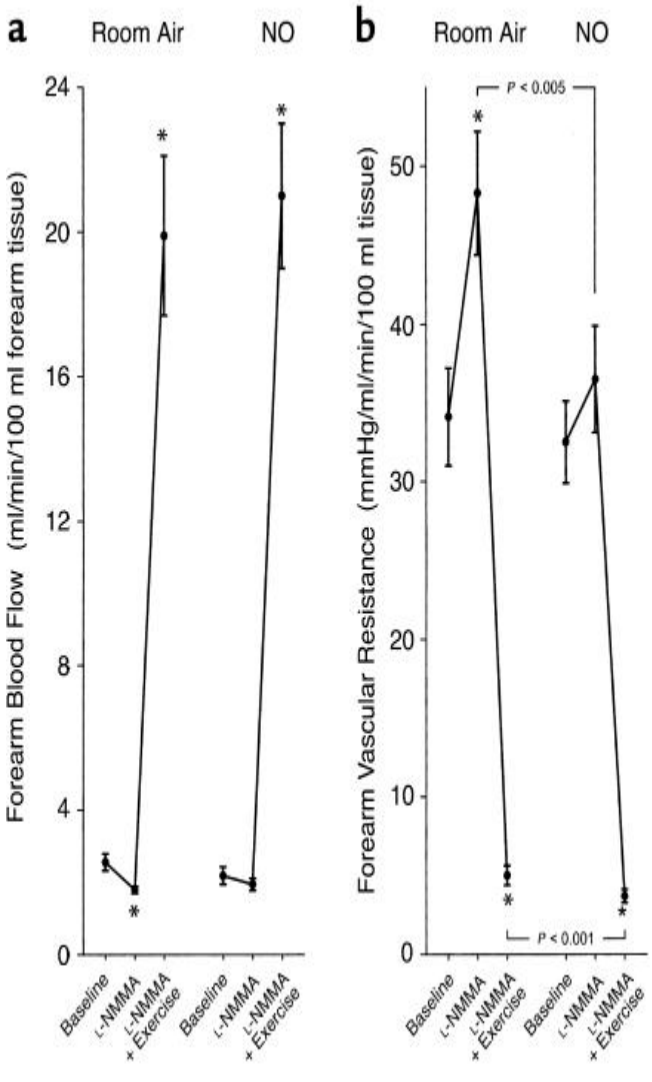

Figure 1: Forearm blood flow (a) and vascular resistance (b) at baseline and during intra-arterial infusion of l-NMMA (to inhibit forearm NO synthesis), followed by forearm exercise. Initial measurements were made on room air, then repeated during NO breathing at 80 ppm. Data are mean ± SEM. *P < 0.001 compared with baseline.

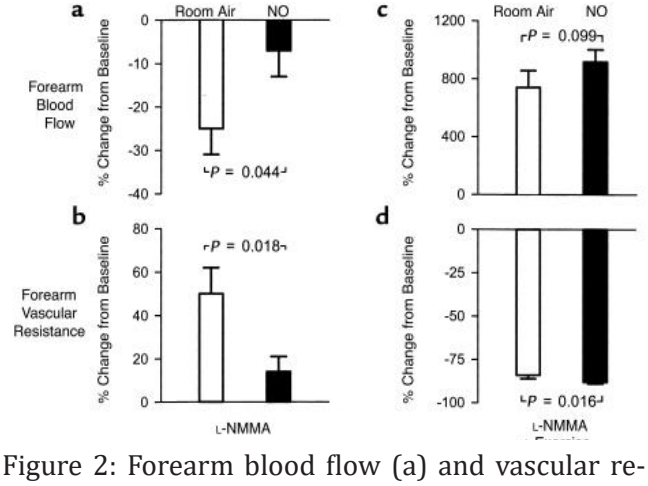

Figure 2: Forearm blood flow (a) and vascular resistance (b), expressed as the relative change from baseline during intra-arterial infusion of l-NMMA,

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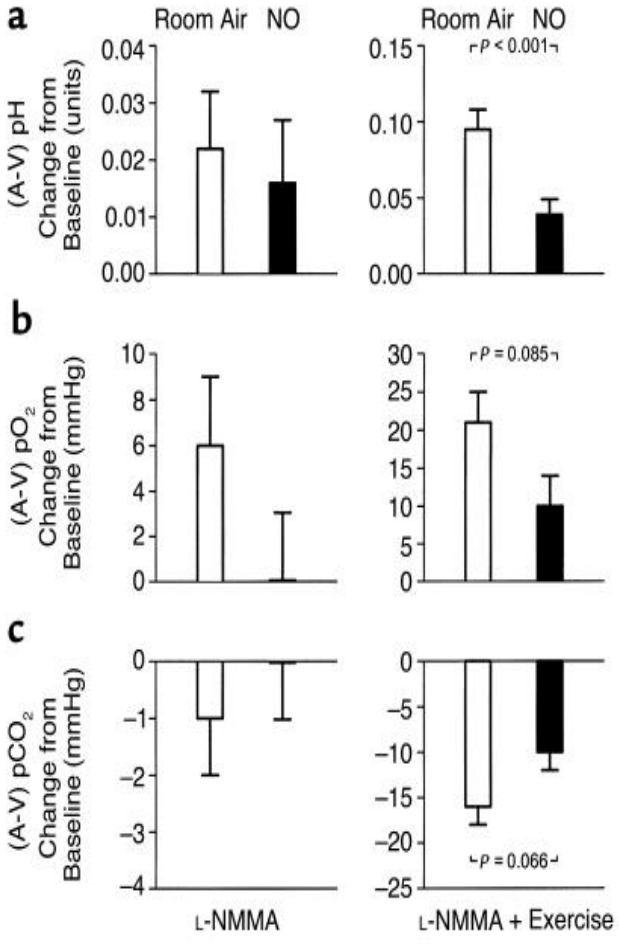


Figure 3: Forearm artery-to-vein (A-V) differences in pH (a), pO2 (b), and pCO2 (c) expressed as change from baseline during intra-arterial infusion of l-NMMA (left column), followed by forearm exercise (right column). Initial measurements were made on room air, then repeated during NO breathing at 80 ppm. Data are mean ± SEM.

After termination of exercise, l-NMMA infusion was discontinued, 5% dextrose in water was resumed, and inhalation of NO was initiated. After 1 hour of inhalation, mean blood pressure tended to increase (from 80 to 85 mmHg; P = 0.067) compared with baseline measurements on room air. NO inhalation did not significantly alter blood flow from baseline room air values (2.19 ± 0.24 vs. 2.56 ± 0.23 ml/min per 100 ml forearm tissue, P = 0.083), and resistance values were similar (32.5 ± 3.6 vs. 34.1 ± 3.1 mmHg/ml/min per 100 ml forearm tissue; P = 0.652). The pO2 levels in the artery (92 ± 2 vs. 100 ± 2 mmHg; P = 0.001) and vein (27 ± 2 vs. 41 ± 4 mmHg; P = 0.002) were significantly reduced during NO breathing compared with room air values, with a nonsignificant increase in the artery-to-vein pO2 gradient (66 ± 3 vs. 59 ± 4 mmHg; P = 0.115). NO breathing did not change arterial pH (7.383 ± 0.007 vs. 7.382 ± 0.005 units; P = 0.910), venous pH (7.343 ± 0.007 vs. 7.353 ± 0.008 units; P = 0.151) or the artery-to-vein pH gradient (0.039 ± 0.009 vs. 0.029 ± 0.008 units; P = 0.272) compared with room air baseline values. These results are consistent with minimal effects of inhaled NO on basal blood flow in the arm, but an increase in pulmonary blood shunting.

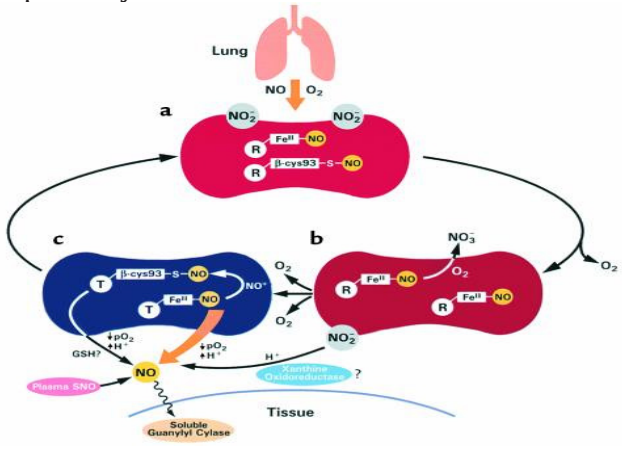
While there was minimal effect of NO inhalation on baseline blood flow, the l-NMMA–induced decrease in blood flow (Figure (Figure1a1a and Figure Figure2a)2a) and increase in resistance (Figure (Figure1b1b and Figure Figure2b)2b) measured during room air breathing were prevented by inhaled NO during reinfusion of l-NMMA, resulting in lower absolute resistance (Figure (Figure1b).1b). In contrast to the effect of l-NMMA during room air breathing, there was no effect of l-NMMA on artery-to-vein pO2 gradients (from 66 ± 3 to 66 ± 4 mmHg; P = 0.889) and artery-to-vein pH gradients (from 0.039 ± 0.009 to 0.057 ± 0.009 units; P = 0.132) compared with the baseline values after 1 hour of NO breathing.

During repetitive hand-grip exercise with continuation of intra-arterial l-NMMA infusion and NO inhalation, blood flow tended to increase to a greater extent from the preceding baseline compared with the blood flow response on room air (Figure (Figure2c).2c). The percentage of change (decrease) in forearm vascular resistance with exercise during NO inhalation was significantly greater than the decrease in resistance on room air (Figure (Figure2d)2d) and resulted in significantly lower absolute resistance (Figure (Figure1b).1b). This increase in blood flow during NO inhalation resulted in metabolic evidence of increased oxygen delivery: The artery-to-vein pO2 gradient (76 ± 2 vs. 79 ± 2 mmHg; P = 0.162) and pCO2 gradient (–14 ± 2 vs. –18 ± 2 mmHg; P = 0.096) during exercise with l-NMMA infusion and NO inhalation tended to be less than room air exercise values, with significantly lower venous pCO2 (54 ± 2 vs. 58 ± 2 mmHg; P = 0.049) compared with room air exercise values. The artery-to-vein pH gradient during exercise and NO inhalation was significantly less than room air exercise values (0.078 ± 0.015 vs. 0.124 ± 0.012 units, P < 0.001) due to significantly higher venous pH during NO breathing (7.289 ± 0.012 vs. 7.263 ± 0.011 units; P = 0.013) (Figure (Figure33).

NO species in blood

Consistent with the high affinity of NO for the heme groups of hemoglobin and the preponderance of oxyhemoglobin in the pulmonary circulation, the primary reaction products during NO inhalation were methemoglobin and nitrate (the by-products of the reaction of NO and oxyhemoglobin). Nitrate levels increased almost fourfold during NO breathing (P < 0.001), but without significant artery-to-

vein gradients (Figure (Figure4b).4b). Methemoglobin levels, converted to micromolar concentrations, were similar to the nitrate concentrations: during room air breathing, levels were 18.8 ± 2.4 μM, 18.8 ± 2.4 μM, and 18.1 ± 2.3 μM at baseline during l-NMMA infusion and subsequent exercise, respectively. During NO breathing, levels were 106.3 ± 9.9 μM, 112.5 ± 10.0 μM, and 121.9 ± 10.1 μM at baseline, during l-NMMA infusion, and subsequent exercise, respectively.



The most fundamental and important observation of this study is that NO gas introduced to the lungs can be stabilized and transported in blood and peripherally modulate blood flow.

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Cite this article: Nitric Oxide Therapy: Regional Blood Flow are Consistent with Intravascular Nitric Oxidedelivery. Am J Ang and Surg . 2018; 1(1): 001-006.