Effects of Nitroglycerin on Erythrocyte Rheology and Oxygen Unloading

Novel Role of S-Nitrosohemoglobin in Relieving Myocardial Ischemia

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Background—We hypothesized that nitroglycerin improves O2 delivery to ischemic tissue by altering erythrocyte rheology and O2 unloading through an increase in bioactive nitric oxide (NO) content.

Methods and Results—Twelve dogs with resting flow-reducing single-vessel stenosis were studied at rest and during intracoronary infusion of nitroglycerin (0.3 to 0.6 μg · kg⁻¹ · min⁻¹). Half the dogs also had occlusion of the remote coronary artery to remove any collateral effects. Systemic and coronary hemodynamics, myocardial blood flow (MBF), whole blood viscosity (WB η), erythrocyte charge (EC) and mobility (EM), regional myocardial O2 delivery and consumption, and tissue O2 pressure (PO2) were measured. No changes in systemic hemodynamics were seen with nitroglycerin. Despite flow-limiting stenosis, MBF increased significantly in the central 25% of the ischemic bed, which was associated with an approximately 19% decrease in WB η. There was a good correlation (r=0.87) between the two. The decrease in WB η was associated with a decrease in EC and an increase in EM (r=0.83). The nitroglycerin-induced increase in tissue PO2 was disproportionate to the increase in MBF, indicating enhanced O2 unloading. Erythrocyte S-nitrosothiol content (reflecting mainly S-nitrosohemoglobin) was significantly higher for blood exposed in vitro to 0.1 μmol/L nitroglycerin or the NO donor SNAP, as compared with control (18.9±8.8 and 10.5±6.5 versus 2.6±0.5×10⁻⁵, P<0.05).

Conclusions—The augmented MBF in the ischemic microcirculation during nitroglycerin administration occurs in tandem with increased erythrocyte S-nitrosothiol content, EM, and O2 unloading. These additional microvascular mechanisms may contribute to the powerful antiischemic effects of nitroglycerin, especially during low-flow states. (Circulation. 2006;113:2502-2508.)

Key Words: nitroglycerin ■ microspheres ■ oxygen ■ nitric oxide

Several investigations have examined the putative mechanisms whereby nitroglycerin exerts its antiischemic effects. Most of these have been focused on its systemic hemodynamic and epicardial coronary artery vasodilatory effects.1 The Hagen-Poiseuille equation states that flow (Q) in a tube can be calculated as follows: [(ΔP · π · r⁴)/8 · l] · l/η, where l and r are the length and radius of the tube, respectively, and η is viscosity of the fluid flowing through the tube. By analogy to Ohms’s law, the total resistance to flow is given by ΔP/Q or Q=ΔP/R. By combining the two equations, we get [(8 · l)/((π · r⁴)) · η]. That is, total resistance equals the product of vascular resistance and viscosity.2 In large vessels (>30 μm in diameter), vascular resistance is the major determinant of total resistance, with viscosity playing a minor role. In vessels <30 μm in diameter, however, viscosity assumes a greater role, with relative effective viscosity increasing 6- to 7-fold at the level of the capillaries.3 Because the effects of vascular resistance and viscosity are multiplicative, small changes in viscosity produce a large difference in total resistance.2 The total resistance in capillaries is almost 2-fold higher for the same blood hematocrit than in the same-sized glass tubes—probably because of the interaction between the blood components and the endothelium.4

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Total resistance to flow can be altered by changing surface charge and the resultant electrostatic repulsive forces among individual erythrocytes.5 In vitro studies have demonstrated that nitric oxide (NO) can exert a direct effect on erythrocyte deformability,6 and studies of the hepatic circulation have shown that nitroglycerin increases O2 release without increasing flow.7 Additionally, the role of erythrocytes in NO

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metabolism has evolved in recent years.8 Erythrocytes are now thought to facilitate NO-related signaling through context-sensitive processing of redox-related NO congeners, such as S-nitrosothiols (SNOs), which confer NO synthase products with bioactivity remote from the site of synthesis. Specifically, R-state hemoglobin quenches and T-state hemoglobin deploys net NO bioactivity.9 Consequently, differential processing of NO by erythrocytes in response to O2 gradients in the microcirculation can help ameliorate ischemia, which could be the mechanism for the antiischemic effects of inhaled NO donors10,11 and may also be important in modulating the physiological response to other NO donors such as nitroglycerin.

We therefore hypothesized that the in vivo antiischemic effects of nitroglycerin on the myocardium are also related to its effects on erythrocyte SNO content, microvascular erythrocyte rheology, and O2 unloading, all of which are interrelated.

**Methods**

**In Vivo Experimental Design and Protocol**

The in vivo experiments were performed to measure the direct effects of nitroglycerin on microvascular erythrocyte rheology and tissue O2 pressure (P02). To circumvent any confounding effects of nitroglycerin-induced changes in systemic hemodynamics, the drug was administered directly into the left main coronary artery, and the dose (0.3 to 0.6 μg · kg⁻¹ · min⁻¹) was adjusted so as not to cause any systemic hemodynamic effects. To exclude the direct hemodynamic effects of nitroglycerin on the collateral circulation, the central 25% of the ischemic bed was studied. We have previously shown that collateral flow is minimal in this region.12 In half the dogs, the site of 2DE imaging was cut into 16 wedge-shaped pieces, and each piece was measured. Tissue P02 was measured directly.

The study protocol was approved by the Animal Research Committee and conformed to the American Heart Association Guidelines for the Use of Animals in Research. All dogs underwent placement of a severe single-vessel stenosis (either the left anterior descending or the left circumflex artery), which resulted in reduced resting coronary blood flow. Half the dogs also underwent occlusion of the remote coronary artery. The stenosis severity was judged by the resting coronary blood flow, and stenosis resistance was calculated by use of the equation (mean aortic pressure − mean distal coronary pressure)/mean coronary blood flow. Myocardial vascular resistance (MVR) was calculated by dividing the coronary driving pressure (mean aortic or mean distal coronary pressure − mean right atrial pressure) by regional MBF (see below) and converting the value into dyne · s · cm⁻².

**Regional MBF Measurements**

Two sets of radiolabeled microspheres were used in each animal (one at baseline and one during nitroglycerin infusion). Approximately 2 · 10⁸ 11-μm microspheres (Bristol Myers Squibb Medical Imaging) were injected into the left atrium at each stage, and dual-reference samples were withdrawn by using constant-rate withdrawal pumps. Postmortem, a short-axis slice of the left ventricle corresponding to the 2DE image was cut into 16 wedge-shaped pieces, and each piece was further divided into epicardial, midcardial, and endocardial portions. The tissue and arterial reference samples were counted with a multichannel analyzer (model 1282, LKB Wallac, Washington, DC), and corrections were performed for activity spilling from one energy window to another.

MBF to each portion was calculated from the equation Qm = (Cm · Q) / Cr, where Qm is blood flow to the myocardial segment (mL · min⁻¹), Cm is tissue counts, Q is the rate of arterial sample withdrawal (mL · min⁻¹), and Cr is arterial reference sample counts.12 Transmural MBF (mL · min⁻¹ · g⁻¹) to each segment was calculated as the quotient of the summed flows to the individual pieces within that segment and their combined weight. Transmural MBF in the stenosis-supplied bed was calculated by averaging values within the central 25% and 75% of that region. Similar values were also obtained for the central 75% of the normal bed in group 1 dogs.

**Measurements of Erythrocyte Rheology**

Blood samples (18 mL) were withdrawn from the coronary sinus. WBV was measured immediately in heparinized blood by using a rotational viscometer (EW-9893600, Cole-Parmer, Vernon Hills, Ill) at 37°C with shear rates of 7.34 s⁻¹. EM measurements are based on the principle that in a solution with a specific pH and ionic strength, EM in an electrical field gradient will be determined by cell surface charge density.13 EM is expressed as (μS)²/(V · cm⁻¹). Before the measurements, the erythrocytes were washed 3 times with Dulbecco phosphate-buffered saline (pH 7.4, Gibco/Invitrogen) and centrifuged. EC was determined as an electrokinetic potential (zeta potential, mV) measured by using phase-analysis laser Doppler velocimetry (Zeta-PALS Zeta Potential Analyzer Version 3.24, Brookhaven Instruments, Holtsville, NY). All measurements were repeated thrice and averaged.
Regional Myocardial O2 Delivery and Consumption and Tissue O2 Pressure

Paired samples of arterial and coronary venous blood were analyzed, and O2 content was calculated using the formula 1.39 · hemoglobin concentration · hemoglobin O2 saturation +2.241 · 0.00136 · PO2. Regional myocardial O2 delivery was calculated as the product of MBF and coronary arterial O2 content, whereas regional myocardial O2 consumption was calculated as the product of MBF and the coronary arterial and venous O2 content difference.

Tissue PO2 levels were determined by using O2-dependent quenching of phosphorescence (PMOD 2000, Harvard Apparatus, Boston, Mass, and Oxygen Enterprises, Philadelphia, Pa), which is based on the principle that a Pd-porphyrin molecule that been excited by light can either release this absorbed energy as light (phosphorescence) or transfer it to O2.14 Energy transfer to O2 results in the release of absorbed energy from the Pd-porphyrin molecules without phosphorescence. Hence, phosphorescence intensity and decay time are dependent on the tissue O2 concentration.

Pd-meso-tetra (4-carboxyphenyl)porphyrin (20 mg · kg−1) was administered as an aqueous solution (7 mg · mL−1 in saline containing 60 mg · mL−1 bovine serum albumin, pH 7.45) through the femoral vein. The excitation light from the PMOD 2000 U passed into the flexible bifurcated fiberoptic light guide cable. The common end of the bifurcated light guide was placed on the surface of a region-of-interest area on the heart through a 2-mm-thick glass slice. The phosphorescence light signal from the dye within the tissue traveled back through the fiberoptic light guide and entered the measurement path of the PMOD 2000 U through a 630-nm cutoff filter. Three successive measurements of tissue PO2 at 5-second intervals were taken and averaged.

Regional Function Analysis

Several endocardial and epicardial targets were defined by the observer in each frame from end diastole to end systole. These points were then automatically connected by using cubic-spline interpolation to derive endocardial and epicardial contours. To correct for systolic cardiac rotation, the junction of the posterior left ventricular wall and the right ventricular free wall was defined over the epicardium in each frame, and 100 equidistant chords between the 2 contours were generated starting at this point. Each chord represented the shortest distance between the endocardial and epicardial contours. The observer then selected the myocardial regions in which the chord lengths were averaged on the basis of the microbubble-defined perfusion beds. Plots of percent wall thickening over the entire systolic contraction sequence in the central 25% and 75% of each region were automatically generated with time represented in deciles. Maximal thickening was selected from each plot to represent percent wall thickening.15

In Vitro Experiments

In vitro experiments were performed to measure erythrocyte S-nitrosothiol content after nitroglycerin exposure. Heparinized venous blood was obtained from separate dogs (group 3) and exposed to 0.1 μmol/L nitroglycerin (n = 3), 0.1 μmol/L SNAP (n = 3), or vehicle (n = 4) for 5 minutes, after which the erythrocyte suspensions were washed 3 times in 10 mmol/L PBS, pH 7.4, 0.5 mol/L EDTA. Whole-cell SNO content in intact, washed erythrocytes were then assayed as previously described.16 In this assay, SNOs are selectively converted to NO in a cuprous chloride and carbon monoxide–saturated cysteine solution. Reductively released NO is then detected by means of chemiluminescent reaction with ozone. Total hemoglobin concentration in samples was determined by the cyanomethemoglobin method; sample SNO content was indexed to this value and expressed as a molar ratio of SNO/hemoglobin.

Statistical Methods

Data are presented as mean±SD. Comparisons between groups were performed by using either a paired or an unpaired Student t test, as appropriate. ANOVA were performed between multiple groups and variables, and Tukey post hoc test was used to identify differences within groups. Correlations were tested by using least-squares fit linear regression analysis. Differences were considered significant at P<0.05 (2 sided). The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

In Vivo Experiments

No changes were noted in systemic hemodynamics or hematocrit after nitroglycerin administration into the left main coronary artery. However, MBF increased significantly in the normal and stenosis-supplied (central 25% as well as entire) beds in both groups of dogs, although the percent increase in the central 25% of the stenosis-supplied myocardium was significantly less than in the entire bed (Table 1). There was no significant difference in the endocardial versus transmural MBF. The increase in MBF was associated with a significant drop in MVR (Table 1).

The decrease in MVR and increase in MBF were associated with a significant decrease in WBη (Table 1). There was no relation between either the decrease in MVR or the increase in MBF versus the change in WBη in both the normal (group 1 dogs) and the entire stenosis-supplied (in both groups of dogs) beds. However, there was a strong correlation between the decrease in MVR and the increase in MBF versus the change in WBη in the central 25% of the stenosis-supplied myocardium (Figure 1). This finding indicates that the increase in MBF in the center of the ischemic bed during nitroglycerin administration is due to the reduction in MVR induced by the decrease in WBη. EM and EC decreased significantly during nitroglycerin administration (Table 1). The percent increase in EM was related to the percent decrease in WBη (Figure 2).

Table 2 lists the changes in myocardial O2 delivery and consumption as well as tissue PO2 during nitroglycerin administration. Myocardial O2 delivery increased significantly to both normal and ischemic myocardium, but myocardial O2 consumption was not significantly affected. There was a slight but insignificant increase in coronary venous O2 in both groups of dogs. Interestingly, the percent increase in tissue PO2 was greater than the percent increase in MBF in the central 25% of the stenosis-supplied bed (58±28% versus 33±18%, P<0.05), a finding not seen in the normal myocardium (Figure 3). There was a fair relation between the percent increase in tissue PO2 and the percent increase in MBF in the central 25% of the stenosis-supplied but not the normal myocardium (Figure 3).

The increase in wall thickening in the central 25% if the stenosis-supplied bed during nitroglycerin administration (from 15±3% to 23±2%, 59%) was significantly greater (P<0.05) than the 30±17% increase in MBF (Table 1).

In comparison, the increase in wall thickening in the normal myocardium in the group 1 dogs after nitroglycerin (from 34±2% to 37±2%, change of 9±4%) was much more modest (<0.01) than the 57±31% increase in MBF (Table 1). Figure 4 illustrates the relation between wall thickening and MBF at various stages in all myocardial regions. All data points fall on the same line, indicating that percent wall
thickening was related to MBF rather than any other direct effects of nitroglycerin.

In Vitro Experiments
Erythrocyte SNO-hemoglobin content, expressed as the SNO-to-hemoglobin molar ratio, was significantly ($P<0.05$) higher for blood exposed to 0.1 μmol/L nitroglycerin or the NO donor SNAP, as compared with control samples (18.9±8.8, 10.5±6.5, and 2.6±0.5×10⁻⁶, respectively) The hemoglobin saturation for these measurements, which is known to allosterically regulate SNO-hemoglobin, was 96%.

Discussion
The new information in the present study is that nitroglycerin has direct actions on the myocardial microvasculature of ischemic tissue that are independent of its effect on systemic hemodynamics. These direct effects on erythrocyte rheology, SNO content, and tissue O₂ content appear to be interrelated and may contribute to the powerful antischemic effects of the drug, especially during low-flow states.

Effect on Erythrocyte Rheology
The elastic properties of erythrocytes are attributable to their 2-dimensional protein skeleton. The outer lipid membrane has a negative charge from the presence of sialic acid in the sugar moiety of the membrane-bound glycoprotein. The EM and EC of the erythrocyte are directly proportional to its membrane sialic acid content. The negative EC on the erythrocytes contributes to the electrostatic repulsive forces among them, and reducing the negative EC results in axial migration of erythrocytes without causing aggregation. Removal of sialic acid from the erythrocytes increases microvascular resistance to flow by approximately one third.

In this study, we have shown that negative EC is reduced and EM is increased in ischemic myocardium by delivery of intracoronary nitroglycerin, which resulted in a decrease in microvascular MVR and an increase in MBF. This effect was

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\begin{array}{c|c|c|c|c|c}
\text{Variable} & \text{Baseline Group 1} & \text{Baseline Group 2} & \text{Nitroglycerin Group 1} & \text{Nitroglycerin Group 2} & \text{P} \\
\hline
\text{Transmural MBF, mL·min⁻¹·g⁻¹} & 1.06±0.15 & 1.63±0.23* & 0.004 & \\
\text{Normal bed} & 0.84±0.10 & 0.60±0.12 & 1.24±0.13* & 0.90±0.12* & <0.001 & \\
\text{Entire ischemic bed} & 0.69±0.06 & 0.53±0.11 & 0.88±0.12* & 0.69±0.09* & <0.001 & \\
\text{Center of ischemic bed} & 1.12±0.15 & 1.70±0.28* & 0.007 & \\
\text{Endocardial MBF, mL·min⁻¹·g⁻¹} & 0.81±0.09 & 0.58±0.11 & 1.31±0.13* & 0.98±0.12* & <0.001 & \\
\text{Normal bed} & 0.64±0.06 & 0.50±0.10 & 0.87±0.12* & 0.69±0.07* & <0.001 & \\
\text{Entire ischemic bed} & 6204±831 & 7751±2166 & 4729±830* & 5614±898* & 0.006 & \\
\text{Center of ischemic bed} & 5124±811 & 7000±2129 & 3345±430* & 4304±682* & <0.001 & \\
\text{WBn, mPa·s} & 8.03±1.66 & 7.23±2.08 & 6.50±1.35 & 5.68±1.41 & 0.11 & \\
\text{WBn, mPa·s} & 7.63±1.84 & 6.09±1.38* & 0.01 & \\
\text{EM, (μ·s⁻¹)/(V·cm)⁻¹} & 7.63±1.84 & 6.09±1.38* & 0.01 & \\
\text{EC, mV} & 15.5±1.6 & 18.7±1.8* & 0.005 & \\
\text{MVR, ×10⁻³ dyne·s·cm⁻³·g⁻¹} & 5607±1460 & 3531±469* & <0.001 & \\
\text{Normal bed} & 5124±811 & 7000±2129 & 3345±430* & 4304±682* & <0.001 & \\
\text{Entire ischemic bed} & 6204±831 & 7751±2166 & 4729±830* & 5614±898* & 0.006 & \\
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\end{array}
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*Compared with baseline.
most pronounced in the center of the ischemic bed. The exact mechanism by which EC was reduced was not addressed in our study but is possibly related to the associated increase in erythrocyte nitrosothiol content. It has been shown that NO contributes to membrane fluidity during progesterone\textsuperscript{19} and leptin\textsuperscript{20} treatment and that addition of NO to erythrocytes enhances erythrocyte deformability in vitro.\textsuperscript{6}

Another indirect effect of change in shear stress caused by a decrease in \(WB/H\) should also be considered. When flow is reduced to very low levels associated with low shear stress, erythrocytes have been shown to adhere to activated platelets and neutrophils through a receptor-mediated mechanism, which can result in in vivo microthrombus formation and further reduction in MBF.\textsuperscript{21,22} Enhanced EM and nutrient MBF induced by nitroglycerin could conceivably increase microvascular shear stress and reduce microthrombi formation in situ.

**Effect on MBF and \(O_2\) Unloading**

Nitroglycerin has been shown to cause coronary vasodilation in humans with coronary artery disease.\textsuperscript{23,24} In animal models and ex vivo preparations, this vasodilation has been documented in larger epicardial coronary arteries and not resistance vessels.\textsuperscript{25–28} However, these experiments were not performed during ischemia. Our data show that during ischemia, MBF and tissue \(P_O_2\) are enhanced during nitroglycerin administration even in non–collateral-dependent perfusion beds, which implies that nitroglycerin has direct effects on the myocardial microvasculature. Although this may be due to augmentation of nitroglycerin bioactivation during ischemia,\textsuperscript{26,30} our data suggest that context-sensitive differential processing of nitroglycerin by erythrocytes may play an important role.

Heretofore, NO activity was thought to be quenched immediately on entry to the vascular space through terminal reactions with hemoglobin. The new paradigm is that erythrocytes serve as a regulatory node in hypoxia- and redox-responsive signaling. It has been proposed that hemoglobin conformational transition governs the intramolecular disposition of NO between heme and a globin chain thiol,\textsuperscript{9} thereby either trapping circulating NO on heme or forming an intra-erythrocytic SNO with vasoactive potential. Subsequent hemoglobin conformational transition across a falling \(O_2\) gradient during circulatory transit initiates export of SNO from erythrocytes by transfer to their membrane\textsuperscript{31} and then to extra-erythrocytic thiols,\textsuperscript{16,32} putatively forming low-mass SNOs in circulating plasma, which can be bioactive at concentrations as low as 1 to 5 nmol/L.\textsuperscript{33,34} Thus, NO processing by erythrocytes as regulated by hemoglobin con-

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**Figure 3.** Relation between percent increase in MBF and percent increase in tissue \(P_O_2\) during nitroglycerin administration in the normal bed (open circles) and the central (25%) of the stenosis-supplied bed (filled circles). See text for details.

**Figure 4.** Relation between transmural MBF and \% wall thickening in all beds (normal in group 1 dogs and central 25% of ischemic in both group 1 and 2 dogs) at baseline and during nitroglycerin administration. See text for details.
formation couples delivery or capture of NO to O₂ gradients, thereby matching bioactivity to perfusion.

We believe that the increase in erythrocyte SNO after nitroglycerin exposure under low O₂ variations can mechanistic implications with regard to the effects of nitroglycerin in the ischemic microcirculation. Erythrocyte vasoactivity in hypoxia varies as a function of SNO content.⁶⁻⁷ Notably, erythrocyte SNO content is elevated in humans with congestive heart failure.⁸ Similar to us, others have also shown an increase in erythrocyte SNO content after administration of nitroglycerin.⁹ The role of thiol interactions on nitroglycerin bioactivity has also been explored.⁴⁰⁻⁴³ Specifically, it has been shown that L-cysteine selectively potentiates nitroglycerin-induced dilation of small coronary microvessels,⁴⁴ probably through formation of the low-mass nitrosotiol SNO-, shown by the same group to dilate small (60 to 100 μm) coronary microvessels.⁴⁵ Finally, in other work, we have demonstrated export of erythrocyte SNO to extra-erythrocytic contents. Additionally, the effect of targeted NO release from erythrocytes on platelet⁴⁵,⁴⁶ and leukocyte adherence⁴⁶,⁴⁷ (combined with the direct effect on erythrocyte rheology) may increase MBF in ischemic tissue.

It has also been shown that the O₂ dissociation curve shifts to the right in the presence of nitroglycerin,⁴⁸ presumably by altering heme-globin coupling under the burden of excessive NO loading at heme. It has been proposed that this phenomenon, by facilitating O₂ unloading from erythrocytes, explains the finding that nitroglycerin can increase O₂ delivery in hepatic tissue independent of increased intravascular NO because of nitroglycerin effects. This mechanism is unlikely to have been operative in our study because the dose of nitroglycerin used was orders of magnitude (approximately 10 000 times) less than in these studies.

Critique of Our Methods
We administered nitroglycerin directly into the left main coronary artery to obviate its systemic effects. To avoid measuring the effect of nitroglycerin on collateral vessels and flow, we analyzed the central 25% of the ischemic bed in all dogs, and in half of the dogs we occluded the remote artery so that no collateral flow could reach the ischemic myocardium. The central 25% of the risk area receives minimal collateral-derived MBF.¹² Our methods for measuring MBF, EC, EM, tissue O₂, myocardial O₂ delivery and consumption, wall thickening, and erythrocyte SNO-hemoglobin content have been well validated.

For placement of the light guide for tissue O₂ measurements, we identified the central portion of the ischemic bed by injecting microbubbles directly into the bed through the distal coronary catheter. The technique to assess O₂ measurements tissue O₂ only in the epicardium (superficial 1 to 2 mm of the myocardium). Because nitroglycerin increased endocardial MBF to the same extent as epicardial MBF in these experiments, it is likely that these values reflected tissue O₂ in the endocardium as well. In experiments in which collateral flow is not abolished, epicardial MBF is higher in the presence of stenosis; however, because we abolished collateral blood flow, we did not see this MBF gradient in our study.

Finally, our study was not designed to measure the temporal relation between change in rheology and MBF after nitroglycerin administration. Our study was also not designed to study the effect of nitroglycerin tolerance on rheology and microvascular MBF or O₂ unloading.

Conclusions
Our study is the first to show that nitroglycerin has direct actions on the myocardial microvasculature of ischemic tissue that is independent of its effect on systemic hemodynamics. The augmented MBF in the ischemic microcirculation occurs in tandem with increased EM and O₂ unloading. Formation of SNO in erythrocytes during low-flow states may be responsible for these antithrombotic effects of nitroglycerin.

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Disclosures
None.

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**CLINICAL PERSPECTIVE**

The new information in this study is that nitroglycerin has direct actions on the myocardial microvasculature of ischemic tissue that is independent of its effect on systemic hemodynamics. These direct effects on erythrocyte rheology, S-nitrosothiol content, and tissue O2 content appear to be interrelated and may contribute to the powerful antiischemic effects of the drug, especially during low-flow states. These results offer new insights into the mechanism of action of nitroglycerin.
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In the article, “Effects of Nitroglycerin on Erythrocyte Rheology and Oxygen Unloading: Novel Role of S-Nitrosohemoglobin in Relieving Myocardial Ischemia” by Bin et al that appeared in the May 30, 2006, issue (Circulation. 2006;113:2502–2508), Dr Allan Doctor’s name was incorrectly listed as Dr Allan in the Sources of Funding. This has been corrected in the online PDF (http://circ.ahajournals.org/cgi/reprint/113/21/2502).

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