Nitrite Anion Provides Potent Cytoprotective and Antiapoptotic Effects as Adjunctive Therapy to Reperfusion for Acute Myocardial Infarction

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Background—Accumulating evidence suggests that the ubiquitous anion nitrite (NO$_2^-$) is a physiological signaling molecule, with roles in intravascular endocrine nitric oxide transport, hypoxic vasodilation, signaling, and cytoprotection. Thus, nitrite could enhance the efficacy of reperfusion therapy for acute myocardial infarction. The specific aims of this study were (1) to assess the efficacy of nitrite in reducing necrosis and apoptosis in canine myocardial infarction and (2) to determine the relative role of nitrite versus chemical intermediates, such as S-nitrosothiols.

Methods and Results—We evaluated infarct size, microvascular perfusion, and left ventricular function by histopathology, microspheres, and magnetic resonance imaging in 27 canines subjected to 120 minutes of coronary artery occlusion. This was a blinded, prospective study comparing a saline control group (n=9) with intravenous nitrite during the last 60 minutes of ischemia (n=9) and during the last 5 minutes of ischemia (n=9). In saline-treated control animals, 70±10% of the area at risk was infarcted compared with 23±5% in animals treated with a 60-minute nitrite infusion. Remarkably, a nitrite infusion in the last 5 minutes of ischemia also limited the extent of infarction (36±8% of area at risk). Nitrite improved microvascular perfusion, reduced apoptosis, and improved contractile function. S-Nitrosothiol and iron-nitrosyl-protein adducts did not accumulate in the 5-minute nitrite infusion, suggesting that nitrite is the bioactive intravascular nitrite species accounting for cardioprotection.

Conclusions—Nitrite has significant potential as adjunctive therapy to enhance the efficacy of reperfusion therapy for acute myocardial infarction. (Circulation. 2008;117:2986-2994.)

Key Words: apoptosis ■ ischemia ■ magnetic resonance imaging ■ myocardial infarction ■ nitric oxide
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Figure 1. Schematic diagram of experimental protocol and major measurements. MRI was performed at baseline, was performed between 30 and 50 minutes during the first hour of ischemia, was repeated with similar timing during the second hour of ischemia, and was performed between 4 and 6 hours after reperfusion. Microspheres were injected after each MR scan except the baseline scan. Histopathology was performed at least 6 hours after reperfusion for optimal TTC staining. MR indicates times of MRI scans; S, times of microsphere injections; and Path, time of euthanasia for histopathology.

The aim of this study was to determine whether a low dose of intravenous nitrite would enhance the efficacy of reperfusion therapy for acute MI in a protocol compatible with typical delays from onset of chest pain to emergent intervention. We also sought to understand the relative role of nitrite versus nitrite metabolites in these experiments. We formulated 2 hypotheses: (1) a low dose of nitrite over 60 minutes reduces infarct size; and (2) if the mechanism of cardioprotection involved a direct biochemical effect on the reperfusion phase of injury rather than simple vasodilation of collaterals, then a 5-minute infusion would also reduce infarct size. We also sought to determine whether the effect is mediated by intravascular nitrite or requires bioconversion to an S-nitrosothiol or iron-nitrosyl intermediate.

Methods

Animal Preparation

Experiments were approved by the National Heart, Lung, and Blood Institute Animal Care and Use Committee. Twenty-seven 12- to 23-kg mongrel dogs were anesthetized with acepromazine (0.2 mg/kg), thiopental sodium (15 mg/kg), and isoflurane (0.5% to 2.0%). After midline sternotomy and instrumentation, MI was induced by occluding the left anterior descending artery for 2 hours followed by 6 hours of reperfusion. Anesthetized animals were euthanized with potassium chloride after heparin administration (10,000 U).

Chemical Preparation

Sterile sodium nitrite approved by the Food and Drug Administration for human use (Investigational New Drug No. 70 411) was prepared on the day of the experiment by the National Institutes of Health Pharmacy Development Service.

Determination of Plasma and Whole Blood Nitrite and Nitric Oxide–Hemoglobin Adducts

For plasma nitrite measurements, blood samples were collected in nitrite-free heparin and centrifuged (3000 g for 5 minutes) immediately to avoid nitrite metabolism by erythrocytes. Plasma was removed and frozen immediately for later analysis. The nitrite in whole blood and plasma was measured by triodiode-based reductive chemiluminescence with a NO analyzer (model 280, Seivers, Boulder, Colo) as previously described and validated. To determine the levels of specific NO adducts, each sample was separated into 3 aliquots and treated as follows: aliquot 1, no treatment (to measure total nitrite, S-nitrosotriol, and Rx-NO [mercury-stable NO adducts consistent with iron-nitrosyl, N-nitrosamines, or nitrated lipids]); aliquot 2, reaction with acidified sulfanilamide (0.5% vol/vol) to measure S-nitrosothiols and Rx-NO; and aliquot 3, reaction with acidified sulfanilamide and mercuric chloride (5 mmol/L to measure Rx-NO). Subtraction of the signal of aliquot 2 from aliquot 1 yielded the concentration of nitrite in the sample. The signal from aliquot 3 was subtracted from aliquot 2 to calculate S-nitrosothiol concentration. The signal from aliquot 3 was representative of the total Rx-NO concentration in the sample.

Assessment of Left Ventricular Function

Left ventricular function was evaluated by cine magnetic resonance imaging (MRI) at 4 time points: (1) baseline; (2) 30 minutes into the first hour of occlusion; (3) 30 minutes into the second hour of occlusion; and (4) 4 to 6 hours into reperfusion on a 1.5-T Magnetom Avanto MRI scanner (Siemens AG Medical Solutions; Erlangen, Germany) with a segmented ECG-gated steady state free precession (TrueFISP) cine MRI sequence.

Assessment of Area at Risk

The area at risk (AAR) was assessed at 30 minutes into ischemia by first-pass myocardial perfusion MRI (dual-bolus administration of gadopentetate dimeglumine; 0.005 mmol/kg followed by 0.10 mmol/kg). The images were acquired every other heartbeat to allow volumetric coverage.

Myocardial Blood Flow by Fluorescent Microsphere

Microspheres were injected for 3 reasons: (1) to verify that an ischemic period was induced; (2) to observe whether the 60-minute nitrite infusion improved perfusion during the occlusion via collateral vessels; and (3) to assess reperfusion in all 3 groups. Approximately 5 million fluorescently labeled microspheres 15 μm in diameter (IMT Laboratories, Irvine, Calif) were injected. Two adjacent pathological slices were aligned and treated as a single slice for microsphere analysis (8 circumferential sectors further subdivided into epicardial and endocardial portions).

Histopathology Analysis

Infarct size was measured with 1% triphenyltetrazolium chloride (TTC) staining at 37°C to 40°C, then rinsed with 0.9% saline (~ten 3- to 4-mm-thick slices). Tissue was submerged in isotonic saline and photographed.

Apoptosis Analysis

A transmural section of anterior left ventricular myocardium was used for terminal deoxynucleotidyl transferase–mediated dUTP biotin nick end labeling (TUNEL) staining (Histoserv, Inc, Germantown, Md) in an area with AAR and infarct. Five high-power fields evenly spaced from the endocardium to the epicardium were photographed. To aid in differentiating red apoptotic nuclei from blue or
purplish nuclei, a gray-scale image was calculated as the ratio of the red channel divided by the blue channel. In this ratio image, the apoptotic nuclei appear white or light gray versus the normal nuclei, which are black or dark gray. The apoptotic nuclei were manually counted by 2 readers blinded to treatment group (interobserver correlation: \( r = 0.92; y = 0.81x + 1.30 \)).

**Microvascular Obstruction Analysis**

The amount of microvascular obstruction was measured on first-pass perfusion images acquired ~1 hour before euthanasia. The peak intensity of normal myocardium was estimated with histogram analysis. A threshold 50% below peak normal intensity defined dark pixels.\(^{35}\)

**Statistical Analysis**

One-way and 2-way repeated-measures ANOVA analyses were performed with the SigmaStat (SAS Institute Inc, Cary, NC) followed by sequential Bonferroni procedures. To minimize loss of statistical power due to multiple Bonferroni corrections, the sequential correction method worked from largest to smallest differences until a nonsignificant comparison was found, after which no further testing was performed. The Kruskal-Wallis test was used if data were not normally distributed or had unequal variance. Results are mean±SEM unless specifically indicated otherwise. \( P<0.05 \) was considered significant.

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The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Nitrite Levels in Whole Blood and Plasma**

In the 60-minute nitrite infusion group, arterial plasma nitrite levels peaked after 60 minutes of nitrite infusion and remained significantly elevated until 30 minutes after reperfusion (Figure 2A). Significant arterial-to-venous gradients in plasma nitrite were observed during infusions consistent with systemic nitrite consumption (data not shown). Changes in whole blood nitrite followed a similar course, with peak levels of 5 \( \mu \)mol/L at 30 and 60 minutes (Figure 2A), with appreciable artery-to-vein gradients (data not shown).

During the 5-minute nitrite infusions, plasma nitrite levels increased to a maximum at 5 minutes \( (P<0.001) \) and returned to baseline levels by 90 minutes into the reperfusion period (Figure 2B). With the 5-minute infusion protocol, we observed minimal changes in whole blood nitrite (Figure 2B).
Nitrite Reduces Cardiomyocyte Apoptosis

Prior studies in mice demonstrated an effect of low-dose nitrite on inhibiting apoptosis after ischemia/reperfusion in the liver, but these studies have not been performed in the heart or in a larger mammal. We therefore evaluated transmyocardial cardiomyocyte apoptosis using TUNEL staining at 5 transmural locations from endocardium to epicardium, and the degree of apoptosis was defined as the number of apoptotic nuclei per high-power field (Figure 5). We observed a significant effect of both 60 minutes and 5 minutes of nitrite infusion on apoptosis compared with control across all anatomic locations (Kruskal-Wallis test of ranks, \( P=0.001 \) and \( P=0.002 \) at transmural layers 3 and 4, respectively).

**Cardioprotective Effects of Nitrite Are Not Mediated by Hemodynamics**

The enhanced myocardial salvage associated with the 5-minute nitrite therapy was not explainable by changes in preload (inversely related to end-diastolic wall thickness; Figure 6, left panel), afterload (systolic wall stress; Figure 6, middle panel), or rate-pressure product (Figure 6, right panel). The beneficial effects of the 60-minute nitrite infusion cannot be separated from hemodynamic effects because the preload, afterload, and rate-pressure product deviate from the control group in directions that could reduce infarct size. However, the 5-minute nitrite group tracks closely with the control group, indicating that myocardial salvage is more likely explained by the biochemical mechanisms than hemodynamic factors during ischemia.

**Nitrite Improves Global Left Ventricular Function**

The left ventricular ejection fraction was significantly reduced below baseline values after 30 minutes of left anterior descending coronary artery occlusion (Figure 7) in all 3...
groups \((P<0.001)\). Trends for change in left ventricular ejection fraction during the second hour of occlusion were not significant in any group. However, both groups receiving nitrite displayed a significant recovery of left ventricular ejection fraction at 4 to 6 hours into reperfusion relative to occlusion (60-minute nitrite infusion, \(P<0.01\); 5-minute nitrite infusion, \(P<0.001\)), whereas the control group did not significantly recover left ventricular ejection fraction.

### Effects of Nitrite on Perfusion During Ischemia and Microvascular Obstruction During Reperfusion

Myocardial perfusion, measured by microspheres, showed severely reduced perfusion 30 minutes into the occlusion and during the second hour of occlusion in all 3 groups (Figure 8). Thus, the 60-minute nitrite treatment did not recruit enough collateral blood flow to explain marked reductions in infarct size. At reperfusion, both nitrite treatment groups demonstrated better recovery of endocardial microsphere blood flow than the control group, a finding consistent with less severe microvascular obstruction in the nitrite-treated animals. Epicardial and transmural microsphere blood flows were not significantly different between the 3 groups, a result that verifies that macrovascular reperfusion was achieved in all 3 groups.

More MRI evidence of microvascular obstruction was found in the control group \((11\pm6.1\% \text{ of the left ventricle})\) than in either of the nitrite treatment groups (Figure 8B and 8C); evidence was also found that the microvascular obstruction was mostly localized within the endocardium. These results indicate that nitrite limits the endocardial “no-reflow phenomenon.”

### Nature of the NO Store: Nitrite or \(S\)-Nitrosothiol?

Because nitrite may undergo facile bioconversion to \(S\)-nitrosothiols, iron-nitrosyl complexes, and possibly nitrated lipids, we tested whether the vasodilatory effects and ischemia/reperfusion effects of nitrite occur secondary to intravascular \(S\)-nitrosothiol, \(N\)-nitrosamine, or iron-nitrosyl formation. We therefore directly measured plasma and red cell \(S\)-nitrosothiols and mercury-stable NO adducts (which include the iron-nitrosyl and \(N\)-nitrosamine complexes and are referred to as Rx-NO) in blood using reductive chemiluminescence during the nitrite infusion protocols.

At baseline, the concentration of whole blood (red cell and plasma) \(S\)-nitrosothiols was \(<10 \text{ nmol/L} \) in all groups and...
remained relatively unchanged in the control group over the course of the experiment. In the group receiving the 60-minute nitrite infusion, the \(S\)-nitrosothiol levels and Rx-NO levels (mercury-stable NO adducts consistent with iron-nitrosyls, \(N\)-nitrosamines, or nitrated lipids) peaked 60 minutes into the nitrite infusion to 54.5\(\pm\)21.2 and 24.3\(\pm\)12.5 nmol/L, respectively, and then decreased after reperfusion (Figure 2C and 2D). Importantly, no statistically significant increase in \(S\)-nitrosothiol levels was found during or after the 5-minute infusion of nitrite (data not shown). The appreciation of robust cardiomyocyte cytoprotection during the 5-minute nitrite infusion protocol with no change in intravascular \(S\)-nitrosothiol levels supports the thesis that nitrite is the primary mediator of these biological effects. The cytoprotection afforded by nitrite does not require measurable NO equivalent (NO\(^{\cdot}\)) transfer to form a secondary \(S\)-nitrosothiol in blood.

**Discussion**

This study demonstrates that the anion nitrite (NO\(_2\)\(^{-}\)) potently limits MI and apoptosis in the reperfusion phase of injury. The mechanism of myocardial protection is independent of the time/ischemia severity integral because a brief 5-minute infusion of nitrite during the end of a 2-hour occlusion reduced infarct size and apoptosis almost as much as a 60-minute infusion, and the short infusion caused virtually no hemodynamic perturbations. The improved myocardial salvage associated with the 5-minute nitrite infusion was not explainable on simple hemodynamic factors such as preload, afterload, rate-pressure product, or the AAR. Both nitrite infusion protocols had beneficial effects on global left ventricular function and minimized endocardial “no-reflow” phenomenon, characterized by microvascular occlusion in the infarct core. Therefore, we conclude that nitrite provides a direct cellular cardioprotective mechanism in the reperfusion phase of injury. Furthermore, nitrite can provide this remarkable degree of cardioprotection on a time scale compatible...
with intravenous adjunctive therapy to emergent percutaneous interventions for acute MI.

Two recent studies suggest that nitrite potently limits ischemia/reperfusion cytotoxicity with a maximal effect observed at low concentrations.\textsuperscript{14,15} Although the protective effect was maximal at blood concentrations of 10 \textmu mol/L (48-nmol dose for a mouse), even doses as low as 1.2 nmol, which were associated with increases in blood levels of nitrite from 700 to 900 nmol/L, reduced the infarct size by 50%.\textsuperscript{15} The cytoprotective effect of nitrite reduced apoptosis and was associated with intracellular reduction of nitrite to NO, independent of the NO synthase and heme oxygenase 1 enzymes. In the present study, this cytoprotective effect is recapitulated in a large mammal exposed to a longer ischemic time and more extensive infarction relative to AAR. Remarkably, a 5-minute infusion of nitrite in the present study increased plasma levels of nitrite in dogs from \textasciitilde 1 \textmu mol/kg at baseline up to 5 \textmu mol/L, with no associated increases in plasma or red cell S-nitrosothiols. These near-physiological increases in nitrite decreased MI size from 70% to 20% of the AAR and improved cardiac contractile function.

NO that diffuses into blood reacts rapidly with both oxyhemoglobin and deoxyhemoglobin to form methemoglobin/nitrate and iron-nitrosyl-hemoglobin (HbFe\textsuperscript{II}-NO), respectively.\textsuperscript{25,36} These reactions shorten the half-life of NO in blood to \textasciitilde 2 ms and thus maintain endothelial-derived NO as a paracrine vasoregulator.\textsuperscript{37,38}

Although NO per se is inactivated by reactions with hemoglobin, it may be stabilized in blood by the formation of NO-modified proteins, peptides, and lipids and oxidation to the anion nitrite. It is increasingly clear that a number of intravascular chemical NO-modified species are capable of mediating vasodilation, including S-nitrosothiols,\textsuperscript{16,17} nitrite,\textsuperscript{1,3,18,19} N-nitrosamines,\textsuperscript{21–24} iron-nitrosyls,\textsuperscript{25} and recently identified nitrated lipids.\textsuperscript{26–29}

Both human blood flow experiments and studies of ischemia/reperfusion over the last 2 years suggest that nitrite is one of the major endocrine NO species in blood. In earlier physiological studies, we observed artery-to-vein gradients in nitrite across the human forearm, with increased consumption of nitrite during exercise stress, suggesting that nitrite is metabolized across the peripheral circulation.\textsuperscript{1} Although nitrite was considered biologically inert, we found that nitrite induced concentration-dependent vasodilation in healthy human volunteers.\textsuperscript{3} Nitrite levels even as low as 900 nmol/L produced vasodilation in humans during exercise stress with concurrent NO synthase inhibition with \textsuperscript{N}\textsuperscript{c}-monomethyl-L-arginine, suggesting a physiological role for nitrite in vascular homeostasis.\textsuperscript{3} The potent vasodilating effects of nitrite have been verified in a number of models.\textsuperscript{1,2,14,19,20,39}

The degree to which nitrite-induced vasodilation and coronary collaterals contribute to myocardial protection warrants consideration. It would require a very large sample size to determine the extent to which the statistically insignificant increase in microsphere blood flow (60-minute nitrite group) contributes to myocardial protection because the magnitude of effect is very small. In the 5-minute nitrite group, nitrite-induced vasodilation cannot significantly alter the net deficit in the time/blood flow integral and thus is biologically unlikely to confer protection by a mechanism related to reduced ischemia as a result of collateral blood flow. However, collateral blood flow may provide a route for nitrite to reach into the ischemic myocardium and thus indirectly facilitate protection afforded by mechanisms that directly modulate the biochemical mechanisms underlying ischemia/reperfusion injury.

The cardioprotective effects of nitrite infusion in the present study were associated with specific increases in plasma nitrite at near physiological concentrations. Although the 60-minute infusion of nitrite was associated with increases in both plasma nitrite and blood S-nitrosothiols, only nitrite levels increased during the 5-minute infusion protocol. These data support the thesis that nitrite is an endocrine intravascular NO species that modulates systemic response to hypoxic/ischemic injury.

During cardiac ischemia and reperfusion, nitrite in tissue is reduced to NO and forms iron-nitrosylated (Fe\textsuperscript{II}-NO) and S-nitrosated modified proteins via reactions with deoxymyoglobin and other cellular heme proteins.\textsuperscript{3,10,40,41} The rapid, facile metabolism of nitrite to NO with subsequent modification of target proteins has been documented in the heart and liver during both regional and global ischemia/reperfusion injury.\textsuperscript{15,42,43} The formation of NO in the heart during ischemia has been documented with the use of electron paramagnetic resonance and liquid and gas phase chemiluminescence. We have recently found that nitrite will specifically posttranslationally S-nitrosate complex I of the mitochondrial electron transport chain; this effectively reduces electron flow through the mitochondrial electron transport chain and reduces reactive oxygen species formation during reperfusion.\textsuperscript{44} This damping or tuning of electron transport inhibits opening of the mitochondrial permeability transition pore, decreases cytochrome c release, and limits apoptosis. The nitrite-dependent decrease in TUNEL staining is consistent with this mechanism of cytoprotection. Other intracellular targets for S-nitrosation by nitrite during ischemia/reperfusion exposure could include the L-type calcium receptor.\textsuperscript{45} In addition, stabilization of myoglobin as iron-nitrosylated myoglobin may limit heme on the basis of oxidation reactions in the cardiomyocyte.\textsuperscript{15}

In this study, we have shown an increase in iron-nitrosylation with nitrite treatment. Although this increase reflects nitrosylation of heme proteins, such as myoglobin, it may also indicate nitrosylation of non-heme iron. Cellular non-heme iron content plays a role in determining the sensitivity of cells to NO-mediated apoptosis,\textsuperscript{46} with increasing concentrations of non-heme iron rendering cells less susceptible to NO-mediated apoptosis. Non-heme iron is able to bind NO (forming Fe-NO), which decreases the bioavailability of NO, as well as oxidizes NO to NO\textsuperscript{+} to promote S-nitrosothiol formation (including the S-nitrosation of caspases). In the case of nitrite, if nitrite is reduced to NO, which then mediates S-nitrosation of tissue components to illicit cytoprotection, tissue non-heme Fe would catalyze S-nitrosothiol formation and promote the antiapoptotic effects of nitrite. This may be consistent with the increase in Fe-NO seen in tissues after nitrite administration during ischemia/reperfusion.
Although current reperfusion therapies are efficacious in the treatment of acute MI, intrinsic and practical delays between symptom presentation and intervention compromise the amount of myocardial salvage. Despite great advances in percutaneous coronary interventions that result in excellent restoration of coronary blood flow, the mortality after MI remains at 7%, and virtually all patients suffer some degree of myocardial necrosis. The extent of the MI predicts future cardiac function. Post-MI heart failure represents a huge burden on our healthcare system. Adjunctive pharmacological therapies that improve the amount of myocardial salvage after reperfusion of an acute MI could positively affect cardiac function and possibly prognosis. Such adjunctive therapies should possess the following characteristics: (1) significant cardioprotection after prolonged ischemia; (2) simple administration; (3) low expense; (4) low dose required for pharmacological action; (5) short half-life and rapid onset of action; (6) minimum associated regional and systemic side effects; and (7) a cardioprotective mechanism that is not dependent on vasodilation or changing rate-pressure product. Nitrite satisfies these requirements.

The present study has limitations. Although it would have been desirable to also study cardioprotection with 2 doses of nitroglycerin, this was not practical for sample size considerations because of the large number of potential comparions. Nitrite provided better cardioprotection than nitroglycerin in a mouse model, and inhaled NO was more potent than nitroglycerin in a swine model. Even in the present set of experiments, power to detect differences between groups is limited. Thus, one must interpret statistics showing no change between groups with caution. However, the key findings that nitrite provides cardioprotection and reduces infarct size are supported with statistical confidence. Furthermore, biological factors that modulate infarct size such as rate-pressure product, residual perfusion during ischemia, and systolic wall stress all indicate that the 5-minute nitrite group faced challenges that directionally should have led to larger infarcts than the control group.

In conclusion, nitrite possesses the characteristics of an ideal adjunctive therapy for acute MI. From a feasibility perspective, nitrite can be administered intravenously, and the 5-minute dose does not alter hemodynamics significantly. In patients with acute MI, the 5-minute infusion of nitrite could be initiated on arrival to the catheterization laboratory shortly before percutaneous coronary intervention.

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Drs Gladwin and Cannon are named as coinventors on a National Institutes of Health patent application for the use of nitrite salts in cardiovascular diseases.

References
Although current therapies directed at reestablishing blood flow and limiting ischemia are efficacious in the treatment of acute myocardial infarction, intrinsic and practical delays between symptom presentation and intervention compromise the availability of reperfusion therapies. Emergency percutaneous reperfusion of an acute myocardial infarction could have substantial beneficial impact on cardiac function and possibly prognosis. The present study in a canine model of acute myocardial infarction indicates that emergent percutaneous reperfusion of an acute myocardial infarction could have substantial beneficial impact on cardiac function and possibly prognosis. The present study in a canine model of acute myocardial infarction indicates that


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