Hemodynamic Effects of Inhaled Nitric Oxide in Right Ventricular Myocardial Infarction and Cardiogenic Shock

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OBJECTIVES

We sought to determine whether or not inhaled nitric oxide (NO) could improve hemodynamic function in patients with right ventricular myocardial infarction (RVMI) and cardiogenic shock (CS).

BACKGROUND

Inhaled NO is a selective pulmonary vasodilator that can decrease right ventricular afterload.

METHODS

Thirteen patients (7 males and 6 females, age 65 ± 3 years) presenting with electrocardiographic, echocardiographic, and hemodynamic evidence of acute inferior myocardial infarction associated with RVMI and CS were studied. After administration of supplemental oxygen (inspired oxygen fraction [FIO2] = 1.0), hemodynamic measurements were recorded before, during inhalation of NO (80 ppm at FIO2 = 0.90) for 10 min, and 10 min after NO inhalation was discontinued (FIO2 = 1.0).

RESULTS

Breathing NO decreased the mean right atrial pressure by 12 ± 3%, mean pulmonary arterial pressure by 13 ± 2%, and pulmonary vascular resistance by 36 ± 8% (all p < 0.05). Nitric oxide inhalation increased the cardiac index by 24 ± 11% and the stroke volume index by 23 ± 12% (p < 0.05). The NO administration did not change systemic arterial or pulmonary capillary wedge pressures. Contrast echocardiography identified three patients with a patent foramen ovale and right-to-left shunt flow while breathing at FIO2 = 1.0. Breathing NO decreased shunt flow by 56 ± 5% (p < 0.05) and was associated with markedly improved systemic oxygen saturation.

CONCLUSIONS

Nitric oxide inhalation results in acute hemodynamic improvement when administered to patients with RVMI and CS. (J Am Coll Cardiol 2004;44:793–8) © 2004 by the American College of Cardiology Foundation

Right ventricular myocardial infarction (RVMI) is observed in up to 50% of patients with acute left ventricular (LV) inferior-posterior wall infarction (1), many of whom manifest significant hemodynamic abnormalities, including cardiogenic shock (CS) characterized by increased venous pressure, a low cardiac output, and systemic hypotension (2,3). The current treatment of RVMI patients includes optimization of right ventricular (RV) and LV preload with intravenous fluids, coronary reperfusion, maintenance of atrioventricular synchrony, administration of inotropic agents, and intra-aortic balloon pump counterpulsation (2,4–6). Many RVMI patients with impaired cardiac function improve with these therapies, particularly after early percutaneous coronary intervention (PCI) (4). Dobutamine and nitrovasodilators have been infused to improve the cardiac index (CI) of patients with CS complicating RVMI (6), but their utility is limited by arrhythmias, systemic vasodilation, and hypotension. Furthermore, RVMI patients with a patent foramen ovale may develop hypoxemia as a result of right-to-left shunting (7) that is resistant to conventional therapy including supplemental oxygen. Overall, RVMI patients with CS have in-hospital mortality similar to that of LV myocardial infarction (MI) patients with CS (4,8).

Afterload reduction therapy for the failing RV with a selective pulmonary vasodilator might be expected to lead to improved cardiac performance without producing systemic vasodilation and hypotension (9,10). Pulmonary vasodilation can occur when inhaled nitric oxide (NO) diffuses to smooth muscle cells in lung arterioles and activates soluble guanylate cyclase to generate cyclic 3',5'-monophosphate (11,12). This intracellular messenger leads to a reduction in the intracellular concentration of calcium and inhibition of myosin light chain kinase, producing smooth muscle cell relaxation and vasodilation (13). The vasodilator effects of inhaled NO are restricted to the pulmonary circulation, as NO is readily bound to hemoglobin in circulating erythrocytes and inactivated (14). Breathing NO has been shown to decrease pulmonary vascular tone in adults and children with pulmonary hypertension of diverse etiology without causing systemic vasodilation, including patients with congenital heart disease (15), primary pulmonary hypertension (9), and pulmonary hypertension secondary to a variety of etiologies (10). Inhaled NO has also been shown to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in newborns with persistent pulmonary hypertension and hypoxic respiratory failure (16,17). Furthermore, inhaled NO has been observed to decrease RV afterload in a porcine model of RVMI (18).
The objective of this study was to assess whether or not NO inhalation could improve cardiac performance in patients with RVMI and CS.

METHODS

This protocol was approved by the Massachusetts General Hospital Subcommittee on Human Studies.

Study population. Patients with acute inferior MI (defined as an episode of chest pain lasting >30 min and electrocardiographic evidence of ≥1 mm ST elevation in inferior leads within the past 7 days) presenting to the Massachusetts General Hospital were prospectively screened for electrocardiographic (RV dilation and free wall akinesis or dyskinesis) evidence of RVMI.

Informed consent was obtained from 19 patients meeting these criteria. Diagnostic coronary angiography was performed, and PCI was carried out at the discretion of the attending cardiologist. The success of PCI was assessed using both the Thrombolysis In Myocardial Infarction (TIMI) study criteria for successful reperfusion (<50% residual stenosis and restoration of TIMI flow grade 3 in the distal right coronary artery [19]) and the more stringent criteria of Bowers et al. (4) requiring complete reperfusion of the right coronary artery and all RV marginal branches >1 mm in diameter. Transthoracic echocardiography and right heart catheterization were then performed. Patients received intravenous normal saline if their pulmonary capillary wedge pressure (PCWP) was <15 mm Hg. Patients were then included for further study if their right atrial (RA) pressure was >10 mm Hg, their PCWP was no >5 mm Hg higher than the RA pressure, and their CI was <2.5 l/min/m². Patients were excluded from study if they had severe pulmonary edema (PCWP >25 mm Hg; n = 4), mechanical complications of MI requiring urgent surgical correction (n = 0), severe mitral or aortic valvular disease (n = 1), persistent hemodynamically significant tachyarrhythmias (n = 1), or a history of clinically significant pulmonary disease (n = 0). Thirteen patients underwent further study.

Study procedure. To minimize hypoxic pulmonary vasoconstriction and to standardize the concentration of oxygen administered to patients participating in the study, the inspired oxygen fraction (FiO₂) was increased to 1.0 in patients who were intubated with an endotracheal tube (n = 10), and 100% oxygen was administered via a tight-fitting face mask to patients who were not intubated (n = 3) (Table 1). After 10 min, the following parameters were recorded: RA, pulmonary arterial (PA), PCWP, and mean systemic arterial pressure (SAP), as well as heart rate (HR). Cardiac output was determined by the Fick oxygen technique. The CI, stroke volume index, pulmonary vascular resistance (PVR), and systemic vascular resistance were calculated using standard formulas. Patients then breathed 80 ppm NO at FiO₂ = 0.90 for 10 min, and hemodynamic

Table 1. Patient Characteristics at the Time of Study Enrollment

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>PCI Success*</th>
<th>Time to Enrollment‡ (h)</th>
<th>IABP</th>
<th>Vasopressors§</th>
<th>Dobutamine</th>
<th>Mechanical Ventilation</th>
<th>FiO₂</th>
<th>SaO₂ (%)</th>
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<td>-</td>
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<td>+</td>
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<td>82</td>
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<td>74</td>
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<td>5</td>
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<td>+</td>
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<td>+</td>
<td>0.8</td>
<td>92</td>
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<tr>
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<td>F</td>
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<td>-</td>
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<td>49 ± 11</td>
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<td></td>
<td></td>
<td></td>
<td>0.6 ± 0.1</td>
<td>92 ± 2</td>
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*Successful percutaneous coronary intervention (indicates patients in whom PCI did not result in restoration of right ventricular perfusion). †Time from onset of symptoms to study enrollment. §Norepinephrine or phenylephrine administration. ||Oxygen delivered by face mask or nasal prongs. Values expressed as mean ± SEM.

FiO₂ = inspired oxygen fraction; IABP = intraaortic balloon counterpulsation; N/A = PCI not attempted; PCI = percutaneous coronary intervention; SaO₂ = systemic arterial oxygen saturation as measured by pulse oximetry.
Nitric oxide administration was stopped, patients resumed breathing at F\textsubscript{O\textsubscript{2}} = 1.0, and a third set of hemodynamic measurements was recorded 10 min later. We chose an inhaled concentration of 80 ppm NO because this dose has been reported to provide a greater pulmonary vasodilator response than lower doses (20). Moreover, breathing 80 ppm NO for 10 min is not associated with adverse effects such as methemoglobinemia in adults (20).

In patients with a systemic oxygen saturation ≤95% despite breathing at F\textsubscript{O\textsubscript{2}} = 1.0, contrast echocardiography was used to identify the presence of right-to-left shunting via a patent foramen ovale. The magnitude of right-to-left shunt flow was assessed by oximetry (21). The pulmonary venous oxygen content was calculated using the alveolar gas equation (22), as there were no patients with significant pulmonary disease, and all patients were breathing at F\textsubscript{O\textsubscript{2}} = 1.0.

**NO administration.** Nitric oxide gas was supplied in tanks containing 800 ppm NO in N\textsubscript{2} (INO Therapeutics Inc., Clinton, New Jersey) and was administered using an INOvent (Datex-Ohmeda Inc., Andover, Massachusetts) to supply NO at a concentration of 80 ppm to the inspiratory limb of a ventilator circuit or a tight-fitting mask. A flow rate of ≥30 l/min of NO gas mixed with oxygen was maintained to meet the inspiratory flow demands of the patient and to minimize the transit time of the inspired gas and hence the formation of higher nitrogen oxides. Nitric oxide, NO\textsubscript{2}, and F\textsubscript{O\textsubscript{2}} were monitored continuously; in all cases, NO\textsubscript{3} was <2 ppm.

**Statistical analysis.** Continuous variables are expressed as mean ± standard error, with median values provided where the data were not normally distributed as assessed by the Wilk-Shapiro test. Hemodynamic and gas exchange alterations in response to NO breathing and its discontinuation were analyzed using repeated measures analysis of variance followed by the Neuman–Keuls procedure, when appropriate. Data samples were assessed for equal variance before analysis of variance. A value of p < 0.05 was considered significant.

**RESULTS**

**Baseline characteristics.** The characteristics of the study population are summarized in Table 1. There were seven men and six women, age 65 ± 3 years. The right coronary artery was dominant in all patients. Two patients (#9 and #11) received thrombolytic therapy before coronary angiography. Two patients (#6 and #11) had a >95% proximal stenosis of the right coronary artery with TIMI grade 2 distal flow, and the nine remaining patients had total occlusion of the proximal right coronary artery. The PCI was successful, as assessed by the TIMI criteria, in 9 of the 11 patients in whom it was attempted. However, PCI resulted in complete reperfusion of the right coronary artery and all RV marginal branches >1 mm in only four patients. The elapsed time from the onset of symptoms to the PCI procedure was 21 ± 10 h (median: 8 h). In two patients (#1 and #4), PCI was not attempted.

At the time of enrollment in the study, 9 patients required intra-aortic balloon pump counterpulsation, 10 patients required treatment with norepinephrine or phenylephrine, and 6 patients required treatment with dobutamine. Ten patients required mechanical ventilation via an endotracheal tube, including a positive end-expiratory pressure ≥5 cm H\textsubscript{2}O. Five patients (#2, #3, #5, #8, and #10) had bradycardias requiring ventricular pacing. The elapsed time from the onset of chest pain to initiation of the NO inhalation study was 49 ± 11 h.

The hemodynamic parameters of the patients at the time of enrollment are presented in Table 2. The mean RA, PA, and PCWPs were elevated, as were the PVR and systemic vascular resistance. The mean PA systolic pressure was 36 ± 2 mm Hg. The CI was low (1.7 ± 0.1 l/min/m\textsuperscript{2}). All patients had RV dilation and systolic dysfunction by echocardiography. The LV ejection fraction was 0.42 ± 0.04.

### Table 2. Hemodynamic Parameters at the Time of Study Enrollment

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>RAP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>SAP (mm Hg)</th>
<th>CI (l/min/m\textsuperscript{2})</th>
<th>PVR (dynes·cm⁻⁵)</th>
<th>SVR (dynes·cm⁻⁵)</th>
<th>LVEF</th>
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<td>147</td>
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</table>

Mean values expressed as mean ± SEM.

CI = cardiac index; LVEF = left ventricular ejection fraction; PAP = mean pulmonary arterial pressure; PCWP = mean pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = mean right atrial pressure; SAP = mean systemic arterial pressure; SVR = systemic vascular resistance.
Hemodynamic effects of inhaled NO administration. The effects of breathing 80 ppm NO for 10 min are shown in Figure 1. When compared with breathing at $\text{FiO}_2 = 1.0$, the addition of NO decreased the RA pressure by 12\%$, mean PA pressure by 13\%$, and PVR by 36\%$ (all $p < 0.05$). The NO administration increased CI by 24\%$ and stroke volume index by 23\%$ (both $p < 0.05$) but did not change SAP and PCWP, systemic vascular resistance, or HR. Ten minutes after discontinuation of NO, the RA pressure, PVR, and CI had returned to values similar to those measured immediately before NO administration. The mean PA pressure, however, remained $5\%$ lower than before NO administration ($p < 0.05$). Inhaled NO was well tolerated in all patients without any side effects.

Four patients had a systemic oxygen saturation $\leq 95\%$ despite breathing at $\text{FiO}_2 = 1.0$ and underwent contrast echocardiography. In three patients ($\#1$, $\#4$, and $\#5$), right-to-left shunting of bubble contrast medium through a patent foramen ovale was observed, and a shunt flow of $0.67 \pm 0.08$ L/min was measured by oximetry. Inhaled NO decreased right-to-left shunting by $56\%$ ($p < 0.05$) associated with an increase of systemic arterial oxygen saturation to $>95\%$ in all three patients (Fig. 2). In one patient ($\#2$) with a systemic oxygen saturation $\leq 95\%$, transthoracic echocardiography was technically limited, precluding identification of a patent foramen ovale. Nonetheless, breathing NO increased the systemic oxygen saturation in this patient.

DISCUSSION

We observed that short-term administration of inhaled NO to a group of patients with RVMI and CS resulted in beneficial hemodynamic effects, as reflected by a decrease of RA and PA pressures and an increase of CI. Nitric oxide inhalation produced pulmonary vasodilation but did not alter SAP and PCWP or the HR. In three patients with
significant right-to-left shunting through a patent foramen ovale that was refractory to oxygen administration, NO inhalation reduced shunt flow and improved systemic oxygenation. Short-term administration of inhaled NO was well tolerated by all patients without significant side effects.

All of the patients with RVMI and CS that were studied had an abnormally elevated PVR. The elevation in PA pressure observed in our patients was similar to that reported by Jacobs et al. (8) in their registry of patients with RVMI and CS. The increased pulmonary vascular tone in our patients with RVMI and CS is likely multifactorial in etiology. A low cardiac output results in a decreased mixed venous blood oxygen content, which enhances PA vasoconstriction (23). The intravenous infusion of alpha-adrenergic vasoconstrictors can contribute to pulmonary vasoconstriction, as has been reported in animal models (24,25). Mechanical ventilation with positive end-expiratory pressure >5 cm H2O, as was used in five of the patients in this study, can increase the PVR through compression of the pulmonary vasculature (26). Finally, interstitial pulmonary edema, which may have occurred in some of our patients with an elevated PCWP, can also cause pulmonary constriction (27). Our observations of a selective pulmonary vasodilator effect of breathing NO are consistent with previous studies of patients with pulmonary hypertension secondary to a variety of etiologies in which pulmonary vasomotor tone is increased (9,10,15), suggesting that the increased PVR in our patients is related to an increase in pre-capillary vasomotor tone rather than compressive effects on pulmonary capillaries.

The increase of CI and reduction of RA pressure observed in RVMI patients breathing NO are likely due to selective pulmonary vasodilation, resulting in a reduction of RV afterload and subsequent improvement in RV performance. These effects are in agreement with those reported in two previous case reports of RVMI patients treated with inhaled NO (28,29).

The selectivity of inhaled NO for the pulmonary circulation offers a significant advantage over non-selective pulmonary and systemic vasodilators, such as nitroprusside, for the treatment of RVMI patients. Dell’Italia et al. (6) reported that systemic administration of nitroprusside to RVMI patients increased CI without augmenting stroke volume index, and was associated with decreased SAP and PCWP and an increased HR. The nitroprusside-induced increase of HR suggests that nonselective vasodilation in RVMI patients can increase sympathetic tone, which may augment ischemia, arrhythmias, and promote infant expansion. Dell’Italia et al. (6) also reported that administration of the beta-adrenergic antagonist dobutamine to RVMI patients increased CI and stroke volume index but was associated with arrhythmias and recurrent ischemia. In contrast, we observed that breathing NO for 10 min increased CI and stroke volume index without decreasing SAP or PCWP or increasing the HR in our patients with RVMI and CS. Previous studies have shown that inhaled NO does not affect RV or LV contractility (9,30) and therefore may prove superior to currently available therapies for the low CI and systemic venous congestion seen in RVMI patients with CS, improving cardiac performance without producing adverse myocardial effects.

In this study, PCWP did not change during NO inhalation by RVMI patients, as has been previously observed during its administration to patients with severe LV systolic dysfunction (20,31). In patients with severe LV systolic dysfunction, which is usually accompanied by poor diastolic ventricular compliance, breathing NO is thought to increase pulmonary venous return, resulting in an increase in LV filling pressure (32). The RVMI patients in this study had primarily RV systolic and diastolic function, and the degree of LV dysfunction was not as severe as in those patients in whom the PCWP has been reported to increase during NO inhalation. Furthermore, RVMI patients have been observed to have a shift of the interventricular septum towards the left ventricle, impairing LV diastolic compliance and increasing LV filling pressure. In our patient population, NO inhalation decreased RV filling pressure, which may have decreased the deleterious effect of the RV on LV compliance, counterbalancing any effect that increased LV filling might have had on the PCWP.

Right-to-left shunt flow through a patent foramen ovale caused by elevation of RV filling pressure is a well-described complication of patients with RVMI and can produce refractory systemic hypoxemia (7). Systemically administered vasodilator or inotropic therapy has limited efficacy in decreasing shunt flow, as agents that decrease RA pressure simultaneously reduce the left atrial pressure, leaving the transatrial pressure gradient unchanged. Attempts to mechanically close a patent foramen ovale to decrease interatrial shunting in RVMI patients have had variable success (33,34). In our study, we observed that 3 of 13 RVMI patients had significant right-to-left shunting through a patent foramen ovale despite breathing at FiO2 = 1.0, whereas breathing NO consistently reduced the shunt flow and improved systemic oxygenation.

Our study expands upon the previous report of Bowers et al. (4), who observed that failure to achieve early, successful reperfusion of the RV myocardium in RVMI patients resulted in a high incidence of refractory hypotension, CS, and death. In our group of RVMI patients with severe hemodynamic compromise, the majority of whom did not obtain prompt reperfusion of their RV myocardium, breathing 80 ppm NO increased the CI and stroke volume index. If this effect can be sustained, inhaled NO therapy offers the potential to improve cardiac performance in patients who fail to benefit from early revascularization and who remain critically ill despite the use of intra-aortic and/or pharmacologic circulatory support.

The prognosis for most RVMI patients who survive their initial hospitalization is excellent, even when their course is complicated by CS (35), and significant improvement of indices of RV systolic function have been measured at long-term follow-up (36). Bowers et al. (4) reported that in RVMI patients with unsuccessful early perfusion and he-
modynamic compromise who survive their initial hospitalization, RV systolic wall motion at one month is similar to patients in whom early, successful RV myocardial reperfusion was achieved. Further study is necessary to ascertain if the beneficial hemodynamic effects observed with short-term inhaled NO in our study of RVMI patients with CS or refractory hypoxemia can reduce early mortality, permitting the eventual recovery of RV function.

In summary, administration of inhaled NO results in significant hemodynamic improvement and a reduction of right-to-left shunting when administered to patients with acute RVMI and CS.

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