Inhaled Nitric Oxide in Sickle Cell Disease with Acute Chest Syndrome

Andrew M. Atz, M.D.* and David L. Wessel, M.D.†

THE acute chest syndrome (ACS), characterized by fever, chest pain, and radiographic evidence of new pulmonary infiltrate, effusion, or edema in patients with sickle cell disease is a significant cause of morbidity and death.1 The often rapid resolution of severe ACS after exchange transfusion suggests that pulmonary vascular occlusion and ischemia and infarction play an important pathophysiologic role regardless of the etiology.2 Recent appreciation of the importance of interactions between sickle erythrocytes and vascular endothelium has added to the understanding of the pathogenesis of vasoocclusion in sickle cell disease.3-5 Inhaled nitric oxide has been demonstrated to selectively dilate the pulmonary circulation and to improve oxygenation when ventilation-perfusion inequalities exist. Inhaled nitric oxide may be especially useful in conditions where pulmonary vascular endothelial dysfunction is prominent.6 We hypothesize that patients with ACS may represent a particular type of acute lung injury in which inhaled nitric oxide may improve oxygenation, cause specific pulmonary vasodilation, and potentially ameliorate the underlying vasoocclusive process.

Case 1

A 4.5-year-old boy with sickle cell disease was admitted with nonspecific abdominal pain and mild desaturation. Over 48 h, he developed increasing respiratory failure and hypoxia requiring mechanical ventilation and exchange transfusion, which reduced his percent sickle hemoglobin below 30%. An echocardiogram estimated right ventricular systolic pressure of 60 mmHg. Using high frequency oscillatory ventilation (mean airway pressure, 30 cm H2O; amplitude pressure, 52 cm H2O; rate, 10 Hz; FiO2, 0.90), arterial blood gas values were pH 7.24; PCO2, 62; PaO2, 69; saturation, 94%. Oxygen saturation in the right atrium was 70%. After obtaining written informed consent from the parents, a trial of inhaled nitric oxide was performed according to a protocol approved by the Food and Drug Administration (FDA) and the Human Investigative Committee at Children’s Hospital. After 15 min of nitric oxide inhalation at 80 ppm, repeat measurements showed pH 7.29; PCO2, 55; PaO2, 176; arterial oxygen saturation, 100%; and right atrial oxygen saturation, 81%. An echocardiogram now predicted right ventricular systolic pressure of 40 mmHg. The calculated intrapulmonary shunt fraction (Qs/Qt) decreased from 0.41 to 0.29.

Nitric oxide was decreased, and the patient’s ventilator settings were reduced rapidly. Successful discontinuation of nitric oxide from 5 ppm after 92 h was associated with a transient, well-tolerated decrease in PaO2 from 96 to 71 mmHg. The child was converted to a volume limited mode of ventilation and extubated uneventfully 4 days later. During nitric oxide therapy, nitrogen dioxide was ≤ 2 ppm, and methemoglobin remained ≤ 0.3%.

Case 2

A 9-year-old girl with sickle cell disease presented with a 5-day history of fever, cough, and back pain. She developed right lower and middle lobe infiltrates and right pleural effusion. A right-sided chest tube drained 300 cc of sterile serosanguineous pleural fluid. She developed increasing hypoxia with PaO2 of 63 on 100% nonrebreathing mask. She was intubated, ventilated in a time-cycled, pressure-limited mode with peak inspiratory pressure of 32 cm H2O, end expiratory pressure of 10 cm H2O, rate of 14, FiO2 of 0.5, and underwent exchange transfusion, which reduced the percent sickle hemoglobin below 30%. A Swan-Ganz catheter was placed, and measurements demonstrated pulmonary artery pressure, 54/31 mmHg; mean, 41 mmHg; wedge pressure, 11 mmHg; cardiac index, 5.15 L·min⁻¹·m⁻²; and calculated pulmonary vascular resistance, 5.8 Wood units. She met institutional criteria for the use of inhaled nitric oxide, and parents gave written informed consent.

After 15 min of nitric oxide inhalation at 80 ppm, the pulmonary artery pressure was 37/18, mean was 26 mmHg, wedge was 12 mmHg; cardiac index was 6.43 L·min⁻¹·m⁻²; and pulmonary vascular resistance was 2.2 Wood units. There was improvement in PaO2 from 107 to 185 mmHg. After 47 h, nitric oxide was discontinued without clinical changes. The child subsequently weaned and was extubated 2 days later. Maximal nitrogen dioxide and methemoglobin levels were ≤ 2 ppm and ≤ 0.5%, respectively.
Discussion

We describe patients with sickle cell disease who developed acute chest syndrome with respiratory failure and pulmonary hypertension despite aggressive medical therapy including positive pressure ventilation and exchange transfusion. Inhaled nitric oxide resulted in rapid and significant pulmonary vasodilation and improved oxygenation. Prolonged therapy with inhaled nitric oxide was safely performed and may have been an important factor in the successful weaning and extubation of both patients.

The overall prognosis for patients with sickle hemoglobinopathies has continued to improve. However, a large proportion of deaths occur during an episode of ACS. The specific inciting etiology of ACS is difficult to discern. Infections, fat embolism, and hypoventilation–atelectasis accompany and enhance intravascular sickling and vascular occlusion. The vasculature manifestations of sickle cell disease involve a complex and dynamic sequence of events in the microcirculation. Any change in the vessel tone that would either facilitate the passage of sickled red cells or hasten the passage of cells about to sickle would reduce vascular obstruction, although systemic vasodilator therapy can be dangerous, and fatal hypotension with small bowel infarction has been reported in a patient with ACS.

Sickled red cells interfere with endothelium-dependent vasorelaxation, possibly by inhibition of nitric oxide. They are more adherent to cultured endothelial cells than are normal red cells, and they are able to accelerate the clotting process in vitro. Exposure of human endothelial cells to previously sickled red cells resulted in a four- to eightfold transcriptional induction of the gene coding for the vasoconstrictor endothelin. Elevation of local nitric oxide levels by nitric oxide donors attenuated basal and sickle cell induced expression of endothelin transcripts.

Additionally mononuclear cells from sickle cell disease patients release more superoxide than healthy control subjects in vitro. Considering that superoxide produces oxidant damage and inhibits the pharmacologic actions of nitric oxide, this greater production may represent an additional risk factor for the obstruction of the microcirculation and tissue damage in these patients.

Inhaled nitric oxide has shown variable improvements in oxygenation and pulmonary hypertension in patients with adult respiratory distress syndrome. Selective pulmonary vasodilation may be most pronounced in patients with the greatest degree of pulmonary vasoconstriction and baseline pulmonary vascular resistance may be the best marker predicting beneficial response to inhaled nitric oxide. Inhibition of platelet aggregation has been suggested as an additional beneficial effect of nitric oxide in respiratory failure. The response to nitric oxide in the sickle cell disease population may be exaggerated compared with others with respiratory failure due to a greater degree of baseline pulmonary hypertension, overproduction of vasoconstrictors, inhibition of endothelium-derived vasorelaxation, and acceleration of the clotting process. Our institutional protocol included an initial 15-min trial of nitric oxide at 80 ppm followed by rapid reduction in the dose. Although our patients incurred no toxic side effects during our study, optimal dosage of nitric oxide may vary with each patient and the biologic circumstance, which was not addressed in this study.

Approximately 80%–90% of inhaled nitric oxide is absorbed into the bloodstream and reacts with hemoglobin within the erythrocyte to form first nitrosylhemoglobin and then methemoglobin. The heme tetramer in nitrosylhemoglobin is locked in the relaxed conformation and is unable to polymerize when the sickle mutation is present. As red cells pass through small arterioles in the lung exposed to nitric oxide, significant amounts of nitrosylhemoglobin may form and reduce the amount of sickle polymerization as deoxygenation occurs.

Inhaled nitric oxide may therefore be beneficial in patients with ACS by dilating the pulmonary vascular bed, reducing afterload on the right ventricle, redistributing pulmonary blood flow to better ventilated areas of lung, and potentially reducing sickling in the lung. Proper large prospective trials will need to be undertaken to further elucidate the importance of this novel therapy in ACS. Early use of inhaled nitric oxide in this group of patients may decrease the incidence of ACS or reduce the need for more aggressive therapies such as exchange transfusion or mechanical ventilation.

References

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Factor XII Deficiency and Cardiopulmonary Bypass: Use of a Novel Modification of the Activated Clotting Time to Monitor Anticoagulation

Mark A. Gerhardt, M.D., Ph.D.,* Charles S. Greenberg, M.D.,† Thomas F. Slaughter, M.D.‡
Mark Stafford Smith, M.D., C.M., F.R.C.P.C.,‡

FACTOR XII is a component of the contact activation complex that contributes to initiation of the intrinsic pathway of coagulation. Although Factor XII deficiency is relatively common in the general population (2.3%) and is more prevalent in patients with coronary artery disease, severe Factor XII deficiency is rare. Despite a markedly prolonged activated partial thromboplastin time (aPTT) in the presence of severe Factor XII deficiency, these patients do not experience an increased risk of bleeding. Monitoring a heparin effect during cardiac surgery in patients with severe Factor XII deficiency is problematic because the usual in vitro tests of the intrinsic coagulation pathway (e.g., activated clotting time [ACT], aPTT) require Factor XII to accurately reflect in vivo anticoagulation. There are no published methods that allow appropriate monitoring of heparin therapy in Factor XII deficient patients without additional risks. We present a modification of the ACT test that compensates for the absence of Factor XII to provide an accurate measure of heparin effect.

Case Report

A 74-year-old man with mitral regurgitation due to chronic rheumatic heart disease was scheduled to undergo elective mitral valve replace-