

## Inhaled Nitric Oxide for Treatment of Sick Cell Stroke

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STROKE is a highly fatal complication of sickle cell disease (SCD) in children, particularly between the ages of 4 and 15 yr. Children with SCD carry a 300-fold increased risk for stroke; consequently, sickle cell anemia is the most common cause of childhood stroke.<sup>1</sup> We report the case of a 13-yr-old African-American boy diagnosed at age 6 months old with hemoglobin SS disease, who had a nonhemorrhagic stroke after a routine anesthetic and was treated with inhaled nitric oxide (INO).

### Case Report

This child underwent a simple, uneventful surgical procedure for central venous access to allow for exchange transfusion to achieve a hemoglobin S value of less than 20%. He received general anesthesia with sevoflurane, oxygen, midazolam, and fentanyl. There was no hypotension or hypoxia during the procedure. Three days before this surgical procedure, he received an erythrocyte transfusion. His preoperative laboratory results were as follows: erythrocyte count,  $4.99 \times 10^6/\text{mm}^3$ ; hemoglobin, 15.1 g/dl; hematocrit, 44.1%; mean corpuscular volume, 84  $\text{mm}^3$ ; erythrocyte distribution width, 14.2%; leukocytes,  $12.5 \times 10^3/\text{mm}^3$ ; neutrophils, 62%; lymphocytes, 28%; monocytes, 3%; eosinophils, 4%; basophils, 1%.

Shortly after surgery in the postoperative care unit, his mother noted that he became unresponsive preceding seizure activity. He was emergently taken for magnetic resonance imaging and magnetic resonance angiography, which revealed right-sided cerebrovascular accident in the distribution of the right middle cerebral artery, and severe bilateral internal carotid artery stenosis. This stroke limited left-sided facial, arm, and leg movements. He was transferred to the Pediatric Intensive Care Unit and, after consultation with the Neurology and Stroke Service, it was decided to treat him with an exchange transfusion. Anesthesiology was also consulted to review the surgical record, and after concluding that the anesthetic and surgical procedures were within the normal standards of care, a trial of INO for this patient was discussed with the parent.

United States Food and Drug Administration approval for off-label use of INO was obtained; emergency institutional review board approval was granted (Partners Human Research Committee, Boston, Massachusetts), and the patient's mother signed a consent-to-treat form

before the exchange transfusion. INO was administered by facemask at 80 parts per million by volume. Blood samples were obtained before INO and after 3 and 22 h of therapy.

To estimate endogenous nitric oxide, we measured plasma nitrite and nitrate levels, which are stable end products of nitric oxide. Indirect measurements of nitric oxide are needed because its half-life in whole blood is in milliseconds.<sup>2</sup>

Plasma was separated from whole blood by centrifugation, and measurements of plasma nitric oxide metabolites (NOx) were made using a Sievers Nitric Oxide Analyzer 280 (Sievers Instruments, Inc., Boulder, CO). Samples (5  $\mu\text{l}$ ) were injected into the headspace through the septum of an oxygen-free purger vessel containing 5–6 ml vanadium (III) chloride in HCl. The vanadium III, heated to 94°C by a circulating water bath, reduced nitrites and nitrates to nitric oxide gas, which was measured by the NOA 280 chemiluminescence detector (Sievers Instruments, Inc.). NOx concentrations were determined as area under the curve of three separate injections of samples and integrating the peaks. The areas were compared with calibration curves produced by the injection of sodium nitrate standards.

Nitric oxide metabolite levels were dramatically low (14.8  $\mu\text{M}$ ) before initiating INO therapy (fig. 1). NOx levels increased (82  $\mu\text{M}$ ) after 3 h of nitric oxide breathing and were further increased (106  $\mu\text{M}$ ) at 22 h (fig. 1). The patient became neurologically responsive within 3 h of INO therapy and before exchange transfusion. INO was continued for 48 h, at which time the patient had a near complete neurologic recovery.

### Discussion

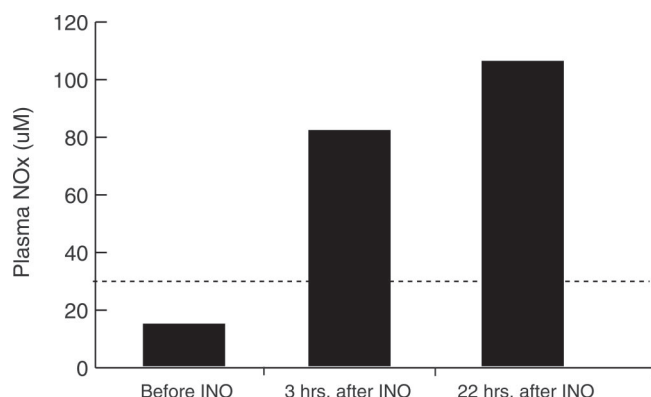
*Sickle cell disease* is a genetic disorder whose manifestations are caused by a single point mutation that results in the substitution of valine for glutamic acid at the sixth position  $\beta$ -globin subunit.<sup>3</sup> Sickle hemoglobin forms polymers during deoxygenation. When deoxygenated, sickle hemoglobin aggregates and produces a viscous gel composed of multistranded helical polymers, resulting in rigid and deformed erythrocytes. In the microvasculature, adhesion of the sickle erythrocytes to the vascular endothelium occurs. This produces slowing and obstruction of the microcirculation, creating localized ischemia and infarction. The resulting acute and chronic organ damage is a major cause of pain, morbidity, and mortality associated with SCD.<sup>4</sup> By age 20 yr, approximately 11% of homozygous SCD patients will experience a stroke.<sup>1,5,6</sup> Most strokes in SCD pediatric patients are nonhemorrhagic.<sup>1</sup> It is unclear whether general anesthesia or surgical trauma triggered the acute stroke in this child. However, the close temporal relation with the minor surgical procedure suggests this to be the case.

Available evidence supports the occurrence of ischemia-reperfusion injury-like events in the vasculature of SCD patients due to erythrocyte adhesion. This injury produces a dysfunctional endothelium favoring a procoagulant state.<sup>7</sup> Moreover, such dysfunctional endothe-

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**Fig. 1.** Plasma nitric oxide metabolite levels before inhaled nitric oxide (INO) and at 3 and 22 h after therapy. The dashed line represents the normal/control level of plasma nitric oxide metabolites (NOx).

lium is less capable of producing nitric oxide.<sup>8-10</sup> In addition, endogenous nitric oxide is avidly scavenged and consumed by the large amounts of free hemoglobin and by the overproduction of reactive oxygen species occurring in SCD.<sup>11-13</sup> These factors acting together may significantly reduce nitric oxide bioavailability and could play an important role in the pathogenesis of SCD stroke. This may explain the low NOx measured in this patient before INO therapy. It is well known that nitric oxide is a central player regulating platelet aggregation, cell adhesion, and vascular tone. Therefore, repletion of nitric oxide by inhalation may provide benefit in this condition.

Inhaled nitric oxide could be beneficial in the treatment of stroke in sickle cell in a multifactorial way. First, it increases nitric oxide bioavailability. Second, it improves blood flow and oxygenation as a result of preventing erythrocyte, platelet, and leukocyte adhesion to the vascular endothelium. Third, as we previously demonstrated using a mouse model of SCD, INO has protective properties in hypoxic stress.<sup>14</sup> Although debated, this protective effect may be related to an increase in oxygen affinity created by a reduction in sickle hemoglobin polymers.<sup>15,16</sup>

Although plasma NOx levels were not measured before surgery, it is possible that this patient may have had a subclinical inflammatory process ongoing, allowing him to be at increased risk for stroke during his anesthesia and surgery.

In this case, plasma NOx levels were extremely low, which correlates with NOx levels published by others during SCD crisis.<sup>17,18</sup> INO therapy was associated with clinical improvement in this child before conventional therapy, including blood exchange transfusion. The rapid improvement in neurologic status was dramatic, suggesting a relation to INO therapy. The clinical improvement was also associated with an increase in plasma NOx (fig. 1). After 24 h of nitric oxide breathing, magnetic resonance imaging and magnetic resonance

angiography analysis did not show significant changes. However, conventional magnetic resonance imaging alone has been reported to correlate poorly with physical recovery in stroke related to SCD.<sup>19</sup> A combination of different radiologic techniques, such as diffusion and perfusion-weighted magnetic resonance imaging preferably in conjunction with positron emission tomography, may have better assessed the effects of nitric oxide in poststroke recovery.<sup>19-21</sup> Although recovery from sickle stroke is possible without INO therapy, our hematologist, who performed the exchange transfusion, believed this stroke would not have resolved naturally. In addition, reduced plasma NOx suggests reduced nitric oxide bioavailability. Hence, in this patient, preoperative NOx measurements may have proven helpful in identifying a risk factor for operative complications. However, without proof, these observations should be interpreted with caution, and clinical trials should be considered to evaluate the potential role of INO in the treatment of sickle stroke.

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## Takotsubo Cardiomyopathy after General Anesthesia for Eye Surgery

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RECENTLY, Dote *et al.*<sup>1</sup> described in Japanese patients a novel type of cardiomyopathy, the Takotsubo syndrome, an entity that resembles an acute myocardial infarction with normal coronary arteries.

Because early left ventriculography or echocardiography reveals peculiar wall motion abnormalities and a balloon-shaped left ventricle, this syndrome was named Takotsubo, the name of a traditional Japanese octopus pot with a wide base and a tapered top.<sup>1-3</sup>

We describe a case with postoperative apical ballooning of the left ventricle, the Takotsubo cardiomyopathy. Because this syndrome may mimic an acute myocardial infarction, early diagnosis and appropriate treatment is crucial.

### Case Report

A 55-yr-old woman was scheduled to undergo cataract extraction surgery. Her medical history revealed type 2 diabetes mellitus treated with diet, hyperlipidemia, and chronic myeloid leukemia in remission. She had no history or symptoms of coronary disease or heart failure, and her functional capacity was good.

The patient was premedicated with 0.25 mg sublingual bromizolam, and as usual, retrobulbar anesthesia was planned. However, after arrival in the operating room, the patient was extremely stressed, and she asked for general anesthesia.

General anesthesia was induced with fentanyl, propofol, and rocuronium. Because of a grade 3 Cormack-Lehane laryngoscopic view, the

patient's trachea was intubated only on the second attempt, with optimal external laryngeal manipulation. Anesthesia was maintained with nitrous oxide in oxygen and isoflurane. A second aliquot of fentanyl was also administered. The procedure lasted 45 min. During surgery, all of the vital functions monitored remained within normal limits. The patient was hemodynamically stable throughout the procedure. At the end of surgery, with a train-of-four ratio greater than 0.8, the effect of the muscle relaxants was reversed, but the impression was that the patient was not ready for extubation. Therefore, she was transferred intubated to the postanesthesia care unit, where extubation was performed 10 min later. Fifteen minutes after extubation, for an unapparent reason, the patient's oxyhemoglobin saturation decreased to 88%, she became apneic, and emergency orotracheal reintubation was performed. She had no signs of partial "curarization," opioid overdose, or laryngospasm. A 12-lead electrocardiogram showed sinus tachycardia (heart rate, 120 beats/min) precordial ST-segment elevation, and QT-segment prolongation. A tentative diagnosis of myocardial ischemia was made, a cardiologic consult was obtained, and the patient was transferred to the cardiac catheterization laboratory. The coronary arteries were normal angiographically, and left ventriculography revealed moderate dysfunction (ejection fraction, 40%) of the left ventricle and apical ballooning (figs. 1 and 2). The creatine phosphokinase-MB fraction and troponin were normal. There were no signs of heart failure, and the chest radiograph was normal. A diagnosis of Takotsubo cardiomyopathy was made. Transthoracic echocardiography performed 8 h later showed normal global and regional left ventricular function. Throughout the patient's hospitalization in the coronary care unit, there were no reports of chest pain. The patient's trachea was extubated 1 day later. Treatment with furosemide and captopril was initiated because of mild symptoms of congestive heart failure. Five days later, the patient was discharged home with normal echocardiography and normal cardiac function.

### Discussion

Typically, Takotsubo syndrome occurs in 62- to 75-yr-old women who present with chest pain at rest (33-71%), although dyspnea and syncope as initial symptoms are not uncommon.<sup>4</sup>

The proposed Mayo criteria (all must be met) for diagnosis of transient left ventricular apical ballooning syndrome include the presence of transient left ventricular apical akinesis or dyskinesis, absence of obstructive coronary disease, new electrocardiographic abnormalities,

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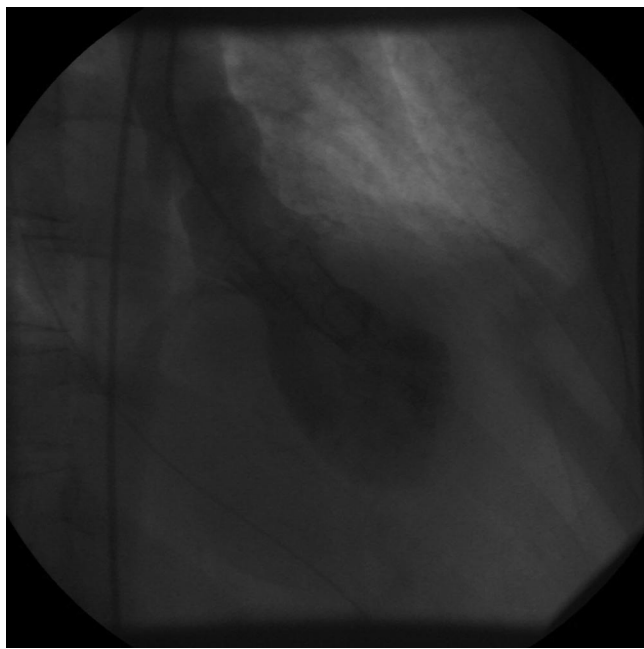


Fig. 1. Left ventriculography showing ballooning during systole.

and absence of concurrent conditions such as head trauma, intracranial bleeding, pheochromocytoma, myocarditis, and hypertrophic cardiomyopathy.<sup>4</sup> All of these criteria were fulfilled in our patient, who had a perioperative stressful event and developed acute myocardial dysfunction without significant coronary artery pathology.

The electrocardiographic findings of this syndrome reveal ST-segment elevation, inverted T waves, and prolonged PR and QT intervals<sup>2-6</sup> with patent coronary

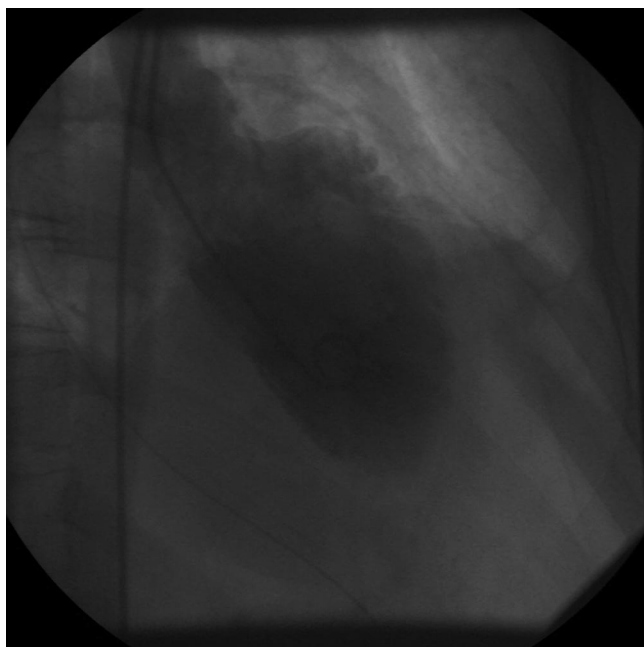


Fig. 2. Left ventriculography showing ballooning during diastole.

arteries even during the hyperacute phase. Similar electrocardiographic changes occurred in our patient. The cardiac enzymes are usually normal or only slightly above the upper limit of normal,<sup>2,5,6</sup> as was the case with our patient. In vascular surgical patients, an abnormal but low postoperative level of cardiac troponin I may herald the development of delayed myocardial infarction.<sup>7</sup>

Patients may exhibit large wall motion abnormalities of the left ventricle chamber,<sup>8</sup> leading to the typical apical ballooning picture (figs. 1 and 2).

Excessive discharge of catecholamines with activation of cardiac catecholamine receptors in the left ventricle and discrepancy in the distribution of sympathetic nerve endings and their receptors could explain the wall motion abnormalities.<sup>4,6</sup>

The intense physical or psychological stress that precedes transient apical ballooning syndrome could be the triggering factor for the acute dynamic subaortic or mid-ventricular obstruction causing apical ischemia.<sup>3</sup> Complications of Takotsubo syndrome include left heart failure, cardiogenic shock in extreme cases, dynamic intraventricular obstruction with acute mitral regurgitation, ventricular arrhythmias, left ventricular mural thrombosis, left ventricular free-wall rupture, and death.<sup>4</sup> However, the overall prognosis of this syndrome seems to be favorable.<sup>4</sup>

This is the first report of anesthesia-related transient left ventricular apical ballooning in a non-Japanese patient undergoing general anesthesia. All three previous case reports from Japan had no specific trigger for development of postoperative Takotsubo cardiomyopathy and resolved within a few days.<sup>9-11</sup> In our case, the transient ballooning was preceded by electrocardiographic changes that mimicked an acute myocardial infarction. Preoperative psychological stress, hypoxemia, laryngoscopy, and reintubation might have caused a catecholamine surge with the consequent development of Takotsubo cardiomyopathy. This transient disorder is managed by supportive therapy.<sup>12,13</sup> Severe left ventricular dysfunction should be treated with load reduction (even using intraaortic balloon counterpulsation).<sup>13</sup> The left ventricular outlet obstruction is treated with  $\beta$  blockers, whereas phenylephrine, a pure  $\alpha$ -adrenergic agonist, can reduce the transient intraventricular dynamic gradient.<sup>12,13</sup> Our patient had a typical benign course and was treated with diuretics and captopril because of mild congestive heart failure. In patients in whom this syndrome has been previously documented,  $\beta$  blockers along with heavy premedication are administered preoperatively. The perioperative  $\beta$  blockade should be instituted according to the American College of Cardiologists–American Heart Association guidelines.<sup>14</sup> For induction of anesthesia, the patient may benefit from a dose-dependent myocardial depression produced by inhalational anesthetic agents. Direct laryngoscopy should be brief, to minimize activation of sympathetic nervous system.

In summary, we describe a case with postoperative apical ballooning of the left ventricle, Takotsubo cardiomyopathy that mimicked an acute myocardial infarction, supposedly caused by excessive perioperative catecholamine release. Patients who develop signs of acute perioperative myocardial infarction should undergo emergency coronary angiography, even if Takotsubo syndrome is suspected, to exclude coronary artery occlusion.

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