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Separation from cardiopulmonary bypass in a nitric oxide non-responder using inhaled nitroglycerin

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ABSTRACT

Separation from cardiopulmonary bypass in a nitric oxide non-responder using inhaled nitroglycerin

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Nitric oxide (NO) inhalation has been used after mitral valve surgery in attempts to control pulmonary hypertension. The cost of NO therapy in some countries has made its use prohibitive and has led to attempts to use aerosolized nitroglycerin. This therapeutic approach may have a place, not only where NO use is a financial hardship, but also as a bridge to, or in lieu of, other traditional therapies for pulmonary hypertension, especially in NO non-responders. Presented here is a case in which aerosolized nitroglycerin was used to separate a NO non-responder with severe pulmonary hypertension and elevated right heart pressures from cardiopulmonary bypass (CPB), his second of two surgeries in a 96 hour period.

Background

Patients with severe pulmonary hypertension may undergo mitral valve replacement with acceptable mortality and good long-term survival [1,2]. Attempts have been made to ameliorate pulmonary hypertension after mitral valve surgery using nitric oxide (NO) [3-5]. However, reoperation for mitral valve surgery in a patient with severe pulmonary hypertension and an ejection fraction (EF) $\leq$ 25% within 4 days of initial coronary artery bypass grafting presents an extremely high risk. Mortality for such a patient approaches 25% [6]. Presented here is a patient who underwent two cardiac surgeries in four days. After the first surgery, coronary artery bypass grafting (CABG), he failed postoperative NO therapy for severe pulmonary hypertension and increased right heart pressure. The postoperative deterioration of mitral and tricuspid valve function necessitated a second procedure to replace the mitral valve and repair the tricuspid valve repair. In view of his non-response to NO, aerosolized nitroglycerin was used to facilitate his separation from CPB. However, three days after his second surgery he expired.

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Case Report

A seventy nine year old white male, 169 cm, 100 kg presented to the emergency department with a history of syncope at home, shortness of breath, and chest pain with progression to ventricular fibrillation and cardiac arrest. He underwent cardiac catheterization after resuscitation with initiation of mechanical ventilation, administration of intravenous vasopressors and

inotropes for circulatory support. A spiral computerized tomography of his chest was negative for pulmonary embolism. His past history included hypertension, obesity, 160 pack-years of tobacco use, chronic obstructive pulmonary disease, gastroesophageal reflux disease, hypothyroidism, renal insufficiency, transurethral resection of the prostate, retinal surgery, right carpal tunnel release, and left hip arthroplasty one week prior to this admission. Home medications included rabeprazole, levothyroxine, iron, warfarin, cephalexin, senna, lisinopril, terazosin, and acetaminophen. Laboratory examination revealed sodium 139 meq/l, potassium 4.6 meq/l, chloride 112 meq/l, carbon dioxide 19 meq/L, blood urea nitrogen of 19 mg/dl, creatinine 106 mmol/L, glucose 219 mg/dl, hemoglobin 10.6 mg/dl, hematocrit 32.5%, platelets 337,000, international normalized ratio (INR) 2.3, prothrombin 24.7 seconds, and partial thromboplastin time 39.4 seconds. The chest roentgenogram after initial intubation showed no evidence of pneumothorax or changes to suggest edema or infiltrate; the heart shadow was enlarged. The initial arterial blood gas, after intubation, resuscitation, and being placed on the ventilator was pH 7.29, pCO2 33 mm Hg, pO2 129 mm Hg, HCO3 15.7 meq/L, on an inspired fraction of oxygen (FIO_2) of 1.00. The patient was on synchronized intermittent mandatory ventilation (SIMV) of 12 breaths per minute, tidal volume (VT) of 800 ml, 5 mm Hg positive end expiratory pressure (PEEP) and 5 mmHg pressure support (PS). He was also providing another 12 spontaneous, non-SIMV breaths (total of 24 respirations per minute).

Coronary angiography revealed total occlusion of the left main coronary artery, 70-80% occlusion of the left anterior descending artery, 75% occlusion of the circumflex artery, and 70% occlusion of right coronary artery. He had significant pulmonary hypertension with a pulmonary artery pressure (PAP) of 50/24 mm Hg, a capillary wedge pressure of 35 mm Hg, a central venous pressure (CVP) of 20 mm Hg, a systemic blood pressure of 80/60 mm Hg, and a sinus tachycardia of 120 beats per minute with ST segment depression in the lateral leads. No v wave was documented on the wedge tracing, although moderate mitral and tricuspid regurgitation were documented in the record by the cardiologist during the coronary artery catheterization. The patient's moderate mitral regurgitation was undiagnosed during his hospitalization for his hip surgery of the previous week. The interventional cardiologist determined the clinical situation was deteriorating and he inserted an intraaortic balloon pump (IABP) through the right femoral artery. This was followed by left main coronary artery stent insertion and the estimated ejection fraction (EF) was 20%. The left main coronary artery quickly reoccluded while the patient was still in the catheterization laboratory (as documented by angiography) and the patient was taken for emergent coronary artery bypass surgery, his first of two surgeries.

Intraoperative transesophageal echocardiography (TEE) demonstrated an EF of 20%, moderate mitral and tricuspid regurgitation and severe left ventricular hypokinesis. A four vessel CABG was performed. Upon separation from CPB the blood pressure was 90/50 mm Hg, PAP was 50/25 mm Hg, CVP was 19 mm Hg. The TEE revealed improved left ventricular wall motion, an EF of 40%, and the mitral and tricuspid regurgitation were unchanged. Doppler ultrasound examination of the grafts revealed them to be patent. He was transferred to the intensive care unit on infusions of dopamine, milrinone, nitroglycerin, aminocaproic acid, epinephrine, vasopressin and amiodarone (ordered by the surgeons for prophylaxis against atrial fibrillation).

On the first postoperative day the PAP varied from 60/30 mm Hg to 80/45 mm Hg with systolic blood pressures from 90-125 mm Hg and CVP of 15-25 mm Hg. The serum creatinine was 159mmol/L postoperatively. The PAP did not respond to intravenous nitroglycerin, sodium nitroprusside or beta blockers. TEE reexamination at this time demonstrated increasingly severe mitral and tricuspid regurgitation and an EF of 25%. The surgical team was concerned about hypotension in the patient and did not allow the use of calcium channel

blockers. Therefore nitric oxide therapy was initiated (INOVENT, INO Therapeutics, Inc).

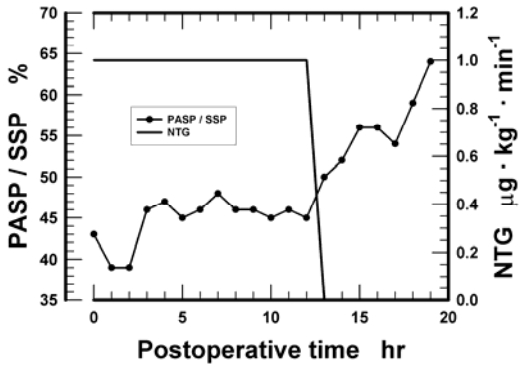
The arterial blood gases at this time were pH 7.44, $PaCO_2$ 42 mm Hg, PaO_2 145 mm Hg, HCO_3 was 28 meq/L (ventilator settings of SIMV10/VT 800 ml/FIO_2 0.6/PS 10 cm H_2O/PEEP 5 cm H_2O), PAP 61/23 mm Hg, pulmonary vascular resistance index (PVRI) 777 dyne-sec-m^2/cm^5, mixed venous oxygen saturation (SVO_2) 63%, blood pressure 107/40 mm Hg, and CVP 21 mm Hg. Over the ensuing 72 hours inhaled NO was delivered in concentrations that varied from 5 to 80 parts per million. The serum creatinine had reached 309 mmol/L. The NO therapy did not improve the PVRI, the PAP, or the CVP. During the period of nitric oxide administration the following were observed: the PAP varied from 50/18-81/33 mm Hg and PVRI varied from 576-1721 dyne-sec-m^2/cm^5 (normal range is 200-400 dyne-sec-m^2/cm^5). In addition the augmented mean arterial blood pressure (MAP) of the IABP ranged from 87-107 mm Hg and the MAP of the peripheral (right radial) arterial line ranged from 59-87 mm Hg during this time frame. Blood pressures, pulmonary artery pressures, and PVRI did not correlate with NO dosage. The patient had increasing problems with oxygenation over three days (sputum cultures were negative and pulmonary capillary wedge pressures were greater than 18 mm Hg), although ventilation remained near normal ($PaCO_2$ = 42 mm Hg). Chest roentgenogram showed diffuse pulmonary infiltrates bilaterally.

Seventy two hours later and just prior to the second surgery the ABG had deteriorated to pH 7.28, $PaCO_2$ 46 mm Hg, PaO_2 60 mm Hg, HCO_3 21 meq/L (ventilator settings of SIMV 16/VT 900 ml/FIO_2 1.0/PS 10 cm H_2O/PEEP 15 cm H_2O, I:E ratio 1:1), PAP 66/30-80/40 mm Hg, PVRI 1082 dyne-sec-m^2/cm^5, SVO2 49%, systolic blood pressure 116-130 mm Hg, and CVP 30 mm Hg. No methemoglobinemia was evident. The chest roentgenogram demonstrated increasingly diffuses bilateral perihilar pulmonary infiltrates consistent with edema. In view of the patient's deteriorating condition and TEE findings of severe mitral regurgitation, moderate to severe tricuspid regurgitation, and an EF of 20%, the surgical team decided to reoperate and perform a mitral valve replacement accompanied by a tricuspid valve repair.

The patient was taken to the operating room on infusions of dopamine 3 mcg/kg/min, milrinone 0.5 mcg/kg/min, nitroglycerin 0.2 mcg/kg/min, epinephrine 0.03 mcg/kg/min, vasopressin 4 units/h, and amiodarone 0.5 mg/min. At the time of anesthetic induction the blood pressure was 144/72, pulse of 85 beats per minute, an SpO2 of 88% on an FiO2 of 1.0, PAP was 85/44 mm Hg, cardiac output (CO) and index (CI) were 4.8 l/min and 2.1 l/min/m^2, respectively, the pulmonary capillary wedge pressure (PCWP) was measured at 40 mm Hg, the PVRI was 1714 dyne-sec-m^2/cm^5, and the CVP was 31mm Hg. The surgery proceeded uneventfully with placement of a bioprosthetic mitral valve and a de Vega repair of the tricuspid valve.

Upon separation from CPB the PAP was 70/44 mm Hg, PCWP was 40 mm Hg, CI 1.2 l/min/m^2, PVRI was 2000 dyne-sec-m^2/cm^5, blood pressure 101/69 mm Hg (MAP was 57 mm Hg), CVP 24 mm Hg, SVO2 48% and IABP 1:1 with atrial pacing at a rate of 90 beats per minute. The ventilator settings were: controlled ventilation with tidal volumes of 900 ml, a respiratory rate of 14, PEEP of 15 cm H_2O, the FIO_2 was 1.0. The peak inspiratory pressure was 40 cm H_2O. In view of the patient's non-response to nitric oxide therapy and the surgeon's reluctance to allow use of diltiazem aerosolized nitroglycerin was delivered at 1 mcg/kg/min. The patient improved quickly and 20 minutes after separation from CPB the PAP was 44/27 mm Hg, PCWP was measured at 25 mm Hg, PVRI was 760 dyne-sec-m^2/cm^5, CI 2.0 l/min/m^2, blood pressure 119/46 mm Hg, CVP 18 mm Hg, and SVO2 69%. The ABG was pH 7.41, $PaCO_2$ 31 mm Hg, PaO_2 418 mm Hg, HCO_3 19.2 meq/L, and a base excess of –4.6 meq/L (on an FIO_2 of 1.0). Neither the intravenous infusion rates nor the ventilator settings had been adjusted; only the aerosolized nitroglycerin had been added.

Figure 1



Again, Doppler ultrasound examination of the grafts revealed them to be patent. TEE examination of the bioprosthetic mitral valve revealed it to be working well. The EF continued to be 20%.

The inhaled nitroglycerin was continued into the postoperative period for approximately 12 hours (see Figure 1) and was then discontinued. The patient's pulmonary artery systolic pressures rebounded upward. After several hours of high pulmonary artery systolic pressures the patient responded to a diltiazem infusion of 5 mg/hr; subsequently the drip was increased to 10 mg/hr with a resultant PAP of 46/24 mm Hg. Unfortunately, the patient went into renal failure over the next several days and was placed on continuous venovenous hemodialysis (serum creatinine was 504 mmol/L); he never awoke after the surgery and he expired due to renal and pulmonary complications three days after his second surgery.

Discussion

This patient was very ill with a EuroScore estimate of perioperative risk before the first operation of 19 (84% risk of death), and a score of 22 (93% risk of death) before the second operation. His non-response to nitric oxide therapy is not exceptional, but the fact the patient did respond to nitroglycerin in the face of nitric oxide non-response is noteworthy because nitroglycerin can be metabolized to produce nitric oxide and thus produce the same effects of inhaled nitric oxide gas. Even though the mechanism of nitric oxide non-response has not been well elucidated, it has been hypothesized that non-response occurs secondary to high blood concentrations of norepinephrine [7], non-delivery of the drug [8], inadequate levels of PEEP [9], severity of hemodynamic abnormalities [10], low baseline levels of cyclic guanosine monophosphate (cGMP) [10], and incremental increases of plasma cGMP level without establishment of a large transpulmonary cGMP gradient [10]. The use of aerosolized nitroglycerin in pulmonary hypertension has been studied in dogs [11,12] and has been used postoperatively after mitral valve surgery [13].

The reasons for inhaled nitric oxide nonresponse, but aerosolized nitroglycerin response, may be difficult to unequivocally extricate from the current literature, however a downstream involvement of a signal transduction cascade may be of a reasonable likelihood. It has been suggested that a cGMP dependent protein kinase that assists cGMP in relaxing vascular smooth muscle by activating a potassium channel may differentiate between responders and non-responders [14,15]. In NO non-responders the metabolic products of aerosolized nitroglycerin (1,2-glyceryl dinitrate, 1,3-glyceryl dinitrate, inorganic nitrite), or a molecular mechanism they influence, may assist in the activation of this potassium channel. NO non-responders may also have increased PDE-5 (cGMP hydrolyzing phosphodiesterase) and PDE1A (calcium/calmodulin dependent PDE) activity that may lower levels of cGMP, thereby allowing smooth muscle contraction [16-18]. A mechanism involving nitroglycerin metabolic products bypassing such vasoconstrictors that inhibit NO can only be suggested. Also, non-responders may not be able to mount a highly compartmentalized NO/cGMP effect that may be responsible for the pulmonary vasodilatory effect [19]. Finally, there is evidence that the effects of vasopressin can be counteracted by NO (via release by nitroglycerin, a study done in rabbits) [20], thus the argument can be made that the protective activity of intravenous nitroglycerin attributed to NO release could be counteracted by concurrent administration of vasopressin. Failure of the delivery of either

nitroglycerin or nitric oxide in this case was excluded.

The patient had a history of obesity, advanced age, gastroesophageal reflux and cardiac arrest. A scenario of aspiration and a coronary crisis with acute mitral valve dysfunction could be hypothesized as the reason for the observed failure of NO therapy. However, there is no history of witnessed regurgitation and aspiration, no expectorated food particles, no particulate matter evident in the hypopharynx and upper airways at the time of intubation, no cyanosis, a negative initial chest roentgenogram, no new adventitial breath sounds, no arterial hypoxemia by pulse oximetry or arterial blood gas analysis. Although there may be no findings on the initial chest roentgenogram, infiltrates could be delayed up to 48 hours. In this patient the progressive decrement over several days in cardiopulmonary function led to bilateral perihilar infiltrates consistent with pulmonary edema on radiographic examination. Typically there is a short latent interval from aspiration to the onset of symptoms (less than one hour) with subsequent rapid progression [21]. However, if aspiration had occurred in this clinical situation, the rapid intubation of the patient, with sedation and emergent surgical intervention, may have masked such early symptoms. This scenario is possible, but unlikely.

Another scenario of potential concern as to the failure of NO therapy concerns the possibility of a pulmonary embolus and coronary crisis with mitral valve dysfunction. The negative spiral CT and the INR of 2.3, in conjunction with initial arterial blood gases clearly exhibiting the ability of the lungs to clear carbon dioxide, demonstrate that the patient likely had adequate thromboprophylaxis and did not have a pulmonary embolic event. Although his large arterial to alveolar gradient does suggest a condition of ventilation/perfusion mismatch, diffusion impairment, or right to left shunt.

The inhaled nitroglycerin showed an effect, but the question can be raised as to why was it delivered by inhalation and not intravenously? The argument can be made that intravenous nitroglycerin can be effective and more easily titrated. However, upon discontinuation of cardiopulmonary bypass the MAP was 57 mm Hg and the PAP was 70/44 mm Hg thus raising a legitimate question as to how much intravenous nitroglycerin would be necessary to decrease the PAP to an acceptable level without severely affecting the MAP. Therefore, the decision to use inhaled nitroglycerin was made.

In any event the following criticisms must be acknowledged: (1) after mitral valve replacement NO was not used, (2) the use of diltiazem earlier may have been effective in lowering the PAP, (3) NO was used for 72 hours before the second surgery when it was evident at an earlier point in time that this therapy was not effective, and (4) correction of the valve abnormalities should not be underestimated in aiding the clinical situation.

Nonetheless, in severe pulmonary hypertension, especially in the face of the failure of nitric oxide therapy and other treatment modalities, arguments can be made for the use of aerosolized nitroglycerin in: (1) countries with more limited resources than the USA, (2) as a bridge to more familiar therapies for pulmonary hypertension, or (3) in the situation of failed therapy with a patient in extremis as described in this communication. More work is needed on the mechanisms of action of NO-inducing drugs, specifically, as to the pathways of signal cascades to explain the contradiction of aerosolized nitroglycerin treatment success and inhaled nitric oxide therapy failure.

Conclusion

Aerosolized nitroglycerin may be used successfully to separate patients with severe pulmonary hypertension after mitral valve surgery from cardiopulmonary bypass. There are more traditional drug therapies to control pulmonary hypertension that can be used to accomplish this separation from CPB. However, in the face of the failure of multiple intravenous vasodilators and beta blockers, the failure or exclusion of calcium channel blockers, the failure of inhaled

nitric oxide therapy, or the inability to procure nitric oxide (financially or otherwise), use of aerosolized nitroglycerin may be a consideration.

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