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Inhaled milrinone for the management of severe pulmonary hypertension in non-cardiac surgery

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Dear Editor,

Pulmonary hypertension may present anesthetic challenges, especially for patients undergoing general anesthesia. This condition is associated with a significant increase in morbidity and mortality for patients undergoing surgery [1, 2]. Pulmonary hypertension is a cardiopulmonary disease characterized by a mean pulmonary arterial pressure greater than 20 mmHg [3]. Patients with pulmonary hypertension are classified according to etiology. Group 1 represents pulmonary arterial hypertension, which includes idiopathic pulmonary hypertension; heritable pulmonary hypertension; as well as pulmonary hypertension due to drugs, infectious disease, and connective tissue diseases [4]. Group 2 pulmonary hypertension is due to left heart disease, while group 3 pulmonary hypertension is due to lung disease or hypoxia [4]. Group 4 pulmonary hypertension is chronic thromboembolic pulmonary hypertension. Group 5 is pulmonary hypertension due to unclear multifactorial causes [4].

Several therapies exist for managing pulmonary hypertension, however the use of these interventions in intra-operative settings remains limited, especially in non-cardiac cases [5, 6]. Some commonly used agents include prostacyclin analogues, such as iloprost and epoprostenol [5]. Although it is indicated for chronic management, intra-operative use of inhaled iloprost has been reported to be effective in reducing pulmonary arterial pressures [6–8]. Epoprostenol has also been studied and has been demonstrated to have beneficial physiological effects on pulmonary artery pressure, right ventricular function, cardiac output, and pulmonary gas exchange [9]. Another agent that has been used intra-operatively is inhaled nitric oxide. It is however regarded to be less effective than iloprost, and current evidence does not suggest improvement in long-term outcomes [8, 10, 11]. Milrinone has also been studied for the treatment of pulmonary hypertension [11]. Milrinone is a phosphodiesterase type 3 inhibitor, which causes vasodilation and ionotropy by activating cAMP-mediated signaling pathways [12]. Inhaled milrinone has been shown to effectively reduce pulmonary arterial pressures in cardiac surgery, although little is known regarding the use of milrinone in non-cardiac surgery [13, 14]. In this report, we present a case entailing the use of milrinone to successfully reduce high pulmonary arterial pressures during carotid bypass surgery.

A 56-year-old man with bilateral carotid disease and extensive cardiac comorbidities presented for a repeat left carotid subclavian bypass to improve cranial blood flow prior to a planned mitral valve replacement procedure under cardiopulmonary bypass. His past medical history included coronary artery disease, two myocardial infarctions, congestive heart failure, mitral and tricuspid insufficiency, peripheral vascular disease (bilateral carotid disease – left occluded), hypertension, dyslipidemia, and a history of smoking. He was also regularly using nitroglycerin spray for CCS class IV angina, his baseline function was NYHA class IV, and his functional capacity was under 4 metabolic equivalents. Transesophageal

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echocardiography prior to surgery demonstrated severe mitral regurgitation and moderate tricuspid regurgitation. The preoperative cardiac echo estimated right ventricular systolic pressure was 65–75 mmHg. His surgical history was remarkable for a remote coronary artery bypass graft, and a failed left carotid subclavian bypass one year prior.

An awake radial arterial line and central venous catheter (9 Fr.) were placed in addition to the standard monitors. A Paceport Swan-Ganz catheter (Edwards Lifesciences Model D200F7) was introduced through the internal jugular line and positioned using waveform guidance prior to the induction of anesthesia. This type of catheter was selected based on availability, and no pacing was anticipated or performed during the case. The initial pulmonary artery pressure reading was 88/62 mmHg, and the simultaneous radial arterial pressure was 110/85 mmHg. A carefully titrated induction was performed with 300 mg of fentanyl, 100 mg of phenylephrine, 70 mg of ketamine, and 100 mg of rocuronium. During induction, pulmonary artery pressure increased to a maximum of 108/58 mmHg but remained below the concurrent arterial blood pressures (138/91 mmHg). General anesthesia was maintained with isoflurane (0.7 MAC) and a remifentanil infusion titrated according to vital signs (0.02 to 0.1 mg kg^{-1} min^{-1}). Following the induction of anesthesia, the patient's pulmonary artery pressure stabilized at approximately 90/45 mmHg, and systemic pressures were approximately 115/75 mmHg. Half an hour following induction, 4 mg of milrinone dissolved in 4 mL of water (Primacor, Sanofi) was introduced into the inspiratory limb of the anesthesia circuit using an ultrasonic nebulizer (Aeroneb-Pro X, Aerogen Limited, Dangan, Galway, Ireland) over a thirty-minute period of time. Two filters were used in the anesthesia circuit at both the outlet and inlet to the circle of the anesthesia machine. No filter was used between the nebulizer and patient. This milrinone treatment reduced the pulmonary artery pressures to 70/28 mmHg, and the systolic pulmonary pressure remained below 80 mmHg for half an hour. No change was observed in left-sided arterial pressures. Pulmonary artery pressures started increasing and plateaued at approximately 100/40 mmHg. A second nebulized 4 mg milrinone treatment was administered, lowering the pulmonary artery pressures to approximately 77/30 mmHg, and the pulmonary pressures remained in this pressure range for the next forty-five minutes, until the end of the general anesthesia. In addition to milrinone, two doses of hydromorphone were administered: the first dose fifteen minutes after the end of the first milrinone treatment phase, and the second dose during the second milrinone treatment phase. No other deliberate interventions were attempted to reduce pulmonary hypertension. Following uneventful surgery and anesthesia, the patient was successfully extubated in the operating room and transported awake and stable to the Post-Anesthesia Care Unit. Written informed consent for publication of this report was obtained from the patient.

Pulmonary hypertension may pose challenges for anesthesiologists: dynamic physiological changes can occur during major surgery, which may precipitate acute right ventricular decompensation and death [15]. This case report presents a patient with severe pulmonary hypertension on a background of severe cardiac disease including unstable angina and heart failure. The patient also had tricuspid regurgitation and severe mitral regurgitation requiring upcoming mitral valve replacement. The surgical team decided to revise the previously failed left carotid artery bypass because of known right carotid stenosis and suspected vascular disease in circle of Willis communications. The surgical plan was to revise the left carotid bypass as a separate procedure to improve the cerebral circulation while on cardiopulmonary bypass and hopefully reduce the patient's risk of stroke during the cardiac procedure. This case demonstrates the potential utility of inhaled milrinone for the intra-operative management of severe pulmonary hypertension in non-cardiac cases. Research supporting the use of inhaled milrinone in non-cardiac surgery cases is very limited. Minimal systemic hypotension is reported to occur when it is administered by nebulization [16]. We observed a minimal effect on left-sided arterial blood pressures from the inhaled milrinone during this case. We noted inhaled milrinone to be a useful alternative to inhaled nitric oxide or prostacyclin analogs. We would encourage other anesthesiologists to consider adding inhaled milrinone to their toolset for managing severe pulmonary hypertension. The equipment required is relatively simple to set up, inexpensive, and does not require expertise outside the normal skillset of an anesthesiologist. While inhaled nitric oxide and inhaled prostaglandins have been demonstrated to be efficacious for intraoperative management of pulmonary hypertension, inhaled milrinone may be a worthwhile consideration, especially in centers where the former two inhaled agents are unavailable.

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