Published in final edited form as:

Anesth Analg. 2017 August ; 125(2): 375–377. doi:10.1213/ANE.0000000000002239.

Inhaled pulmonary vasodilators in cardiac surgery patients – Correct answer is “NO” -

Fumito Ichinose, MD, PhD¹ and Warren M. Zapol, MD²

¹William Thomas Green Morton Professor of Anesthesia, Harvard Medical School, Boston, MA

²Reginald Jenney Professor of Anesthesia, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Pulmonary hypertension often complicates the care of patients who are undergoing cardiac surgery. Severe acute pulmonary hypertension may contribute to the development or worsening of right ventricular (RV) failure. Pulmonary hypertension and RV failure may reduce left ventricular (LV) filling, LV systolic and diastolic pressures and cardiac output, and lead to systemic hypotension. Decreased arterial blood pressure may compromise LV and RV coronary perfusion at a time when RV end-diastolic pressures and RV myocardial oxygen consumption are increased due to increased RV wall tension, thereby leading to RV ischemia.¹ RV ischemia exacerbates RV failure, causing a further reduction in cardiac output and blood pressure. Concomitant LV dysfunction further impairs RV performance due to the loss of the interventricular septal contributions to RV function which are largely determined by LV function. One of the key interventions to break this vicious cycle is to reduce the RV afterload, for example by decreasing pulmonary vascular resistance (PVR), thereby enabling the RV to pump more blood forward. Although systemic vasodilators may reduce PVR, concomitant reduction of systemic blood pressure not only decreases the RV coronary perfusion pressure but also decreases LV contraction, which adversely affects RV function. Inhalation of nitric oxide (NO) produces selective pulmonary vasodilation without reducing the systemic arterial pressure in patients with pulmonary hypertension.² Although the only current FDA-approved indication of inhaled NO is persistent pulmonary hypertension of newborns, off-label use of inhaled NO is widespread. However, inhaled NO is very expensive; a number of other, potentially less expensive, experimental inhaled pulmonary vasodilators have been described, which may provide alternatives to inhaled NO. Despite the need to treat RV dysfunction in patients undergoing cardiac surgery, as well as patients undergoing heart and lung transplantation or requiring the placement of a ventricular assist device, there is no established consensus concerning the use of pulmonary vasodilators for these indications.

Address for Correspondence: Fumito Ichinose, MD, PhD, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, 149 13th St, CNY 149, Room 4315, Charlestown, MA 02129, USA, Tel: 617-643-0987, Fax: 617-643-4490, fichinose@mgh.harvard.edu.

Conflict of Interest: WMZ is head of the SAB of Third Pole. MGH has filed patents on electric NO generators. WMZ has a right to receive royalties.

Contribution of authors: FI drafted and revised the manuscript. WMZ revised the manuscript. Both authors approved the final manuscript.

In the current issue of Anesthesia and Analgesia, Elmi-Sarabi and colleagues report the results of a systematic review and meta-analysis of the effects of aerosolized vasodilators for the treatment of pulmonary hypertension in cardiac surgery patients.³ This is a timely and welcome review which has major implications for the management of some of the most challenging patients undergoing cardiac surgery. The authors searched MEDLINE, CENTRAL, EMBASE, the Web of Science, and clinicaltrial.gov databases from their inception to October 2015. They identified randomized controlled trials (RCT) of adult patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) that compared the efficacy of inhaled aerosolized vasodilators to intravenously administered agents and to a placebo in the treatment of pulmonary hypertension during cardiac surgery. Studies of combination therapies and all crossover trials were excluded. To be considered for their review, patients must have been treated before, during or following surgical intervention. Only ten of the 2,897 identified studies were included in the analysis. The total number of patients in these 10 studies combined was 434. Five studies, involving a total of 205 patients, compared inhaled vasodilators to placebo; the remaining five studies (involving 229 patients) compared inhaled vasodilators to intravenous vasodilators. In this meta-analysis, the primary outcome was the incidence of mortality. Secondary outcomes were the length of stay in the ICU, the length of hospitalization, and an evaluation of the hemodynamic profile. The investigators found that aerosolized vasodilators were not superior to placebo in terms of decreasing mortality. Aerosolized vasodilators also had no effect on length of hospitalization and, compared to placebo, were associated with an increased duration of stay in the ICU. There were insufficient data to perform a meta-analysis on mortality or the length of stay in the ICU or hospital when comparing aerosolized to intravenously administered agents. While the meta-analysis showed no improvement in hemodynamic profile associated with inhaled aerosolized vasodilators compared with a placebo, a significant increase in RV ejection fraction (EF) was associated with inhaled aerosolized agents compared to intravenous vasodilators even after a Bonferroni correction for multiple comparisons.

Minimizing RV afterload while optimizing RV performance is an important physiological goal in the clinical management of RV failure during cardiac surgery. The use of inhaled vasodilators would be expected to minimize PVR and thereby contribute to improved RV function. However, whether or not treatment of pulmonary hypertension with inhaled vasodilators during cardiac surgery alters clinically important patient outcomes (i.e., mortality and the length of ICU stay and hospitalization) is unknown. This is the question Elmi-Sarabi and colleagues addressed by meta-analysis in this systematic review. Although their analysis showed a physiological benefit of inhaled vasodilators (i.e., significantly increased RVEF) compared to intravenously administered vasodilators, their analysis fell short of determining whether or not inhaled vasodilators improve important clinical outcomes. The primary reason why the authors were unable to draw conclusions on the “hard outcomes” in their systematic review is the small number of RCTs included in the analysis of clinical outcomes. Out of the 10 RCTs included in this analysis, only 6 trials (4 studies comparing inhaled vasodilators to a placebo control and 2 studies comparing to intravenous vasodilating agents) reported mortality. The length of stay in the ICU and duration of hospitalization was reported in only 4 trials (3 studies comparing inhaled vasodilators to placebo and 1 study comparing inhaled to intravenous agents). In addition, all

of the included trials consisted of small numbers of participants and were highly inhomogeneous in their design. Seven of the 10 RCTs included fewer than 50 patients (fewer than 20 in each arm). Several different drugs (inhaled NO in 3 trials, epoprostenol in 1 trial, iloprost in 1 trial, milrinone in 3 trials, and inhaled NO and epoprostenol in 2 trials) were administered at varying doses at differing time points (i.e., before or after CPB or in the ICU). The apparent lack of RCTs examining the treatment of pulmonary hypertension in cardiac surgery patients is likely due to the difficulty of conducting clinical trials in these challenging patients. Treatment of pulmonary hypertension is usually initiated in cardiac surgery patients when RV function is deemed inadequate or progressively deteriorates despite implementation of other measures to optimize pulmonary function and RV and LV performance. Due to the acuity of the situation, randomization of these patients is often impractical and or unacceptable. Therefore, while it is certainly disappointing, it is not surprising that only 10 RCTs were identified and included in the current analysis.

The design of the study by Elmi-Sarabi and colleagues raises additional concerns, including the choices of primary and secondary endpoints for analysis. “Hard” clinical outcomes, such as mortality or duration of hospitalization, in cardiac surgery patients are determined by a large number of factors including the comorbidities of patients, quality of surgical repair, duration of cardiopulmonary bypass and surgery, and intraoperative and postoperative supportive care. Even the minimization of RV afterload requires not only the use of vasodilating agents, but also the optimization of ventilation, acid-base status, systemic vascular tone, and LV contractility. Therefore, improvement in “hard” clinical outcomes in cardiac surgery patients with an inhaled vasodilator as compared to an intravenous vasodilator or placebo may be too high a bar to use as endpoints.

Despite the small number of trials included in the meta-analysis, the authors observed a significant increase in RVEF in patients treated with inhaled aerosolized, compared to intravenous, vasodilators. The increase in RVEF was associated with reduced PVR and increased mean arterial pressure (MAP). Although the beneficial effects on PVR and MAP were not significant after Bonferroni corrections for multiple comparisons, these results are consistent with a number of preclinical and clinical studies that examined the effects of inhaled vasodilators and support the hypothesis that selective pulmonary vasodilation improves RV function in patients with pulmonary hypertension during and after cardiac surgery.

A secondary goal of this meta-analysis, as indicated by Elmi-Sarabi and colleagues in the Introduction, was the comparison between inhaled NO and other alternative inhaled aerosolized vasodilators. Unfortunately, this sub-group comparison could not be conducted due to the small number of trials included in the analysis. Successful clinical use of inhaled NO as a selective pulmonary vasodilator prompted the search for other alternatives, at least in part due to the very high cost of inhaled NO therapy, which currently relies on a proprietary inhalation and monitoring device and gas cylinder delivery networks.⁴ Because aerosolization of common systemic vasodilating agents is less expensive than inhaled NO, a wide variety of systemic vasodilators were clinically used via the inhaled route. It was expected that inhalation of vasodilators would maximize drug levels in the lung while minimizing their systemic effects. However, the efficacy and safety profile of aerosolized

vasodilators have not been established. For instance, while a very brief exposure to inhaled epoprostenol decreased PVR to a similar extent as inhaled NO,⁵ epoprostenol is known to cause hypotension.⁶ The plasma half-life of epoprostenol is sufficiently long (5 min) to produce systemic vasodilation. Furthermore, epoprostenol must be dissolved in a highly viscous and basic glycine diluent (pH=10.5) that can produce tracheitis,⁷ interstitial pneumonia,⁸ and ventilator valve malfunction.⁹ Lastly, although the drug cost associated with inhaled epoprostenol is reported to be less than that of inhaled NO, a careful cost comparison that takes into account the impact of prolonged therapy on overall cost, has not been performed. For example, if inhaled NO therapy reduced the length of ICU stay by 1 day or the need for a RV assist device or ECMO perfusion, the difference in drug cost would be incidental.

In terms of the cost comparison, it is important to follow recent developments in making NO economically from air for inhalation therapy. A simple, safe method was reported in *Science: Translational Medicine*,¹⁰ employing a spark generator and a filter and NO₂ scavenger system. This method for producing NO from air was tested in 35 kg sheep and provided reliable pulmonary vasodilation. More recently, the spark generator filter and scavenger was tested at MGH in six volunteers and six patients with chronic pulmonary hypertension whose PVR decreased in response to inhaled NO from a cylinder.¹¹ The NO produced by the spark generator was equal in vasodilator efficiency to NO produced by diluting gas from a NO/N₂ cylinder. The electrical spark device with a scavenger/HEPA filter produced pure and clean NO with a low NO₂ level and was similarly effective to expensive cylinder gas. Recently, a company, Third Pole (<http://www.pole3.com>) was formed to produce lightweight, simple devices to make economical production of NO from air for use in hospitals worldwide. We look forward to the availability of economical and simple NO inhalation vasodilator therapy. Future studies, appropriately powered and designed, are needed to better define the role of inhaled selective pulmonary vasodilators in cardiac surgery patients.¹²

Acknowledgments

Funding information: This work was supported by NIH R01HL110378.

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