flow, such as during instrumentation of CPB. Figure 1 demonstrates that as pulmonary blood flow decreases, as evidenced by carbon dioxide delivery, exhaled NO concentrations increased. Summary data from 7 patients indicate that reduction of pulmonary arterial blood flow at the onset of CPB increases peak exhaled NO levels from 7.4 ± 1.2 ppb to 13.7 ± 1.5 ppb. These data confirm in human beings earlier suggestions that pulmonary blood flow is not required for exhaled NO, which is produced locally in the lung, and that gas-phase NO concentrations are influenced by uptake into the pulmonary circulation and blood.

Where do we go from here? This discussion highlights the fact that Humpl and colleagues¹ have undertaken a complex task in attempting to delineate the complex influence of changes from supernormal to normal pulmonary blood flow and CPB-associated partial and transient ischemia-reperfusion and systemic inflammatory response on the pulmonary release of NO from its many sources. Although exhaled NO could represent an exciting novel diagnostic tool to monitor biochemical events of crucial importance to cardiac surgery, important methodologic issues that remain.^{7,8} Moreover, even at this early stage it is obvious that there will be crucial limitations of the methodology. More controlled studies and continued dialog with international consensus and society recommendations are needed to clarify these issues in ventilated and critically ill patients. (Exhaled Biomarkers in mechanically ventilated patients [submitted ATS/ERS Project, Marczin N, Gustafsson LE, Erzurum SC, Choi AM, Risby T, and Schumbert JJ]).

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References

- Humpl T, Campbell R, Stephens D, Van Arsdell G, Benson LN, Holby HM, et al. Levels of exhaled nitric oxide before and after surgical and transcatheter device closure of atrial septal defects in children. *J Thorac Cardiovasc Surg.* 2002;124:806-10.
- Marczin N, Riedel B, Gal J, Polak J, Yacoub M. Exhaled nitric oxide during lung transplantation. *Lancet.* 1997;350:1681-2.
- Brett SJ, Quinlan GJ, Mitchell J, Pepper JR, Evans TW. Production of nitric oxide during surgery involving cardiopulmonary bypass. *Crit Care Med.* 1998;26:272-8.
- Tworetzky W, Moore P, Bekker JM, Bristow J, Black SM, Fineman JR. Pulmonary blood flow alters nitric oxide production in patients undergoing device closure of atrial septal defects. *J Am Coll Cardiol.* 2000;35:463-7.
- Sartori C, Lepori M, Busch T, Duplain H, Hildebrandt W, Bartsch P, et al. Exhaled nitric oxide does not provide a marker of vascular endothelial function in healthy humans. *Am J Respir Crit Care Med.* 1999;160:879-82.
- Marczin N, Riedel B, Royston D, Yacoub M. Intravenous nitrate vasodilators and exhaled nitric oxide. *Lancet.* 1997;349:1742.
- Marczin N, Riedel B, Royston D, Yacoub M. Exhaled nitric oxide in patients undergoing cardiothoracic surgery: a new diagnostic tool? In: Matalon S, Sznajder JI, editors. *Acute respiratory distress syndrome: cellular and molecular mechanisms and clinical management.* New York: Plenum Press; 1998. p. 365-74.
- Marczin N, K Tövesi, Royston D, Yacoub MH. Exhaled nitric oxide in acute lung injury: measurements and physiological implications. In: Matalon S, Sznajder JI, editors. *Etiology and treatment of acute lung injury.* New York: Plenum Press; 2001. p. 186-97. doi:10.1016/S0022-5223(03)01306-0

Reply to the Editor:

We thank Dr Marczin for his interest in our work¹ and the Editor for an opportunity to respond.

The first issue raised concerns the methodology of exhaled nitric oxide (NO) analysis. There are several ways to measure exhaled NO at a constant flow rate in the sedated, intubated, and mechanically ventilated patient. These include syringe aspiration sampling as performed by us,¹ tidal breathing profiles, and single-breath controlled-flow techniques.² The latter is difficult to apply outside the neonatal period. We chose the syringe aspiration sampling method because in our preliminary investigations we found it to be a robust, reproducible technique. Indeed, we confirmed the reproducibility of the method by finding similar changes after cardiopulmonary bypass in a previous study investigating exhaled NO before and after surgical closure of left-to-right shunts in children.³ In the most recent study¹ we measured exhaled NO in an identical manner in both groups of patients, which suggests that the observed differences between groups were independent of the method of NO sampling. The results of Tworetzky and colleagues⁴ are intriguing and fully discussed elsewhere.¹

The next concerns raised by Marczin are the anatomic origin of exhaled NO and

the relationship to endothelial events. Low exhalation single-breath flow rates (<50 mL/s) are characterized by most exhaled NO arising in airways by diffusion, whereas higher flows contain a larger proportion of NO arising in the distal lung.^{5,6} The syringe sampling was performed toward the end of a mechanical tidal breath, when flows are high. Thus the exhaled breath will contain a higher proportion of NO arising in the alveolar region than would a slow single-breath exhalation. We suggest that NO produced in the endothelium of the pulmonary capillary bed may enter the alveolar space and is reflected in air sampled distally. Capillary blood volume has been shown to correlate with exhaled NO.⁷ Notwithstanding the elegant study by Sartori and coworkers,⁸ which was performed in healthy adults, there is evidence to suggest that endothelial derived NO at least partly contributes to exhaled NO levels in cardiovascular disease.^{9,10} Indeed, Marczin's published position is equivocal on this subject, sometimes for¹¹ and sometimes against.

The influence of cardiopulmonary bypass on exhaled nitric oxide levels is likely to be complex and dependant on the disease, the surgical procedure performed as well as the timing of the measurements. Thus Marczin's cited examples of adults undergoing lung transplantation¹² or coronary artery surgery with bronchoalveolar lavage¹³ may not be comparable to children with congenital heart disease. Indeed, our study is perhaps unique in that cardiac correction was achieved with the use of bypass in one group and without in another. The changes in exhaled nitric oxide thus can be more certainly attributed to cardiopulmonary bypass than is possible in other studies.

The changes in pulmonary blood flow during cannulation for cardiopulmonary bypass described by Marczin are fascinating, and we are certain his group will have the opportunity to submit them for peer review. However, they are irrelevant to the investigation we undertook and to our conclusions. Stated simply, after closure of an atrial septal defect exhaled nitric oxide either increases or decreases, and it is the method of closure and sequelae (surgery vs transcatheter), rather than the hemodynamic consequence of closure (reduction in pulmonary blood flow) that influences the direction of change.

We agree wholeheartedly with Marczin's call for continued dialog and international consensus, and we look forward to the recommendations of the proposed task force.

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References

- Humpl T, Campbell R, Stephens D, Arsdell GV, Benson LN, Holtby HM, et al. Levels of exhaled nitric oxide before and after surgical and transcatheter device closure of atrial septal defects in children. *J Thorac Cardiovasc Surg.* 2002;124:806-10.
- Wildhaber JH, Hall GL, Stick SM. Measurements of exhaled nitric oxide with the single-breath technique and positive expiratory pressure in infants. *Am J Respir Crit Care Med.* 1999;159:74-8.
- Beghetti M, Silkoff PE, Caramori M, Holtby HM, Slutsky AS, Adata I. Decreased exhaled nitric oxide may be a marker of cardiopulmonary bypass-induced injury. *Ann Thorac Surg.* 1998;66:532-4.
- Tworetzky W, Moore P, Bekker JM, Bristow J, Black SM, Fineman JR. Pulmonary blood flow alters nitric oxide production in patients undergoing device closure of atrial septal defects. *J Am Coll Cardiol.* 2000;35:463-7.
- Silkoff P, McClean P, Slutsky A, Furlott H, Hoffstein E, Wakita S, et al. Marked flow-dependence of exhaled nitric oxide using a new technique to exclude nasal nitric oxide. *Am J Respir Crit Care Med.* 1997;155:260-6.
- Silkoff PE, Sylvester JT, Zamel N, Permutt S. Airway nitric oxide diffusion in asthma: role in pulmonary function and bronchial responsiveness. *Am J Respir Crit Care Med.* 2000;161:1218-28.
- Cremona G, Higenbottam T, Borland C, Mist B. Mixed expired nitric oxide in primary pulmonary hypertension in relation to lung diffusion capacity. *Q J Med.* 1994;87:547-51.
- Sartori C, Lepori M, Busch T, Duplain H, Hildebrandt W, Bartsch P, et al. Exhaled nitric oxide does not provide a marker of vascular endothelial function in healthy humans. *Am J Respir Crit Care Med.* 1999;160:879-82.
- Rolla G, Colagrande P, Brussino L, Bucca C, Bertero MT, Caligaris-Cappio F. Exhaled nitric oxide and pulmonary response to iloprost in systemic sclerosis with pulmonary hypertension. *Lancet.* 1998;351:1491-2.
- Husain M, Adrie C, Ichinose F, Kavosi M, Zapol WM. Exhaled nitric oxide as a marker for organic nitrate tolerance. *Circulation.* 1994;89:2498-502.
- Marczin N, Riedel B, Royston D, Yacoub M. Intravenous nitrate vasodilators and exhaled nitric oxide. *Lancet.* 1997;349:1742.
- Marczin N, Riedel B, Gal J, Polak J, Yacoub M. Exhaled nitric oxide during lung transplantation. *Lancet.* 1997;350:1681-2.
- Brett SJ, Quinlan GJ, Mitchell J, Pepper JR, Evans TW. Production of nitric oxide during surgery involving cardiopulmonary bypass. *Crit Care Med.* 1998;26:272-8.
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