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Fessler J, Godement M, Pirracchio R, Marandon JY, Thes J, Sage E, Roux A, Parquin F, Cerf C, Fischler M and Le Guen M. Inhaled Nitric Oxide Dependency at the End of Double-lung Transplantation: A Boosted Propensity Score Cohort Analysis. Transplant International 2019; 32: 244–256.

https://onlinelibrary.wiley.com/doi/epdf/10.1111/tri.13381

Abstract “Inhaled nitric oxide (iNO) is usually used during lung transplantation despite controversial postoperative benefits. Our group chose to administer iNO systematically during the procedure and stop at the end of surgery. This study aims to describe the features of patients who cannot be weaned from iNO, the reasons for this and its impact on postoperative outcomes. This is a monocentric cohort study comprised all consecutive patients who underwent double-lung transplantation (DLT) between 1 January 2012 and 1 January 2016. The impact of iNO dependency on postoperative out- comes was estimated using a boosted inverse probability of treatment weighting estimator. A total of 9.8% of the 173 patients included in the study could not be weaned from iNO at end- surgery stage. Body mass index (OR = 2.03, 95% CI = 1.14–3.29, P = 0.02) and intraoperative extracorporeal membrane oxygenation (OR = 1.80, 95% CI = 1.02–2.72, P = 0.04) were risk factors for iNO dependency In the weighted population, iNO dependency was associated with an increased prevalence of grade 3 primary graft dysfunction (adjusted RR = 4.20, 95% CI = 1.75– 10.09, P < 0.001) and decreased postoperative survival during the first 1500 days of follow-up (adjusted HR = 5.0, 95% CI = 1.86–13.48, P < 0.001).

Inhaled nitric oxide dependency is an early marker of a poor prognosis following DLT. “

Comments by Theresa Gelzinis, MD and Barbara Wilkey, MD

This is a retrospective, single center boosted propensity cohort study of bilateral lung transplant recipients attempting to define a relationship between hypoxemia or hemodynamic instability while weaning nitric oxide (iNO) in the operating room and outcome. Additionally, this study aimed to describe the features of these patients and the reasons for their inability to wean. Patients who were unable to wean from nitric oxide without hypoxemia or hemodynamic instability were defined as “iNO dependent”. If patients had underlying pulmonary hypertension the iNO was started at the beginning of surgery. For patients without pulmonary hypertension iNO was started prior to reperfusion.

Anesthetic technique was total intravenous anesthesia with a thoracic epidural. After lung implantation protective ventilation was initiated. At the end of the procedure, the patients on ECMO were weaned off if the mean arterial pressure remained above 60 mmHg with minimal pharmacologic support, and PaO2/FiO2 remained greater than 200 with an ECMO FiO2 of 40% and ventilator FiO2 of 50% or less. iNO was weaned if the PaO2/FiO2 remained above 100. After successful iNO weaning, if the PaO2/FiO2 was greater than 200 the patient was extubated. Patients who failed to wean from iNO were brought to the intensive care unit (ICU) intubated and mechanically ventilated. Of the 173 analyzed patients, 17 or 9.8% failed to wean from iNO at the end of the procedure. Etiologies for failure to wean included severe hypoxemia in 7 patients, hypoxemia and pulmonary hypertension in 6 patients and right ventricular dysfunction most likely due to air embolism in the remaining 4 patients. These 17 patients had an increased



prevalence of grade 3 primary graft dysfunction (PGD) and a decreased postoperative survival during the first 1500 days of follow-up. The authors conclude that use of iNO weaning test may help to determine which patients with risk factors for PGD may go on to develop PGD.

This article outlines another possible role for the ever-so-controversial use of nitric oxide in lung transplantation. The controversy ranges from prevention to treatment of PGD. Several case series in the 1990s showed iNO to improve oxygenation in cases of primary graft dysfunction,(1-3) however a later study in rats showed that iNO could either improve or worsen the effects of hyperoxic lung injury. 4 And while iNO has been shown to transiently improve oxygenation in Acute Respiratory Distress Syndrome (ARDS) it has not improved mortality and actually increases the incidence of renal failure. 5 Currently there is not data to support the routine use of iNO for PGD prevention in lung transplantation. 6 The majority of evidence seems to show no benefit of empiric iNO for prevention of primary graft dysfunction. However, one study that did show benefit started iNO at the beginning of the case and ran it for 48 hours post-operatively. 7 Some of the other studies that did not show benefit only started iNO at reperfusion and ran it for a short time afterward. 8,9

Interestingly, the authors of our featured paper recently published a study outlining their success with intraoperative extubation of double lung transplant recipients. Their anesthetic protocol highlights similar techniques to this paper, and they note the use of “systematic iNO”. They were able to extubate 46% of their bilateral lung transplant recipients. 10 There are not many papers written on the topic of early extubation after lung transplantation. Could the iNO be contributing to their success? Will we ever know? The mystery continues.......

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