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Technique Article

Nitric Oxide on Extracorporeal Life Support-Circuit Modifications for a Safe Therapy

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Abstract: Nitric oxide (NO) incorporation into the sweep gas of the extracorporeal life support (ECLS) circuit has been proposed as a strategy to ameliorate the insults caused by the systemic inflammatory response. This technical study describes circuit modifications allowing nitric oxide to be incorporated into the circuit and describing and validating the oxygenator sweep flow rates necessary to achieve consistent safe delivery of the therapy. For patients requiring sweep rates less than 2 L/min, a simplified setup, incorporating a pressure relief valve/low flow meter in the gas delivery line, was placed in line between the blender/NO injector module and the NO sampling port/oxygenator. This setup allows titration of sweep to low flows without the need to blend in CO_2 while maintaining the manufacturer recommendation of a minimum 2 L/min of sweep gas to safely deliver NO without nitric dioxide (NO_2) buildup. This setup was tested three times at three different FiO_2 rates and eleven different desired low sweep flows to test for reproducibility and safety to build an easy-to-follow chart for making gas flow changes. For patients requiring oxygenator sweep rates greater than 2 L/min, the pressure relief valve/low flow meter apparatus is not needed. Maintaining consistent sweep rate and nitric oxide delivery is required in order to utilize this therapy in ECLS. We demonstrated gas delivery across all flow rates. There were no issues delivering 20 parts per million of NO and negligible NO_2 detection. The results from testing this setup were used to provide the specialist a chart at which to set the low flow meter to produce the desired flow rate at which the patient needs. This has been used clinically on 15 ECLS patients with success. **Keywords:** extracorporeal life support, extracorporeal membrane oxygenation, nitric oxide, thrombosis, platelet activation, inflammation, circuit modification, pressure relief valve. *J Extra Corpor Technol. 2022;54:142–7*

Nitric oxide (NO) incorporation into the sweep gas of the extracorporeal life support (ECLS) circuit has been proposed as a strategy to ameliorate the insults caused by the systemic inflammatory response (1,2). Other benefits of nitric oxide in the extracorporeal circuit may include platelet and leukocyte deactivation, inhibition of apoptosis, decrease myocardial injury, minimizing blood transfusions, and the reduction of acute kidney injury (1,2).

Utilizing the Mallinckrodt Ikaria INOmax DS_{ir} Plus (Mallinckrodt, Ikaria, Victoria, Australia), we describe our circuit modifications allowing nitric oxide to be incorporated into the ECLS circuit. We also describe the oxygenator sweep flow rates necessary to achieve consistent safe delivery of the therapy compared to previously reported use (3). This simplified model using a pressure relief valve may allow other ECLS teams to implement NO use safely and without the addition of carbon dioxide (CO_2). These guidelines have assisted our bedside ECLS specialists in consistently achieving desired parameters for blood gas goals of our patient population.

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DESCRIPTION

The Ikaria INOmax DS_{ir} Plus delivery system is typically used to deliver NO via the inspiratory limb of the patient's ventilator. This device was successfully incorporated into the ECLS circuit to allow NO to be added to the oxygenator gas delivery line at 20 ppm (parts per million). This device requires a minimum gas flow of 2 L/min for the injector module to accurately deliver the desired nitric oxide concentration and to minimize stasis which leads to nitrogen dioxide (NO_2) build up. Incorporating NO in infants who may require a lower sweep rate creates challenges requiring additional circuit modifications (2–4). One method is to set the sweep rate at 2 L/min and add supplemental carbon dioxide into the oxygenator gas delivery line to maintain desired blood gas carbon dioxide levels (2). An alternate method would be to design a system utilizing a second flow meter, where the NO supply rate could be set at 3 L/min, and a second flow meter could be set at the prescribed sweep rate while allowing excess gas and NO to be released into the atmosphere (3).

The ECLS system used at our facility is composed of a LivaNova SCPC centrifugal pump (LivaNova, London, UK), a custom tubing pack (Medtronic, Minneapolis, MN), Sechrist Gas Blender (Sechrist Ind, Anaheim, CA), and a Euroset AMG PMP oxygenator (Abbott, Pleasanton, CA). Our standard oxygenator gas delivery system consists of an air/oxygen Sechrist Gas Blender model 3500 with separate low/high flow meters. For patients requiring oxygenator gas sweep rates of greater than or equal to 2 L/min, the only circuit modifications are the following: addition of INOmax injector module in the gas delivery line 12 inches from the Sechrist blender, and placement of the sampling line using a 1/4-inch × 1/4-inch connector in the gas line at least 24 inches from the injector module

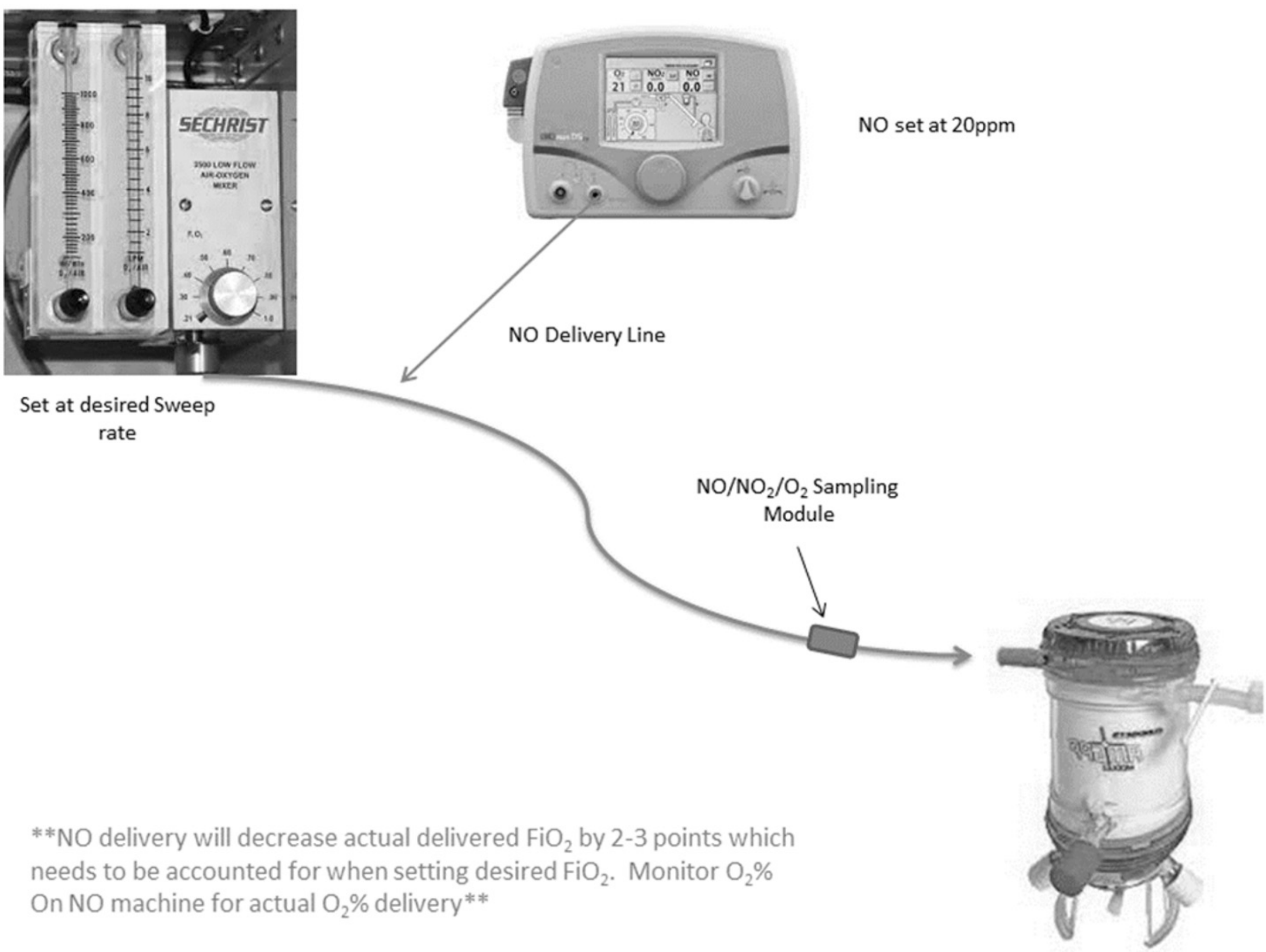

Figure 1. NO Setup for patients requiring sweep rates ≥2 L/min.

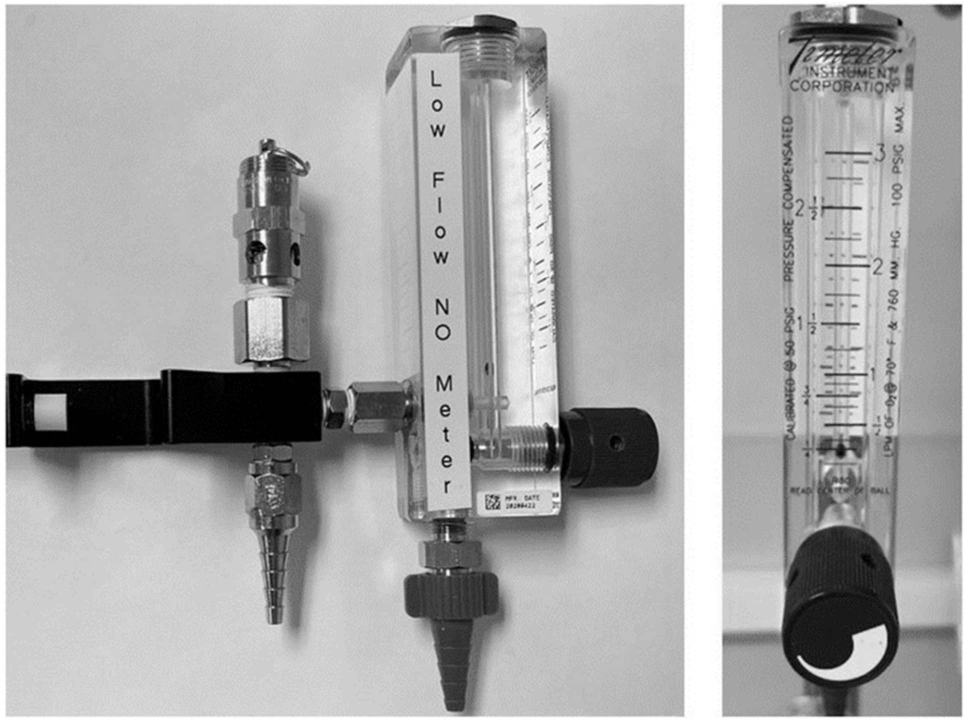

Figure 2. Flow meter with integrated pressure relief valve.

and 6 inches from the oxygenator gas inlet connection (Figure 1). The INOmax DS_{ir} Plus system is programed to sample the gas delivery line continuously at .23 L/min and needs to be accounted for when setting the desired oxygenator sweep gas flow rate. For patients requiring gas sweep rates less than 2 L/min, we augmented a model TB60 oxygen low flow meter (Allied Healthcare Products, St. Louis, MO) with an integrated pressure relief valve (Figure 2), which is placed 24 inches distal to the INOmax injector module and approximately 24 inches proximal to the NO sampling connector (Figure 3). For patients requiring Sechrist blender sweep rates less than 2 L/min, the Sechrist blender is set at 3 L/min and the TB 60 low flow meter is set at the desired sweep using the titration table below (Table 1). Excess gas is purged via the pressure relief valve. For example, if the patient needs a sweep of .5 L/min, then the remaining 2.5 L/min will blow off through the integrated pressure relief valve. When using the low flow configuration (Figure 3), it is especially important to account for the INOmax gas sampling rate of .23 L/min, which has already been accounted for in our flow table.

We validated the TB60 low flow configuration and constructed the desired flow table by testing the setup in a laboratory setting under varying conditions. With the Sechrist blender set 3 L/min and the flow setup placed in the gas delivery at the locations mentioned earlier, we analyzed set flow vs. measured flow, set NO (20 ppm) vs. measured NO, set fraction of inspired oxygen (FiO_2) vs. measured oxygen delivery, and NO_2 levels at 11 different TB 60 low flow meter sweep rates. Set flow vs. measured flow were analyzed three different times and the averages are represented in Table 2 and Figure 4, along with the standard deviation for each measurement. A sweep titration table was then constructed using the information (Table 1). A TSI digital airflow analyzer model 4076 (TSI Inc, Shoreview, MN) was used to measure the actual sweep rate at the oxygenator gas inlet. At each set flow rate, we also evaluated three different FiO_2 settings (.3, .5, and 1.0) and measured the effects on NO_2 and actual delivered oxygen concentrations. Across all conditions tested there were no issues delivering 20 ppm NO, the average NO_2 detected was .24 ppm, and the average delivered oxygen percentage was two to three points lower than what was set.

DISCUSSION

Nitric oxide was initially identified as a potential adjunctive therapy in wet circuit experiments where decreased β-thromboglobulin levels and increased platelet counts were observed (5). Subsequently, the application of iNO (inhaled nitric oxide) was demonstrated to be safe in application to polypropylene membrane oxygenators in terms of membrane integrity, nitrogen dioxide accumulation, and gas transfer (6). The findings of less platelet aggregation were replicated and electron microscope analysis revealed reduced cellular and fibrin depositions (7). The initial

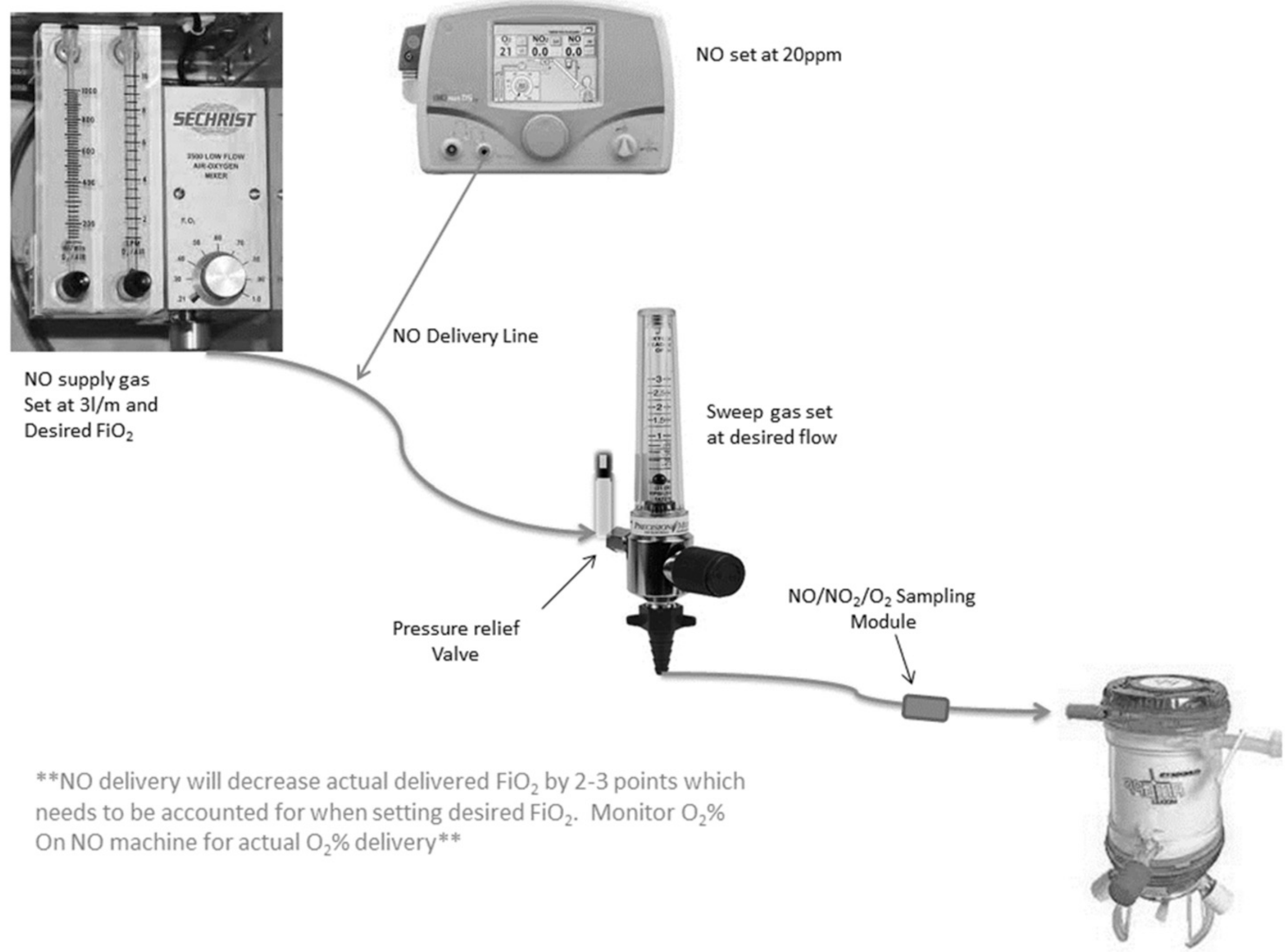

Figure 3. NO Setup for patients requiring sweep rates <2 L/min (low flow configuration).

clinical report was a randomized control trial from Melbourne, which demonstrated less low cardiac output syndrome, shorter length of stay, and less ECLS deployment with the application of iNO (2). Given this success, a multicenter randomized clinical trial is planned for pediatric cardiopulmonary bypass (8).

Table 1. Low flow sweep chart.

Desired Sweep (L/min)	Set Sweep (L/min)
.040	.500
.214	.750
.425	1.0
.531	1.25
.720	1.5
.906	1.75
1.10	2.0
1.28	2.25
1.48	2.5
1.64	2.75
1.84	3.0

Two methods have been described for the incorporation of NO gas to the ECLS oxygenator within the pediatric population. One method described by James et al. uses a sweep flow rate of 2.5–3.0 L/min, the minimum flow needed

Table 2. Desired sweep vs. set sweep data validation with standard deviation.

Average Set Sweep (L/min)	Average Measured Sweep (L/min)	SD
.500	.042	.006245
.750	.214	.007365
1.000	.364	.018751
1.250	.531	.02068
1.500	.720	.018239
1.750	.906	.018246
2.000	1.103	.017078
2.250	1.285	.01291
2.500	1.478	.065
2.750	1.640	.02
3.000	1.837	.00943

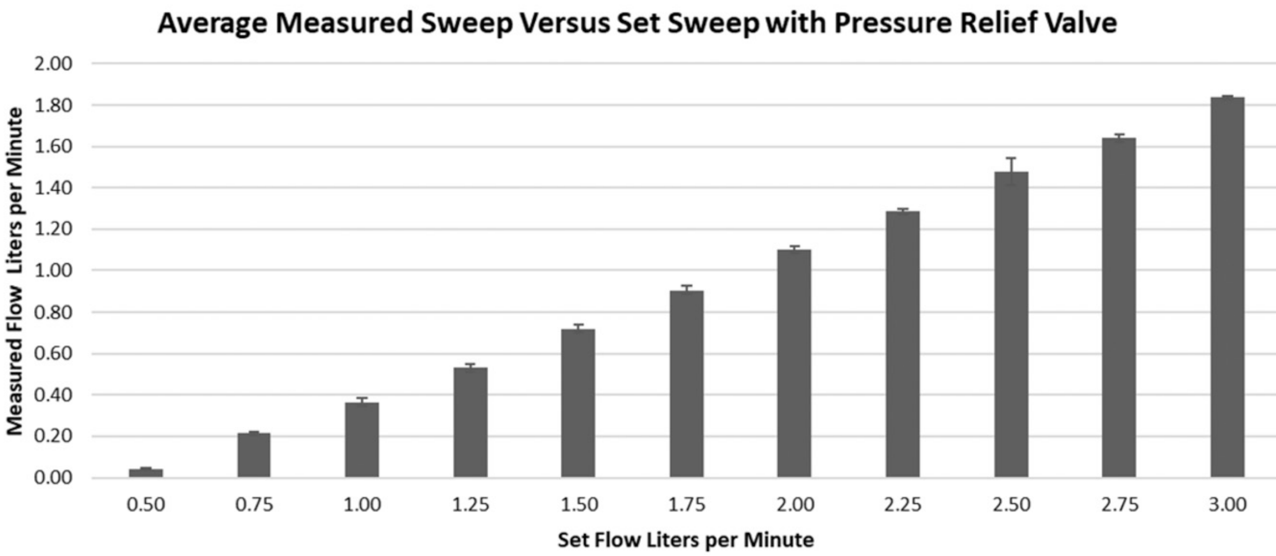

Figure 4. Measured flow as a function of set sweep with pressure relief valve with standard deviation of measured flow.

for adequate mixing and delivery of NO, with the addition of carbon dioxide to the sweep gas delivery line and titrated to maintain physiologic $PaCO_2$ levels (2). Clinicians at Royal Children's Hospital in Melbourne, Australia, used a pressure relief valve and a second flow meter to aid in the delivery of NO to the ECLS oxygenator on pediatric patients. Their method used a sweep gas rate of 3 L/min, which delivered the prescribed oxygen and NO concentrations to a secondary low flow meter that incorporated a pressure relief valve, thus allowing excess gas and NO above the needed oxygenator sweep rate to be released into the atmosphere (3). It was the opinion of the authors that the latter method to be the safest way to incorporate NO to the oxygenator sweep gas due to the elimination of the need to add carbon dioxide to the circuit.

The beneficial effects of nitric oxide on inflammation and coagulation in the context of extracorporeal circuits are diverse. The association with inflammation with the interactions of blood, foreign surfaces, and oxygen with further exacerbation by surgical trauma and reperfusion injury are well recognized (9,10). Recent study with porcine models has demonstrated amplification of the inflammatory response and platelet consumption with introducing air into the circuit, suggesting blood air interactions as an important driver of extracorporeal circuit inflammation (11). Furthermore, in recent animal bypass models, application of nitric oxide in the extracorporeal circuit sweep gas leads to decreased inflammation associated with the air–blood interface (12). The beneficial properties of nitric oxide on platelet activation have been well recognized, particularly in the context of mechanical circulatory support. Early reports demonstrated increased platelet survival and lower plasma beta-thromboglobulin levels, a marker of platelet degranulation, when nitric oxide was applied to the in vitro circuit (5,13,14).

Nitric oxide administered into the sweep of the extracorporeal oxygenator may offer numerous benefits. ECLS programs may routinely implement the use of NO gas in all patients. Attention must be given to how this therapy is introduced into an ECLS program. The potential benefits must be weighed against the costs of NO as well as risk of nitric dioxide exposure and methemoglobinemia. In this report, we share our circuit modification used on 15 patients over the last 12 months and how we validated consistent sweep flow with the addition of NO into the sweep gas, so that this approach could easily be adopted by other ECLS programs.

REFERENCES

1. Checchia PA, Bronicki RA, Muenzer JT, et al. Nitric oxide delivery during cardiopulmonary bypass reduces postoperative morbidity in children–a randomized trial. J Thorac Cardiovasc Surg. 2013;146: 530–6.
2. James C, Millar J, Horton S, et al. Nitric oxide administration during paediatric cardiopulmonary bypass: A randomised controlled trial. Intensive Care Med. 2016;42:1744–52.
3. Chiletti R, Horton S, Bednarz A, et al. Safety of nitric oxide added to the ECMO circuit: A pilot study in children. Perfusion. 2018;33: 74–6.
4. Bennett M, Thuys C, Augustin S, et al. The safe addition of nitric oxide into the sweep gas of the extracorporeal circuit during cardiopulmonary bypass and extracorporeal life support. J Extra Corpor Technol. 2018;50:260–4.
5. Mellgren K, Friberg LG, Mellgren G, et al. Nitric oxide in the oxygenator sweep gas reduces platelet activation during experimental perfusion. Ann Thorac Surg. 1996;61:1194–8.
6. Body SC, FitzGerald D, Voorhees C, et al. Effect of nitric oxide upon gas transfer and structural integrity of a polypropylene membrane oxygenator. ASAIO J. 1999;45:550–4.

7. Rauch ED, Stammers AH, Mejak BL. The effects of nitric oxide on coagulation during simulated extracorporeal membrane oxygenation. J Extra Corpor Technol. 2000;32:214–9.
8. Schlapbach LJ, Horton SB, Long DA, et al. Study protocol: NITric oxide during cardiopulmonary bypass to improve recovery in infants with congenital heart defects (NITRIC trial): A randomised controlled trial. BMJ Open. 2019;9:e026664.
9. el Habbal MH, Smith LJ, Elliott MJ, et al. Cardiopulmonary bypass tubes and prime solutions stimulate neutrophil adhesion molecules. Cardiovasc Res. 1997;33:209–15.
10. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: Pathophysiology and treatment. An update. Eur J Cardiothorac Surg. 2002;21:232–44.
11. Carr BD, Johnson TJ, Gomez-Rexrode A, et al. Inflammatory effects of blood-air interface in a porcine cardiopulmonary bypass model. ASAIO J. 2020;66:72–8.
12. Toomasian JM, Jeakle MMP, Langley MW, et al. Nitric oxide attenuates the inflammatory effects of air during extracorporeal circulation. ASAIO J. 2020;66:818–24.
13. Dunbar JM, Neufeld RR, Lebow LS, et al. Taking charge. The role of nursing administrators in removing restraints. J Nurs Adm. 1997; 27:42–8.
14. Hayashi Y, Sawa Y, Nishimura M, et al. Nitric oxide gas infusion to the oxygenator enhances the biocompatibility of heparin coated extracorporeal bypass circuits. ASAIO J. 1998;44:456–61.