Avaliação do Óxido Nítrico Exalado em Pacientes Submetidos à Revascularização do Miocárdio com Circulação Extracorpórea*

Evaluation of Exhaled Nitric Oxide in Patients Undergoing Myocardial Revascularization with Cardiopulmonary Bypass

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RESUMO

Amorim CG, Malbouisson LMS, Saraiva BM, Pedro FMS, Martins MA, Carmona MJC - Avaliação do Óxido Nítrico Exalado em Pacientes Submetidos à Revascularização do Miocárdio com Circulação Extracorpórea.

JUSTIFICATIVA E OBJETIVOS*: A circulação extracorpórea (CEC) pode causar disfunção pulmonar. As alterações inflamatórias podem afetar a liberação de óxido nítrico (NO). Objetivou-se avaliar o NO exalado em pacientes submetidos à revascularização do miocárdio (RM) com CEC.*

MÉTODO*: Foram estudados prospectivamente nove pacientes adultos submetidos à RM com CEC. Inicialmente, foi coletada amostra de ar para análise de NO no sistema que alimenta o aparelho de anestesia. A seguir, anestesia iniciada por via venosa com etomidato (0,3 mg.kg⁻¹), sufentanil (0,3 µg.kg⁻¹), pancurônio (0,08 mg.kg⁻¹) e mantida com isoflurano (0,5 a 1,0 CAM) e sufentanil (0,5 µg.kg⁻¹.h⁻¹). O volume corrente fixado a 8 mL.kg⁻¹, com FIO₂ de 0,6, exceto durante a CEC. Trinta minutos depois da indução, e trinta após a CEC, três amostras sequenciais de ar exalado foram colhidas para análise de NO, por quimioluminescência. Os dados foram analisados por meio do teste t de Student.*

$MÉTODO$ — rendering: O volume corrente fixado a 8 $mL.kg^{-1}$, com FIO_2 de 0,6.

RESULTADOS: *O valor do NO do ar ambiente foi de 5,05 ± 3,37 ppb. O NO exalado decresceu após a CEC, variando de 11,25 ± 5,65 ppb para 8,37 ± 3,17 ppb (p = 0,031).*

CONCLUSÕES*: A redução do NO exalado pós-CEC observada nesse estudo não permite confirmar o papel dessa molécula como marcador de lesão pulmonar. Entretanto, os variados graus de colapso do parênquima pulmonar, o método de obtenção dos dados, os fármacos utilizados, dentre outros, podem ter contribuído para a redução.*

Unitermos: CIRURGIA CARDÍACA: revascularização do miocárdio, circulação extracorpórea; COMPLICAÇÕES: hipoxemia, lesão endotelial, lesão epitelial; VENTILAÇÃO: controlada mecânica, óxido nítrico exalado.

SUMMARY

Amorim CG, Malbouisson LMS, Saraiva BM, Pedro FMS, Martins MA, Carmona MJC – Evaluation of Exhaled Nitric Oxide in Patients Undergoing Myocardial Revascularization with Cardiopulmonary Bypass.

BACKGROUND AND OBJECTIVES: *Cardiopulmonary bypass (CPB) can cause pulmonary dysfunction. Inflammatory changes may affect the release of nitric oxide (NO). The objective of this study was to evaluate exhaled NO in patients undergoing myocardial revascularization (MR) with CPB.*

METHODS: *This is a prospective study with nine adult patients undergoing MR with CPB. Initially, air samples were collected to analyze the presence of NO in the system that feeds the anesthesia equipment. Intravenous anesthesia was then initiated with ethomidate (0.3 mg.kg⁻¹), sufentanil (0.3 µg.kg⁻¹), and pancuronium (0.08 mg.kg⁻¹), and maintained with isoflurane (MAC from 0.5 to 1.0) and sufentanil (5 µg.kg⁻¹.h⁻¹). Tidal volume was fixed at 8 mL.kg⁻¹ and FiO₂ 0.6, except during CPB. Thirty minutes after induction and 30 minutes after CPB, three sequential samples of exhaled air were collected for NO analysis by chemiluminescence. Data were analyzed by the Student t test.*

RESULTS: *The level of NO in room air was 5.05 ± 3.37 ppb. Levels of exhaled NO decreased after CPB, varying from 11.25 ± 5.65 ppb to 8.37 ± 3.71 ppb (p = 0.031).*

CONCLUSIONS: *The reduction of exhaled NO after CPB observed in this study does not confirm the role of this molecule as a marker of pulmonary lesion. However, the different degrees of pulmonary parenchymal collapse, the method used to collect the data, and the drugs, among others, could have contributed for this reduction.*

Keywords: COMPLICATIONS: hypoxemia, endothelial lesion, epithelial lesion; SURGERY, Cardiac: myocardial revascularization, cardiopulmonary bypass; VENTILATION: controlled mechanical, exhaled nitric oxide.

Evaluation of Exhaled Nitric Oxide in Patients Undergoing Myocardial Revascularization with Cardiopulmonary Bypass (CPB)

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INTRODUCTION

In cardiac surgery, the inflammatory reaction produced by cardiopulmonary bypass (CPB) can lead to postoperative organic dysfunction[1]. Changes in pulmonary capillary permeability may vary from subtle changes in oxygenation to acute respiratory distress syndrome, with pulmonary vascular resistance increase and refractory hypoxemia, partly attributable to the loss of hypoxic pulmonary vasoconstriction (HPV) [2]. Ischemia and reperfusion seen during CPB can lead to endothelial damage and change in the production and release of nitric oxide (NO) [3,4].

Nitric oxide is a potent vasodilator and bronchodilator, and it interferes on the stages of inflammatory reactions by inhibiting platelet aggregation, besides other actions [5]. It causes vasodilation through the activation of soluble guanylate cyclase by binding with the iron in the heme group, which causes an increase in the intracellular production of cyclic 3,5-guanosine monophosphate (cGMP), and relaxing the vascular musculature [6]. Nitric oxide-induced vasodilation can avoid the accumulation of vascular damage mediators and inactivate free superoxide radicals generated by activated leukocytes [7].

In the lungs, NO is produced by the bronchial epithelium, vascular endothelium, interstitial macrophages, and bacteria in the bronchial tree [2]. However, there are controversies on how much of the exhaled NO comes from the endothelium or epithelium and the contribution of the upper airways (rhinopharynx), which can contribute with large amounts [8]. Some authors suggest that the amount of exhaled NO can be up to 50% higher in males [8,9].

Studies have associated exhaled NO to possible endothelial or epithelial lesions and the consequent postoperative pulmonary dysfunction, but that would be different in the post-CPB period, with some authors referring an increase in its concentration while others report a reduction [10-13]. The reasons for such discrepancies may be related with the different methods of collection used. However, studies evaluating the levels of exhaled NO in patients undergoing myocardial revascularization, considering possible interferences associated with variations in respiratory flow during mechanical ventilation and NO concentrations in the gas network of hospitals are lacking. The objective of this study was to evaluate possible changes in the concentration of exhaled NO during myocardial revascularization with CPB.

METHODS

The study was approved by the Scientific Commission of the Instituto do Coração (InCor) and by the Ethics Commission for Analysis of Research Projects (CAPPesq) of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

Nine patients with indication of elective myocardial revascularization (MR) with CPB, weighing from 40 to 90 kg, ages 15 to 70 years, height ranging from 150 to 180 centimeters, physical status ASA II and III, according to the criteria of the American Society of Anesthesiologists (ASA), participated in this prospective study. Individuals with clinical signs suggestive of congestive heart failure (CHF) greater than grade three according to the classification of the New York Heart Association, as well as those with physical status ASA greater than IV, with moderate surgical risk, greater than four according to Higgins [14] stratification criteria, or body mass index (BMI) greater than 35, were excluded from the study.

All patients received intramuscular midazolam, 0.1 to 0.3 mg.kg^{-1}, with a maximal dose of 15 mg, 30 minutes before induction of anesthesia.

Samples of compressed air from the hospital gas-delivery system were collected to analyze the levels of NO before beginning the procedure. Compressed air in this system is delivered by a compressor system and stored under high pressure in a cylinder whose final contents are free of oil and humidity, connected to a pressure regulator that supplies a fixed outlet of 4 kgf.cm^2.

In the operating room, patients were monitored with electrocardiogram at D_{II} and V_5 derivations, pulse oximeter, and invasive blood pressure.

Anesthetic induction was accomplished with the intravenous administration of 0.3 mg.kg^{-1} of ethomidate, 0.3 µg.kg^{-1} of sufentanil, and 0.08 mg.kg^{-1} of pancuronium, followed by manual ventilation with a unidirectional circuit with carbon dioxide absorber, and afterwards patients were intubated with a tracheal tube adjusted for the diameter of the trachea. Isoflurane, at an inhalational concentration adjusted for MAC of 0.5 to 1.0 with the aid of a gas analyzer, whose sample was collected close to the junction with the tracheal tube and 0.5 µg.kg^{-1}.h^{-1} of sufentanil administered by an infusion pump were used for maintenance.

Additional monitoring was instituted after anesthetic induction, such as $P_{ET}CO_2$ by continuous capnography, esophageal temperature, urine output, and right atrial pressure (CVP) by catheterizing the right internal jugular vein.

Patients were ventilated with a circular valve system with carbon dioxide absorber, according to resolution NBR/ABNT nº 10012, using a microprocessed electronic ventilator from the set of the Cícero® anesthesia equipment (Cícero; Dräger and Siemens Company, Lübeck, Germany) with a tidal volume (VT) of 8 mL.kg^{-1}, FiO$_2$ 0.6, 1:2 I:E ratio , respiratory rate (RR) 12 bpm, positive end-expiratory pressure (PEEP) 5 cmH$_2$O, adjusted to maintain $P_{ET}CO_2$ between 35 and 40 mmHg. Measurements were interrupted during CPB.

Sequential samples of exhaled air were collected in three balloons, which were appropriate for the task, 30 minutes after institution of controlled mechanical ventilation, to determine mean NO. Samples of nitric oxide were collected in a three-way system such that, at the beginning of inspiration the flow to the reservoir balloon used to collect the samples was interrupted and released at the beginning of expiration. When the balloons were filled, they were sent for determination of NO concentration by chemiluminescence on a Sievers® equipment (Sievers NOA 280 model, American Thoracic Society, 1999). To determine the exhaled flow, expiratory time, number of exhalations, and the time necessary to fill the 1.5 L balloon were considered. Nitric oxide was collected from the gas delivery system at a flow of 1 L.min^{-1}. Results of NO concentrations are expressed in nanoliter per liter or parts per billion (ppb).

Membrane oxygenator and non-pulsating roller flow (Braile, São José do Rio Preto, Brazil), perfusate with 1,500 mL of Ringer's lactate with 0.8 g.kg^{-1} of mannitol, and heparin were used during the CPB in the study population. Blood or blood products were not added.

Before cannulating the ascending aorta and right atrium, 500 IU.kg^{-1} of heparin were administered intravenously. Perfusion was maintained between 2 and 4 L.min^{-1} during controlled hypothermia, with esophageal temperature varying from 30° to 32° C. Mean arterial pressure was maintained between 60 and 70 mmHg during CPB. At the time of disconnection from CPB, patients were treated with dobutamine, 3 to 5 µg.kg^{-1}.min^{-1}; nitroglycerin, 10 to 80 µg.min^{-1}, or sodium nitroprusside, 0.5 to 1.0 µg.kg^{-1}.min^{-1}.

After supplementing the perfusate in the CPB circuit, any residual heparin was neutralized with 1 mg of protamine/100 IU of heparin.

Thirty minutes after reinstitution of controlled mechanical ventilation, after the end of CPB, other three samples of exhaled air were collected and all balloons, properly identified, were sent for NO analysis.

The sample size was calculated assuming that after CPB, exhaled NO concentrations would be reduced by 5 ppb, with a standard deviation of three ppb, α error of 0.05, and study power of 80% in the Student t test for bicaudal paired measurements. A sample size of at least six patients was proposed.

Demographic data were presented descriptively, and NO values before and after CPB were compared using means and standard deviation.

RESULTS

Tables I and II show the demographic data of patients and the characteristics of exhaled NO collection, respectively.

Figure 1 shows the results of NO analysis in the compressed air network pre- and post-CPB. The level of NO in the compressed air of the gas network was 5.05 ± 3.37 ppb.

The concentration of exhaled NO decreased after CPB, varying from 11.25 ± 5.65 ppb pre-CPB to 8.37 ± 3.17 post-CPB (p = 0.031) when extraction of environmental NO for analysis was not considered.

Table I – Demographic Data of the Study Patients

	Mean	Standard Deviation	Minimal	Maximal
Age (years)	61.8	9.5	47	76
Weight (kg)	79.5	16.3	41.7	98
Height (cm)	164.5	8.6	148	173

Table II – Characteristics of the Collection of Exhaled Nitric Oxide

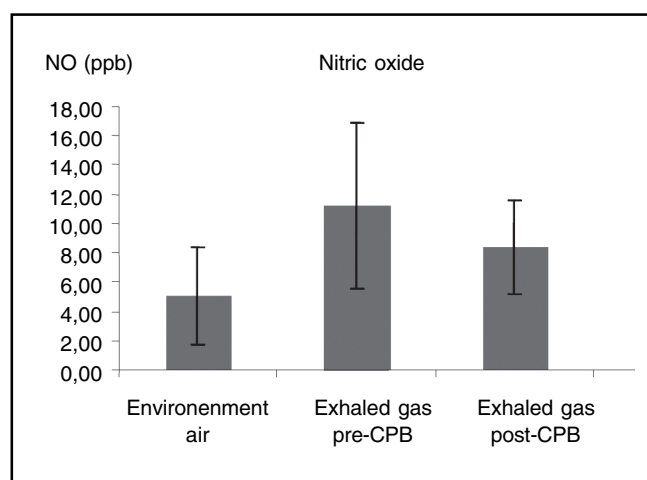|	Mean	SD	Minimal	Maximal
Number of exhalations	23.66	2.44	20	29
Total time (sec)	73.1	7.21	68	98
Exhalation flow (L.sec^{-1})	0.020	0.002	0.015	0.022

Figure 1 – Distribution of Mean Values in the Air, Pre-, and Post-CPB.

Table III – Comparison among Methods of Collection of Exhaled Nitric Oxide

	Present study	Tonberg et al. (2004)	Ishibe et al. (2000)	Sheppard et al. (2004)	Beghetti et al. (1998)
Analysis	Off-line	On-line	On-line	On-line	On-line
VT (mL.kg^{-1})	8	4	12	■	■
RR (bpm)	12	20	8-10	■	■
Ventilation	Volume-controlled	Volume-controlled	Volume-controlled	Pressure-controlled	■
Post-CPB moment	30 min	2 h	6 h	■	30 min
Parameters	[NO] in 1.5 L balloon	pNO for 30 sec and NO output	mNO, pNO, VNO and Q	VNO in a prolonged exhalation	[NO] collected in 20 mL
Values	[NO] =11.3 ppb	pNO = 3.2 ppb Output = 12.2 (ppb.min^{-1})	mNO = 5.7 ppb pNO = 15.4 ppb and VNO=29.16 ppb.min^{-1}	VNO = 2.58 ppb.sec^{-1}	[NO] = 7.0 ppb

VT = tidal volume; RR = respiratory rate; [NO] = concentration of NO; pNO = peak NO concentration; mNO = mean concentration; VNO = NO release rate; Q = ventilatory flow rate

DISCUSSION

The results of the study showed that the compressed air used had a variable concentration of NO, besides a statistically significant reduction in exhaled NO when pre- and post-CPB levels were compared ($p < 0.05$). When including the analysis of NO in the gas delivery system for the anesthesia device, some measurements of exhaled NO, pre- or post-CPB, presented variable results. This observation generated negative means and elevated the standard deviations. Although the final calculation of NO is not simply the result of this subtraction, both analyses (with and without subtracting NO levels in compressed air) demonstrated a tendency for a reduction in exhaled NO levels after CPB ($p < 0.05$). On the other hand, it is possible that the differences found in the levels of the gas delivery network might have not been properly evaluated, since the conditions of flow and time of collection were not the same and were not the objective of this study. Those considerations indicate perspectives for new studies.

Since the molecule of NO is an important element related with the physiology and pathophysiology of microcirculatory mechanisms of the respiratory system, it has been extensively studied [7,10,15-17]. In many studies it is considered an inflammatory marker of the airways, since patients with asthma and other lung diseases have elevated levels of exhaled NO [2,18]. In asthma patients, it seems to indicate both disease exacerbation and the dose-response relationship in the treatment with corticosteroids, especially inhaled [2,18,19]. When the maintenance dose is not adequate, the patient becomes refractory to treatment, or in the case of a fast reduction in the maintenance dose of patients who remain stable during treatment, substantial changes in exhaled NO levels are seen, indicating its interference in endothelial tonus [19]. Nitric oxide also seems to be elevated in patients with bronchiectasis or decompensated chronic obstructive pulmonary disease (COPD) [20-22]. However, regarding myocardial revascularization, the literature does not agree on the behavior observed after CPB, or on the definitive mechanisms that would be implicated in those changes [10,11,16,23-25]. It is known that ventilation patterns in patients on mechanical ventilation are related with the levels of exhaled NO [16]. Changes in minute ventilation (V_m), secondary to changes in respiratory rate (RR) or tidal volume (VT), lead to non-linear changes in exhaled NO levels. Tornberg et al. [10] observed a reduction in post-CPB exhaled NO, both on what they considered as NO output (NO concentration × exhaled airflow × 60) and mean NO peaks (mNO) extracted from reading the curve during the expiratory flow. Unlike the present study, in which off-line measurements were used, those authors used on-line measurements and obtained mNO of 3.2 ppb.L^{-1} and output of 12.2 ppb.min^{-1}, as can be seen in table III, which compares collection methods among this and other studies. Using the same proposal as Tonberg et al. [10], if the pre-CPB level obtained here (11.3 ppb) were considered equivalent to the output, 9.4 ppb.L^{-1} would correspond to the mean study level (*versus* 3.2 ppb.L^{-1}). This difference could possibly be secondary to the exhaled flow, which in the present case was 0.020 L.sec^{-1}, while theirs was 0.063 L.sec^{-1}, obtained using the same equation as before where maintaining the output, mean NO levels would be inversely proportional to the flow. In addition, comparing ventilation data, one observes that the tidal volume (VT) in the present study was greater than in their study (Table III). On the other hand, they used a higher respiratory rate (RR). Thus, the higher VT justifies according to Harefield's [16] group lower levels of exhaled NO or in this case lower output, corroborating this line of thought. Similarly, the higher RR used by those authors should also lead to lower exhaled NO levels when compared with the present study, what was not the case. Even with their higher

RR and the higher VT of the present study, the equation showed higher output (12.2 ppb.min^{-1} *versus* the hypothetic 11.3 ppb), which should also be due to the flow.

Certainly, the variability of the collection methods as shown in table III translates into different results. According to this viewpoint, and using the same line of thought applied in the comparison with the study of Tonberg et al. [10], considering the mean level of 5.7 ppb (*m*ppb) obtained by Ishibe et al. [11] the flow in this case would be 0.085 L.sec^{-1}. Analyzing those results, one observes that the higher NO output (V$_{NO}$ corrected for one minute) – 29.16 ppb.min^{-1} – could also be related with the expiratory flow used for the reading, which was higher than in the present study and in the study of Tonberg et al. [10]. Differences in mean values are probably secondary to the V$_{NO}$/flow ratio and, therefore, the values obtained by Ishibe et al. [11] were between those of Tonberg et al. [10] and the present study.

Although Sheppard et al. [12] did not specify the ventilation parameters used, they mentioned the use of pressure-controlled ventilation (PCV), through which they collected the samples based on a 30-second ventilator pause followed by a prolonged expiration (Table III). The technique of interrupting ventilation followed by a prolonged exhalation increases the exhaled NO curve and maintains it elevated throughout the observation period and, therefore, peak NO levels could be as high as 35 to 40 ppb, which does not reflect the true NO concentration as a normal exhalation does [16,26].

Nitric oxide concentrations in the airways seem to increase when RR or VT is decreased or when the I:E ratio is increased. During prolonged inspiration or exhalation, it is possible to measure mean and peak concentrations, and also the area under the NO release curve. Besides, the plateau of the NO curve seems to occur approximately 20 to 30 seconds, during the ventilator pause, indicating higher values during sustained expiration when compared to inspiration [16]. This detection during inspiration seems to suggest its continuous production/release also observed in the bronchial epithelium [8].

Several studies have emphasized the importance of the flow-dependency mechanism for collection and analysis of exhaled NO concentrations. The European Respiratory Society (ERS) and the American Thoracic Society (ATS) recommend constant expiratory flow and decontamination of NO from the upper airways in patients with spontaneous ventilation [26]. In patients in controlled ventilation, ventilator parameters (type of ventilation, I:E ratio, PEEP, tidal volume, and contamination with inspired air) should be considered [16,26].

On the other hand, evaluation of the behavior of NO in patients undergoing CPB, especially diabetics or patients using the so-called NO donors (nitroglycerine, sodium nitroprusside, and nitrates), should consider those aspects as relevant. In diabetics, the basal level of microcirculatory stress that produces damage mediators, which combine with superoxide anions to form peroxynitrite, leads to NO consumption [27,28]. Both nitroglycerine and sodium nitroprusside,

routinely used, are exogenous NO donors, behaving as antioxidants of radicals produced during CPB, and inhibiting the endogenous production of NO [27,28]. Tonberg et al. [10] observed a reduction in the response of exhaled NO to nitroglycerin infusion, attributing this response either to a reduction in the conversion of nitroglycerin to NO or to an increase in the consumption of NO by free radicals produced during CPB. Some authors have also considered that the type of flow produced by the CPB equipment may interfere with basal NO release [29,30]. During non pulsating CPB, terminal capillaries tend to close as a result of the reduction of the contact with the vessel walls [29,30]. The endothelial release of NO, considered physiological and produced by the stimulation of *eNOS* (endothelial nitric oxide synthetase), seems to be a function of the frequency and amplitude of the pulsating flow [29,30].

Variable degrees of post-CPB atelectasis are related with different pulmonary conditions with the consequent change in gas exchange [31-33], which are also relevant in the evaluation of NO. The reduction in post-CPB exhaled NO can be associated with a reduction in the PaO$_2$/FiO$_2$ ratio, as well as with an increase in the alveolo-arterial gradient (P$_{(A-a)}$O$_2$) [10]. Changes in pulmonary compliance have also been associated with this post-CPB reduction [11]. However, inferences on the effects of different degrees of post-CPB atelectasis on variations in exhalation flow and levels of exhaled NO cannot be found in the literature. Those considerations need to be better understood. If changes in ventilation pattern are related with the curve of exhaled NO, they could become relevant not only during its observation in the post-CPB phase, but also in any major surgery in which precise ventilator monitoring is fundamental, making NO relevant for the detection of sudden changes, may they be epithelial, endothelial, or purely mechanical.

From what was exposed, there is an unquestionable relationship between the production and basal release of NO and the rupture of the physiological mechanisms of gas exchange caused by CPB. Once established, this connection will show its relevance as an online marker of perioperative pulmonary function. However, since more conclusive data are not available, this inference is hasty and certainly NO will continue to be the focus of extensive studies.

The limitations of the present study are related to the lack of distinction between groups of diabetic and non-diabetic patients, more judicious investigation of pulmonary function or inflammatory response parameters, and the lack of quantification of drugs used that have the potential to interfere with basal NO release. Although the study population was considered statistically normal, the paired test with 8 degrees of freedom revealed a low power ($\alpha < 0.800$), indicating the impossibility of detecting differences due to the sample size. To conclude, changes in exhaled NO after cardiopulmonary bypass is multifactorial, and the preoperative condition of patients, effects of CPB on inflammatory activity, variable degrees of pulmonary parenchymal collapse, and the data-collection method should be considered.

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RESUMEN

Amorim CG, Malbouisson LMS, Saraiva BM, Pedro FMS, Martins MA, Carmona MJC - Evaluación del Óxido Nítrico Exhalado en Pacientes Sometidos a la Revascularización del Miocardio con Circulación Extracorpórea.

JUSTIFICATIVA Y OBJETIVOS: *La circulación extracorpórea (CEC), puede causar una disfunción pulmonar. Las alteraciones inflamatorias pueden afectar la liberación de óxido nítrico (NO). Se buscó evaluar el NO exhalado en pacientes sometidos a la revascularización del miocardio (RM) con CEC.*

MÉTODO: *Se estudiaron prospectivamente nueve pacientes adultos sometidos a la RM con CEC. Inicialmente fue recolectada una muestra de aire para el análisis de NO en el sistema que alimenta el aparato de anestesia. A continuación, se inició la anestesia por vía venosa con etomidato (0,3 mg.kg⁻¹), sufentanil (0,3 μg.kg⁻¹), pancuronio (0,08 mg.kg⁻¹) y se mantiene con isoflurano (0,5 a 1,0 CAM) y sufentanil (0,5 μg.kg⁻¹.h⁻¹). El volumen corriente fijado fue 8 mL.kg⁻¹, con FiO2 de 0,6 excepto durante la CEC. Treinta minutos después de la inducción y treinta minutos después de la CEC, tres muestras secuenciales de aire exhalado fueron recogidas para análisis de NO, por quimioluminescencia. Los datos fueron analizados por medio del test t Student.*

RESULTADOS: *El valor del NO del aire ambiente fue de 5,05 ± 3,37 ppmm. El NO exhalado se redujo después de la CEC, variando de 11,25 ± 5,65 ppmm para 8,37 ± 3,17 ppmm (p = 0,031).*

CONCLUSIONES: *La reducción del NO exhalado pos-CEC, observada en este estudio, no permite confirmar el papel de esta molécula como marcador de lesión pulmonar. Sin embargo, los variados grados de colapso del parénquima pulmonar, el método de obtención de los datos, y los fármacos utilizados, entre otros, pueden haber contribuido para esa reducción.*