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Original Article

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Vedat Eljezi, Laetitia Rochette[1], Christian Dualé[2], Bruno Pereira[3], Henri Boby[4], Jean Michel Constantin[5]

Department of Perioperative Medicine, CHU Gabriel Montpied, Clermont-Ferrand, [1]Department of Perioperative Medicine, CHU Estaing, Clermont-Ferrand, [2]Clinical Pharmacology Center (Inserm CIC 1405) CHU Clermont Ferrand, Clermont Ferrand, [3]Biostatistics Unit, CHU Gabriel Montpied, Clermont-Ferrand, [4]Centre Jean Perrin, Clermont-Ferrand, [5]Department of Anesthesiology and Critical Care, Pitié-Salpêtrière Hospital, Sorbonne University, GRC 29, AP-HP, DMU DREAM, Paris, France

ABSTRACT

Background: The aim of this study was to examine the action of inhaled nitric oxide in the patients with pulmonary hypertension administered with a face mask before anesthesia induction.

Methods: Ten adult patients scheduled for heart surgery with sternotomy were included in this prospective, interventional, single centre study. The inclusion criteria were patients scheduled for heart surgery with sternotomy with cardiopulmonary bypass (CPB), aged >18 years which presents a pulmonary hypertension (PH) (class 2 or 3 according to the Dana Point classification) with systolic pulmonary arterial pressure (PAPS) >40 mmHg diagnosed by preoperative right cardiac catheterization or by transthoracic echocardiography. The exclusion criteria were: heart transplant, PH of type 1, 4, 5, according to the Dana Point classification, methemoglobin reductase deficit, incapacity to understand the protocol and sign the consent.

Results: The administration of iNO decrease pulmonary hypertension ($P < 0,001$ compared to room air; $P = 0,01$ compared to pure oxygen administration). The iNO administration did not improve arterial blood oxygenation. The hyperoxia, decrease the cardiac index even with right ventricular post charge decrease. The increased blood oxygenation content cause systemic vascular vasoconstriction and decrease the peripheral oxygen extraction showed with VO_2 linear increase ($P < 0,001$).

Conclusions: The administration of inhaled nitric oxide with a face mask before anaesthesia induction is safe and effective method to reduce pulmonary hypertension. The oxygen and hyperoxia influences the systemic vascular resistance and peripheral oxygen consumption.

Keywords: Anesthesia induction, inhaled nitric oxide, pulmonary hypertension

Address for correspondence: Dr. Vedat Eljezi, Praticien Hospitalier. CHU Clermont-Ferrand, Pôle Médecine Périoperatoire, Chirurgie Cardio-Vasculaire, F-63003 Clermont-Ferrand, France.
E-mail: veljezi@chu-clermontferrand.fr
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INTRODUCTION

Pulmonary hypertension (PH) is a frequent pulmonary disease that represents an independent morbidity and mortality factor in patients who need surgery.[1-4]

Perioperative morbidity represents 25–42% of PH patients,[5] thus accurate preoperative assessment and diligent anesthetic management are crucial for the best outcome.[1] The PH patients had a significantly increased risk for hemodynamic instability, heart failure, postoperative sepsis, and respiratory failure.[6] Acidosis, hypercapnia, hypoxemia, hypothermia, increased sympathetic activity, and arrhythmia are factors that increase pulmonary vascular resistance (PVR) and pulmonary pressures, deteriorate right

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ventricular function, and lead to hemodynamic collapse and death.[4,7] For all these reasons, the induction of anesthesia and the initiation of mechanical ventilation are challenging and critical moments in perioperative management. The anesthetic-agent-induced systemic vasodilatation and mechanical ventilation can lead to a significant drop in mean arterial pressure, reduce coronary perfusion pressure, and affect right ventricular contractility.[6] The most dangerous perioperative complication is hypotension due to right ventricular failure from the exacerbation of PH.[5] The anesthesia administration may expose patients to apnea and hypoventilation, hypoxemia, fluctuations of body temperature, hypotension, and sympathetic stimulations.[8] Oxygen is systematically used before anesthesia initiation to increase oxygen reserves and safe apnea.[9] Nitric oxide (NO), an endogenous mediator produced from the vascular endothelium, is a powerful vasodilator and is used in intensive care through inhalation (iNO) as a selective pulmonary vasodilator.[10-13] The iNO decreases the PVR and the shunt effect, and it improves oxygenation by the optimization of the ventilation-perfusion ratio.[12-14] The short lifetime of iNO (approximately 6 s) allows a fast metabolism without inducing any undesirable effects, such as systemic hypotension.[15]

We hypothesize that iNO added to oxygen should decrease pulmonary artery pressure and avoid PH crisis during anesthesia induction.

MATERIALS AND METHODS

This prospective, interventional, single-center trial was approved by the regional research ethics committee (*CPP Sud-Est VI, date December 04, 2015, Axelle Van Lander*) and registered with EudraCT (N°: 2014-003338-15) and on ClinicalTrials.gov (N°: NCT02345616).

The inclusion criteria were that patients must be scheduled for heart surgery with sternotomy and cardiopulmonary bypass (CPB), be aged >18 years with PH class 2 according to the Dana Point classification, and should have a systolic pulmonary arterial pressure (PASP) of >40 mmHg diagnosed by preoperative right cardiac catheterization or by transthoracic echocardiography. The exclusion criteria were patients who have had a heart transplant, have a PH of type 1, 4, or 5 according to the Dana Point classification, have methemoglobin reductase deficit, or have an incapacity to understand the protocol and sign their consent.

Patients received a detailed explanation of the study during preoperative consultation and have signed their consent according to the modalities described by the Code of Public Health System.

On the evening before surgery and 1 h before anesthesia, the patients received 1mg.kg^{-1} of hydroxyzine. Upon arrival at the operating theatre, they were equipped with one large peripheral intravenous line, a radial arterial line, five-lead electrocardiography, a bispectral index monitor, a pulse-oximetry, and a muscular relaxation monitoring. A central venous catheter and a pulmonary artery catheter (PAC) were inserted under local anesthesia. The right internal jugular vein was localized with the help of an ultrasound machine equipped with a high-frequency linear probe. After administration of local anesthesia at the right jugular region, a central venous catheter and a 7.5F volumetric continuous cardiac output pulmonary artery catheter (Edwards Lifesciences Corporation, One Edwards Way, Irvine, CA 92614) were inserted under the out-of-plane ultrasound-guided technique. The PAC was connected to a Vigilance II monitor (Edwards Lifesciences Corporation, One Edwards Way, Irvine, CA 92614). Arterial blood gas was realized in room air. The mixed venous oxygen saturation (SvO2) measurement was performed and *in-vivo* calibration was performed on the Vigilance II monitor. Before proceeding to measurements, a 3-min pause was made to obtain stabilized hemodynamic measurement data as recommended by the Vigilance II monitor constructor.

We measured the following hemodynamic parameters: heart rate (HR), systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), PASP, pulmonary arterial mean pressure (PAMP), pulmonary arterial diastolic pressure (PADP), SvO_2, continuous cardiac output (CCO), cardiac index (CI), right ventricular end-diastolic volume (RVEDV), right ventricular ejection fraction (RVEF), and stroke volume (SV). Based on these measurements, we calculated the following hemodynamic parameters: systemic vascular resistance (SVR), oxygen delivery (DO_2), oxygen consumption (VO_2), and the PAMP/MAP ratio. We measured the following respiratory parameters: peripheral oxygen saturation (SpO_2), inspired oxygen fraction (FiO_2), expired oxygen fraction (FeO_2), minute volume (MV), pH, arterial oxygen saturation ($SatO_2$), the partial pressure of arterial oxygen concentration (PaO_2), the partial pressure of carbon dioxide arterial concentration ($PaCO_2$), and methemoglobin concentration (MetHb).

All the hemodynamic and respiratory measurements were performed initially at room air which corresponds to T0. Afterward, we started oxygenation with a face mask at 10

L/min (20 ppm) of 100% oxygen via a closed breathing circuit while monitoring the patient's spirometry and other respiratory parameters [Figure 1]. All the hemodynamic and respiratory parameters were obtained every minute for 5 min (T1, T2, T3, T4, and T5). A second arterial blood gas analysis was performed at the end of T5. The iNO at 1.2 L/min was added to oxygen from 6 min to 10 min (T6, T7, T8, T9, T10). All the hemodynamic and respiratory parameters were noted. A third arterial blood gas analysis was performed at the end of the T10 [Figure 2]. After T10 the anesthesia induction was done in the standard way. The iNO weaned progressively after anesthesia induction and orotracheal intubation.

Statistical analysis

Statistical analysis was performed using Stata software, version 13 (StataCorp, College Station, TX, US). The tests were two-sided with a type I error set at $\alpha = 0.05$. Quantitative data were presented as the mean ± standard deviation (SD) or the median (interquartile range) according to statistical distribution (assumption of normality assessed by using the Shapiro-Wilk test). To consider between-patient and within-patient interaction (due to several measures for a single subject), random-effects for correlated measures (random intercept and slope with independent covariance structure) were performed, rather than the usual statistical tests that would not be appropriate due to the hypothesis of independence data not being verified. The normality of residuals from these models has been studied using the Shapiro-Wilk test. When appropriate, a logarithmic transformation was proposed to achieve the normality of dependent data. A Sidak's correction of the type I error was applied to consider multiple comparisons.

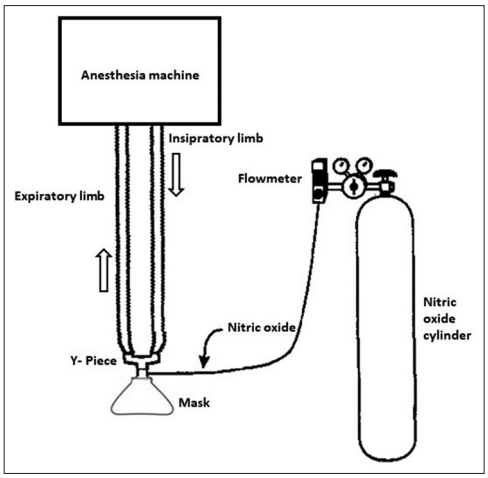

Figure 1: Figure diagram of the circuit used to show the iNO delivery

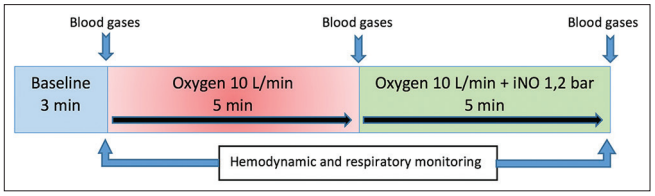

Figure 2: Flow chart

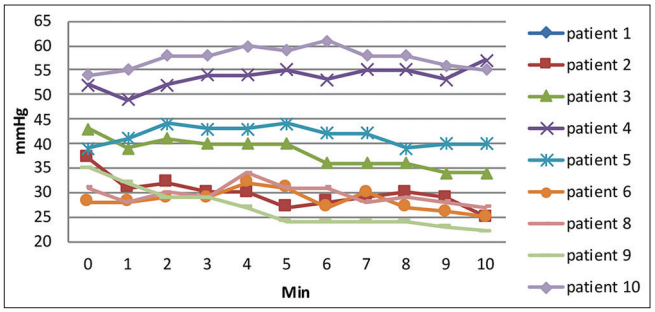

Figure 3: Mean pulmonary arterial pressure

RESULTS

Ten patients were included in the study (3 males and 7 females). The patient characteristics are presented in Table 1. The respiratory and oxygenation parameters measured in room air, after 5 min of oxygen and iNO breathing are shown in Table 2. A 100% hemoglobin saturation in all patients breathing oxygen with a face mask was achieved after 3 min. The addition of iNO to oxygen did not further increase oxygenation as expected. The complete hemodynamic parameters are shown in Table 3. The oxygen alone did not decrease PAMP. The addition of iNO decreased PAMP and PADP compared to room air ($P = 0.01$) and oxygen ($P < 0.001$), as presented in Table 3 and Figure 3. The PAMP and PADP decrease, against all expectations, was associated with a slight increase of RVEDV, a slight decrease of RVEF, and a slight decrease of the CI in the second part when iNO was added to oxygen. The increased arterial blood oxygenation increased SvO_2 and decreased linearly the VO_2 ($P < 0,001$).

DISCUSSION

Inhaled nitric oxide therapy as a selective pulmonary vasodilator in cardiac surgery has been one of the most significant pharmacological advances in managing pulmonary hemodynamics and life-threatening right ventricular dysfunction and failure.[16,17] To our knowledge, this is the first study that evaluates every step-in real-time the effect of oxygen and iNO in respiratory and hemodynamic parameters before another intervention like anesthesia or surgery, measured with a precise accuracy with the help of a volumetric pulmonary catheter.

The primary findings of this study were as follows: 1) oxygen did not decrease pulmonary pressure; (2) the

Table 1: Patients characteristics

Age	Sex	BMI	Disease	SPAP	Euroscore II
44	F	26,8	MVS	65	1,99
72	F	21,2	MVS, AVS, TI	48	3,63
71	F	28,6	AVS	81	3,07
81	F	25,25	MVS, AVS, TI	80	11,38
59	M	38,8	AVS	50	2,09
72	F	31,3	AVS	66	5,67
64	M	29,4	CABG	48	3,95
63	M	23,3	MI, TI	47	32,13
67	F	25,25	MVS	69	1,81
81	F	28,2	MI, TI	74	1,81

Body mass index (BMI); Mitral valve stenosis (MVS); Aortic valve stenosis (AVS); Tricuspid insufficiency (TI); Coronary artery bypass graft (CABG); Mitral insufficiency (MI); Systolic pulmonary artery pressure (SPAP)

addition of iNO to oxygen decreases pulmonary pressure; 3) the addition of iNO to oxygen did not further improve oxygenation through improved ventilation-perfusion ratio; 4) the increase of arterial blood oxygen content, decreases peripheral oxygen consumption.

Pure oxygen administration increases PaO_2 and, progressively, the FeO_2. The addition of iNO to O_2 should logically further increase the PaO_2 by improving the ventilation-perfusion ratio as described before.[13] This did not happen to our patients, the PaO_2 does not increase further with iNO. This can be explained since our patients are not hypoxemic, their basic PaO_2 is 77 mmHg in room air. This phenomenon is emphasized in the review of Rao

Table 2: Respiratory parameters

Parameter	Number of patients	Room air		O_2		O_2 and iNO		
	n	Mean	SD	Mean	SD	Mean	SD	p//O_2
SpO_2	10	95,6	5,3	99,3	2,5	100	0	0,1
FiO_2	10	-	-	97,2	5	97,8	2,2	0,28
FeO_2	10	-	-	81,2	14,4	73,5	11,3	0,001
MV	10	-	-	6,1	2,3	8	2,7	< 0,001
pH	10	7,45	0,06	7,45	0,07	7,45	0,01	0,52
Sat O_2	10	95,5	5,1	99,9	0,1	99,9	0,1	0,99
PaO_2	10	77,7	19,6	385,6	143,8	378,7	112,5	0,81
$PaCO_2$	10	36	6,48	35,1	8,22	33,9	8,8	0,47
MetHb	10	1,25	0,18	1,1	0,22	1,24	0,19	0,01

Respiratory parameters: peripheral oxygen saturation (SpO_2), inspired oxygen fraction (FiO_2), expired oxygen fraction (FeO_2), minute volume (MV), pH, arterial oxygen saturation ($SatO_2$), partial arterial oxygen concentration (PaO_2), partial carbon dioxide arterial concentration ($PaCO_2$), and methemoglobin concentration (MetHb).

Table 3: Hemodynamic parameters

	Room air	O_2	*P*	O_2 and iNO	p // RA	p // O_2
SAP	127.1 ± 20.7, *n* = 9	127.8 ± 19.0, *n* = 45	0.64	126.1 ± 16.3, *n* = 45	0.47	0.04
DAP	63 ± 12.1, *n* = 9	64 ± 11.2, *n* = 45	0.24	64.0 ± 11.3, *n* = 45	0.22	0.92
MAP	86.2 ± 11.6, *n* = 9	87.1 ± 10.3, *n* = 45	0.26	86.5 ± 9.8, *n* = 45	0.76	0.16
HR	84 ± 13.6, *n* = 9	83 ± 13.1, *n* = 45	0.52	82.1 ± 13.5, *n* = 45	0.22	0.33
PASP	56.9 ± 15.3, *n* = 8	56.2 ± 20.1, *n* = 40	0.75	55.3 ± 25.9, *n* = 40	0.49	0.52
PADP	28.2 ± 4.9, *n* = 8	27.4 ± 6.2, *n* = 40	0.3	25.4 ± 6.4, *n* = 40	0.001	<0.001
PAMP	39.9 ± 9.3, *n* = 8	39.0 ± 11.0, *n* = 40	0.36	36.9 ± 12.4, *n* = 40	0.001	<0.001
CI	2.36 ± 0.41, *n* = 8	2.34 ± 0.31, *n* = 40	0.67	2.29 ± 0.34, *n* = 40	0.14	0.07
RVEF	27.3 ± 8.5, *n* = 6	25.5 ± 4.9, *n* = 30	0.07	23.8 ± 6.2, *n* = 30	0.001	0.004
RVEDV	112.8 ± 21.2, *n* = 6	121.5 ± 20.6, *n* = 30	0.002	127.4 ± 21.4, *n* = 30	<0.001	<0.001
SvO_2	67.4 ± 8.0, *n* = 8	75.9 ± 7.4, *n* = 40	<0.001	79.6 ± 7.3, *n* = 40	<0.001	<0.001
CVP	11.4 ± 6.1, *n* = 9	12.4 ± 6.2, *n* = 45	0.11	11.4 ± 5.7, *n* = 45	0.97	0.005
PAMP/MAP	0.45 ± 0.10, *n* = 8	0.44 ± 0.11, *n* = 40	0.22	0.42 ± 0.13, *n* = 40	0.001	<0.001
ISVR	2683 ± 695, *n* = 8	2625 ± 352, *n* = 40	0.5	2714 ± 417, *n* = 40	0.71	0.07
SV	28.2 ± 6.3, *n* = 8	28.2 ± 4.9, *n* = 40	0.96	28.0 ± 5.3, *n* = 40	0.79	0.59
DO_2	356.8 ± 77.3, *n* = 8	369.8 ± 53.4, *n* = 40	0.16	362.4 ± 48.9, *n* = 40	0.54	0.16
VO_2	105.7 ± 24.8, *n* = 8	85.7 ± 20.6, *n* = 40	<0.001	71.6 ± 19.9, *n* = 40	<0.001	<0.001

Data are expressed as means ± SD. p//RA is the difference between room air. p//0_2 is the difference between oxygen-breathing, Hemodynamic parameters: systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), heart rate (HR), pulmonary arterial systolic pressure in mm Hg (PASP), pulmonary arterial diastolic pressure (PADP), pulmonary arterial mean pressure (PAMP), cardiac index (CI), right ventricular ejection fraction (RVEF), right ventricular end-diastolic volume (RVEDV), mixed Venous Oxygen Saturation (SvO_2), central venous pressure (CVP), PAMP/MAP ratio, indexed systemic vascular resistances (ISVR), stroke volume (SV), oxygen delivery (DO_2), and oxygen consumption (VO_2), SAP, DAP, MAP, PASP, PADP, PAMP, CVP are expressed in mmHg. CI is expressed in L/min/m^2. RVEF and SvO_2 are expressed in %. RVEDV is expressed in ml/m^2; ISVR is expressed in dynes-s/cm-5/m^2; DO_2 and VO_2 are expressed in l/min/m^2

et al.[18] Probably the patients do not have important lung portions with hypoxic vasoconstriction and an important intrapulmonary right to left shunting.

Breathing pure oxygen should decrease pulmonary arterial pressure and right ventricular afterload since it is well-known that oxygen has a vasodilatory effect on the pulmonary circulation. This was not reported in our study.

The addition of iNO to oxygen as a selective pulmonary vasodilator decreases pulmonary arterial pressure, as shown in other studies.[16] This pulmonary arterial pressure decrease is not associated with improved right ventricular performance with the decrease of right ventricular end-diastolic volume and the increase of right ventricular ejection fraction as expected. The oxygen and iNO administration did not increase the cardiac index and right ventricular ejection fraction like it did in other studies.[17] This can be explained that iNO has limited action only in the vascular endothelium and does not change the underlying mitral or left ventricular pathology. Only cardiac surgery constitutes the therapeutic alternative to treat the causal underlying condition.[19]

Ventilation with pure oxygen, or hyperoxic ventilation (HV), is thought to decrease whole-body oxygen consumption.[20] We found the same phenomenon: the VO_2 decreases when the patient breathes pure oxygen and decreases further when iNO is added to O_2.

Another interesting finding is that ventilation with oxygen and iNO increases indexed systemic vascular resistances (ISVR) and like in the other studies proves that iNO rapidly scavenged by oxyhemoglobin and has no systemic vasodilating effects.[14] The ISVR probably happens because of hyperoxic arteriolar constriction and reduced functional capillary density, which reduces nutritive organ blood flow and increases peripheral oxygen shunting.[20] The increase in arterial oxygen content by breathing 100% oxygen with constant oxygen peripheral consumption, explains the DO_2 increase and VO_2 decrease in our study. The iNO inhalation has no side effects, and the MetHb level is low. Breathing 100% O_2 significantly decreases oxygen consumption and optimizes oxygen delivery—oxygen consumption balance.[20] The iNO treatment could have another positive protective effect on ischemia-reperfusion damage as demonstrated in more recent discoveries.[21,22]

The limits of this study are the small number of patients included and lack of control group. We are convinced that the inclusion of more patients would not modify the current findings. All the patients included belong to group 2 Dana Point classification of PH and our results could be specific to this group of patients. We considered that a control group is not necessary since every patient represents an intraindividual control through the three steps of the study (during room air, oxygen, and iNO administration). Another limit is the absence of some hemodynamic parameters due to the unexplained non-measurements from the Vigilance II monitor. It should be emphasized that the authors tried to obtain the most accurate values. The SvO_2 was measured with reflection spectrophotometry and the Vigilance II monitor uses thermal energy to calculate cardiac output using thermodilution principles. It was impossible in our study to measure the pulmonary arterial occlusive pressure every minute and PVR cannot be measured without this parameter. The VO_2, DO_2, and ISVR were calculated by the authors in an excel sheet using classical hemodynamic formulas for these parameters. All these parameters cannot be displayed in real-time by the monitor. The pulmonary pressure reduction in our study cannot be related to the reduced amount of blood entering the pulmonary circulation since the central venous pressure (CVP) is constant.

In conclusion, the results of this study confirm that administration of iNO with a face mask is a safe and effective method to reduce pulmonary arterial pressure before the induction of anesthesia in patients with PH. Oxygen and hyperoxia influence systemic vascular resistance and peripheral oxygen consumption.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Thunberg CA, Gaitan BD, Grewal A, Ramakrishna H, Stansbury LG, Grigore AM. Pulmonary hypertension in patients undergoing cardiac surgery: Pathophysiology, perioperative management, and outcomes. J Cardiothorac Vasc Anesth 2013;27:551-72.
2. Denault A, Deschamps A, Tardif J-C, Lambert J, Perrault L. Pulmonary hypertension in cardiac surgery. Curr Cardiol Rev 2010;6:1-14.

3. Kaw R, Pasupuleti V, Deshpande A, Hamieh T, Walker E, Minai OA. Pulmonary hypertension: An important predictor of outcomes in patients undergoing non-cardiac surgery. Respir Med 2011;105:619-24.
4. Pritts CD, Pearl RG. Anesthesia for patients with pulmonary hypertension. Curr Opin Anaesthesiol 2010;23:411-6.
5. McGlothlin D, Ivascu N, Heerdt PM. Anesthesia and pulmonary hypertension. Prog Cardiovasc Dis 2012;55:199-217.
6. Gille J, Seyfarth H-J, Gerlach S, Malcharek M, Czeslick E, Sablotzki A. Perioperative anesthesiological management of patients with pulmonary hypertension. Anesthesiol Res Pract 2012;2012;2012:356982. doi: 10.1155/2012/356982.
7. Strumpher J, Jacobsohn E. Pulmonary hypertension and right ventricular dysfunction: Physiology and perioperative management. J Cardiothorac Vasc Anesth 2011;25:687-704.
8. Sarkar MS, Desai PM. Pulmonary hypertension and cardiac anesthesia: Anesthesiologist's perspective. Ann Card Anaesth 2018;21:116-22.
9. Spoelstra-de Man AME, Smit B, Oudemans-van Straaten HM, Smulders YM. Cardiovascular effects of hyperoxia during and after cardiac surgery. Anaesthesia 2015;70:1307-19.
10. Matamis D, Pampori S, Papathanasiou A, Papakonstantinou P, Tsagourias M, Galiatsou E, *et al*. Inhaled NO and sildenafil combination in cardiac surgery patients with out-of-proportion pulmonary hypertension: Acute effects on postoperative gas exchange and hemodynamics. Circ Heart Fail 2012;5:47-53.
11. Poor HD, Ventetuolo CE. Pulmonary hypertension in the intensive care unit. Prog Cardiovasc Dis 2012;55:187-98.
12. Teman NR, Thomas J, Bryner BS, Haas CF, Haft JW, Park PK, *et al*. Inhaled nitric oxide to improve oxygenation for safe critical care transport of adults with severe hypoxemia. Am J Crit Care Off Publ Am Assoc Crit-Care Nurses 2015;24:110-7.
13. Winterhalter M, Simon A, Fischer S, Rahe-Meyer N, Chamtzidou N, Hecker H, *et al*. Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: A prospective randomized trial. J Cardiothorac Vasc Anesth 2008;22:406-13.
14. Yu B, Ichinose F, Bloch DB, Zapol WM. Inhaled nitric oxide. Br J Pharmacol 2019;176:246-55.
15. Estanove S, Girard C, Bastien O, Piriou V, Lehot JJ. [Inhaled nitric oxide: Therapeutic applications in cardiac surgery]. Bull Acad Natl Med 2000;184:1715-26; discussion 1727-9.
16. Benedetto M, Romano R, Baca G, Sarridou D, Fischer A, Simon A, *et al*. Inhaled nitric oxide in cardiac surgery: Evidence or tradition? Nitric Oxide Biol Chem 2015;49:67-79.
17. Fattouch K, Sbraga F, Sampognaro R, Bianco G, Gucciardo M, Lavalle C, *et al*. Treatment of pulmonary hypertension in patients undergoing cardiac surgery with cardiopulmonary bypass: A randomized, prospective, double-blind study. J Cardiovasc Med Hagerstown Md 2006;7:119-23.
18. Rao V, Ghadimi K, Keeyapaj W, Parsons CA, Cheung AT. Inhaled nitric oxide (iNO) and inhaled epoprostenol (iPGI2) use in cardiothoracic surgical patients: Is there sufficient evidence for evidence-based recommendations? J Cardiothorac Vasc Anesth 2018;32:1452-7.
19. Sardo S, Osawa EA, Finco G, Gomes Galas FRB, de Almeida JP, Cutuli SL, *et al*. Nitric oxide in cardiac surgery: A meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2018;32:2512-9.
20. Lauscher P, Lauscher S, Kertscho H, Habler O, Meier J. Hyperoxia reversibly alters oxygen consumption and metabolism. Scientific World Journal 2012;2012:410321. doi: 10.1100/2012/410321.
21. Bhatraju P, Crawford J, Hall M, Lang JD. Inhaled nitric oxide: Current clinical concepts. Nitric Oxide Biol Chem 2015;50:114-28.
22. Lux A, Pokreisz P, Swinnen M, Caluwe E, Gillijns H, Szelid Z, *et al*. Concomitant phosphodiesterase 5 inhibition enhances myocardial protection by inhaled nitric oxide in ischemia-reperfusion injury. J Pharmacol Exp Ther 2016;356:284-92.