Acta Anaesth. Bel., 2022, 73 (2): *83-90*

Original study

Multicenter international survey on the clinical use of inhaled nitric oxide in the perioperative setting and critically ill patients
Survey on inhaled nitric oxide

K. Van Loon[1], R. Rossaint[2], A. Saraçoglu[3], N. Marczin[4], S. Rex[1,5]

[1]Department of Anaesthesiology, University Hospitals of the KU Leuven, Herestraat 49, 3000 Leuven (Belgium); [2]Department of Anaesthesiology, University Hospital, Rheinisch-Westfälische Technische Hochschule (RWTH) – Aachen (Germany); [3]Department of Anesthesiology and Intensive Care, Marmara University School of Medicine, Istanbul (Turkey); [4]Department of Surgery & Cancer, Section of Anaesthetics, Imperial College of London, London (UK), Department of Anaesthesia and Intensive Care, Harefield Hospital, Royal Brompton & Harefield Hospitals, Harefield (UK), Department of Anesthesia and Intensive Care, Semmelweis University, Budapest (Hungary); [5]Department of Cardiovascular Sciences, KU Leuven, Leuven (Belgium).

Corresponding author: Kathleen Van Loon, Herestraat 49, 3000 Leuven. E-mail: kathleen.vanloon@uzleuven.be

Abstract

Background: **Inhaled nitric oxide (iNO) is a well-established off-label treatment of acute hypoxic respiratory failure and pulmonary hypertension, but high drug cost and lack of consistent proof of clinical benefit have led to restrictive expert recommendations regarding its use.**
Objectives: **To evaluate the current practice of the use of iNO in different hospital settings at an international society level.**
Design & Setting: **Web-based survey distributed via email to ESAIC and EACTAIC members.**
Methods: **Survey responses are depicted as absolute frequencies and percentages that were analysed using Microsoft Excel.**
Results: **One third of the respondents had institutional guidelines for the use of iNO. Pulmonary arterial hypertension, right ventricular failure, persistent pulmonary hypertension of the newborn and adult respiratory distress syndrome were the main indications for treatment with iNO. Prophylactic use of iNO during heart and lung transplantation or VAD implantation surgery was reported by 12-34%. The most frequently reported doses were 10-20 ppm and 20-40 ppm as initial and maximum treatment doses, respectively. Echocardiography was the most universally used form of advanced hemodynamic monitoring during treatment with iNO, followed by pulmonary artery catheterization. Half of the respondents had a fixed strategy to prevent rebound pulmonary hypertension during weaning from iNO, using phosphodiesterase inhibitors, prostacyclins or calcium channel antagonists.**
Conclusion: **In line with the available evidence and expert recommendations, iNO remains a rescue treatment reserved for the most severe cases in highly specialized centres. The observations made in this survey should inspire future research to help better define the role of iNO, also in the setting of an ARDS-pandemic and the emergence of alternative selective pulmonary vasodilators.**

Keywords : **Nitric oxide, pulmonary hypertension, right ventricular failure, acute respiratory distress syndrome, cardiac surgical procedures, lung transplantation.**

Introduction

Inhaled nitric oxide (iNO) is a well-established off-label treatment of acute hypoxic respiratory failure and pulmonary hypertension. Due to its short half-life and profound vasorelaxant properties, iNO has a unique pharmacological profile inducing selective vasodilation in ventilated lung regions without affecting the systemic circulation[1]. By this, right ventricular afterload is decreased and blood is preferentially diverted to ventilated lung areas, improving both right ventricular performance and oxygenation[2]. Unlike systemically administered vasodilators, iNO does not cause arterial hypotension and intrapulmonary right-left shunting is avoided. Multiple randomized controlled trials,

however, have failed to confirm clinical benefit in terms of survival or morbidity in critically ill patients treated with iNO[3]. The lack of hard clinical evidence combined with the high drug costs have led to rather restrictive expert recommendations for the general use of iNO in clinical practice[4]. Nevertheless, cardiac surgical recommendations by the expert panel were more positive and iNO remains an important treatment option for patients suffering from different, frequently life-threatening, pathologies or adverse events in the perioperative period[5]. The purpose of this online survey was to describe current international practice concerning the use of iNO in different clinical settings.

Methods

Survey development and distribution

Initiated by the board of the European Society of Anaesthesiology and Intensive Care (ESAIC), an advisory group consisting of members of the Society was appointed and tasked with developing a questionnaire and conducting the survey on behalf of ESAIC. The survey was also endorsed by the European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTAIC). An e-mail invitation including a brief description of the aim of the survey and containing a hyperlink to the online questionnaire was sent to 37.976 ESAIC and EACTAIC members on June 18, 2020. Additional promotion via social media, ESAIC and EACTAIC newsletters was done subsequently. The survey was closed on July 17, 2020.

Questionnaire

The questionnaire (see appendix) comprised of 29 questions in total and took approximately 15 minutes to answer. The first 13 questions explored the participants' background, including their country of origin, the type of hospital they were affiliated with, and complexity and numbers of surgeries performed in their respective institutions. The following 14 questions focused on the availability, indications and practical considerations regarding the use of iNO. Finally, reimbursement regulations and the availability of alternatives to iNO were addressed.

Respondents were asked to give a ranking of criteria to start iNO therapy (most important to least important indication) in 2 questions. To get an overall impression of most to least important indications, we transformed responses into a weighted sum score by assigning highest weight to the highest rank (e.g. 8 points for a number 1 ranking, 7 points for a number 2 ranking, etc.) and adding up the weighted scores for each criterium. Because of the descriptive nature of this study, no formal statistical analysis was carried out. Results are depicted as absolute frequencies and percentages that were analysed using Microsoft Excel.

Results

524 respondents from 52 countries started to respond to the questionnaire, resulting in 200 responses for which at least the first part of the questionnaire (background questions) was completed. Respondents who did not have inhaled nitric oxide available in their hospital were excluded (n=135). Results from 65 respondents from 27 countries (24 complete and 41 partial answers) were ultimately included for analysis in this paper. The number of responses per participating country is shown in electronic supplementary Table I.

Participants' background

Sixty-five percent (42 of 65) of the respondents were affiliated with university hospitals and represented the largest group of participants. The median number of beds per hospital the respondent was affiliated with was 800 [interquartile range (IQR) 400 to 1200], with a median of 56 [IQR 35 to 83] ICU beds per institution. Most respondents were board certified in anesthesiology (99%) and/or intensive care medicine (59%). This was also reflected by their indicated primary clinical activities, being mostly general anesthesiology (59%), cardiac anesthesiology (51%), surgical intensive care medicine (28%) and medical intensive care medicine (17%). The types and numbers of complex surgeries with an established

Table I. — Type and number of specific high-risk surgeries performed at the institution of the respondent.

Type of surgery	Number of respondents	Annual number of surgeries
Cardiac surgery	53/65 (82)	500 (4-4000)
Congenital cardiac surgery	29/65 (45)	150 (5-2300)
Heart transplantation	25/64 (39)	20 (1-150)
Lung transplantation	18/65 (28)	25 (2-200)
VAD implantation	39/65 (60)	15 (0-58)

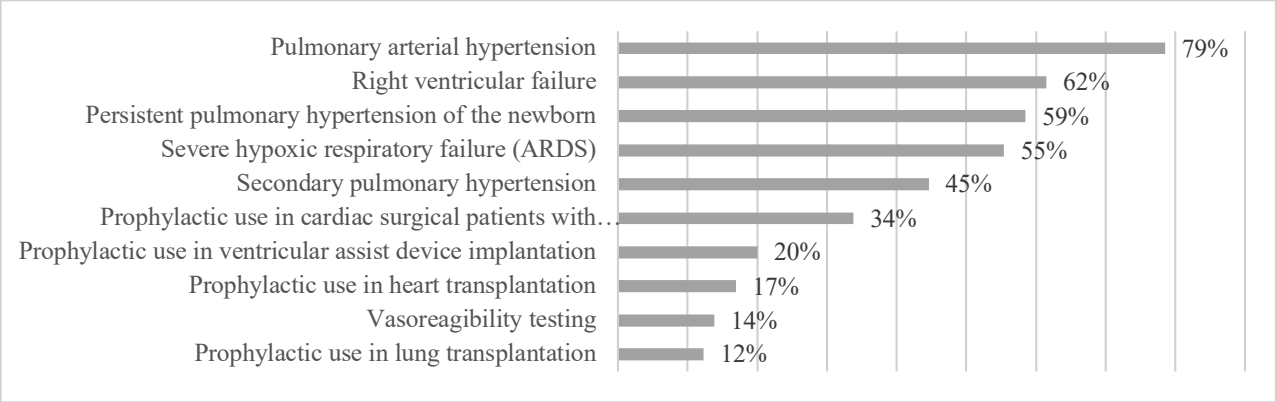

Fig. 1 — Indications for which iNO is used per institution.

indication for pulmonary vasodilators performed at the respondents' institutions are depicted in Table I. The median estimated number of patients treated for severe acute hypoxic respiratory failure in the participants' institutions in the last year was 60 [IQR 20 to 200].

One third (65 of 200) of the responding practitioners had iNO available in their institution, with a median of 4 [IQR 2 to 5] iNO delivery devices available per institution. A median estimated number of 25 [IQR 10 to 76] patients was treated per institution in the last year. In most hospitals (84%, 55 of 65), a dedicated delivery device was used for delivery and monitoring of inhaled nitric oxide. 34% (22 of 65) of institutions had institutional guidelines for the use of iNO, and these guidelines had been published or reviewed in the last two years in most cases (electronic supplementary materials, Fig. 1).

Indications for use of iNO

Indications for which iNO was used varied per hospital. Pulmonary arterial hypertension was the most important indication, followed by right ventricular failure and persistent pulmonary hypertension of the newborn. Use of iNO for vasoreagibility testing and prophylactic use of iNO in transplant surgery were less commonly indicated as reasons to use iNO (Fig. 1).

iNO for treatment of severe hypoxic respiratory failure

While 36 out of 65 (55%) had iNO available for treatment of adult respiratory distress syndrome (ARDS) in their hospital, only 24 of them indicated to routinely use iNO in this context. When asked to rank several different conditions to start iNO treatment in the setting of ARDS, $PaO_2/FiO_2 < 100$ mmHg was deemed the most important criterium. A ranking of the preferred reasons to start iNO therapy in ARDS is represented in Table II.

Echocardiography was the most universally used form of advanced hemodynamic monitoring (83%, 20 of 24) in iNO treatment for ARDS, followed by measurement of pulmonary artery pressures, central venous pressures and $ScvO_2$ (63% each, 15 of 24). 58% of respondents (14 of 24) used pulmonary artery catheter-based measurements of cardiac output and SvO_2 to guide iNO treatment. Two respondents indicated to use PICCO-based cardiac output measurements during iNO-therapy in addition to pulmonary artery catheter-based cardiac output measurements.

An initial iNO dose of either 10 ppm or 20 ppm was used most frequently in the treatment of severe hypoxic respiratory failure. 20 ppm iNO was also the maximum dose used for this indication by

Table II. — Most important criteria to start iNO in ARDS.

Criteria	Number of respondents indicating this as most important criterium	Total sum score
$PaO_2/FiO_2 < 100$ mmHg	10	123
As rescue therapy before ECMO	3	109
Right ventricular dysfunction	3	99
No improvement despite prone position	2	94
PEEP > 15 cmH_2O	0	72
$PaO_2/FiO_2 < 200$ mmHg	3	50
iNO is only used if all other measures have failed	1	41
$PaO_2/FiO_2 < 300$ mmHg	0	10

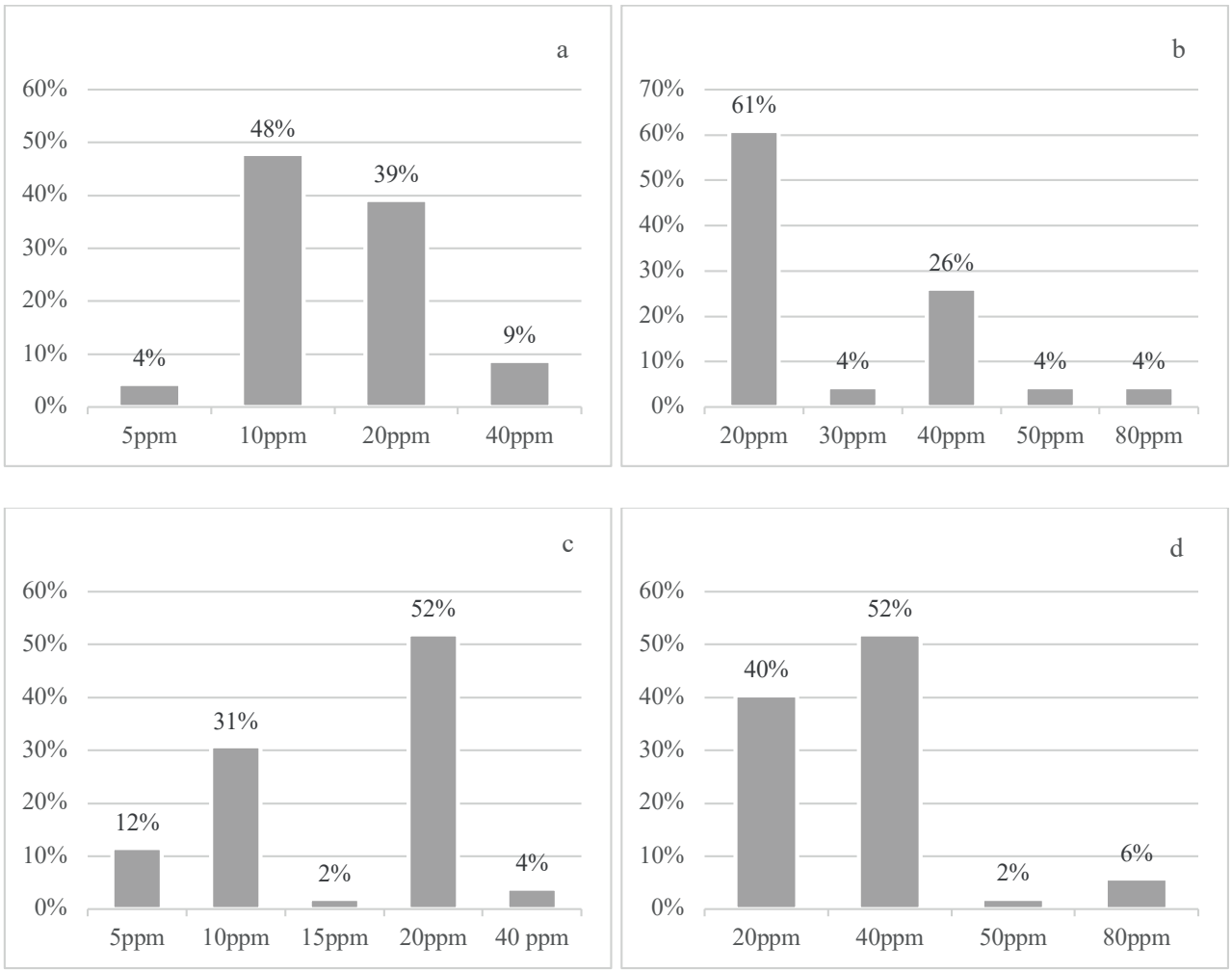

Fig. 2 — Initial (a,c) and maximum (b,d) iNO dose in ARDS and in right ventricular dysfunction.

the majority of respondents, while a quarter of respondents indicated to use higher iNO doses up to 40 ppm. The highest reported maximum dose for treatment of severe hypoxic respiratory failure was 80 ppm (Fig. 2).

iNO for treatment of right ventricular dysfunction

44% (27 of 61) of respondents indicated to routinely use iNO in patients with right ventricular dysfunction, in addition to 41% (25 of 61) of respondents who used it only in exceptional cases of right ventricular dysfunction. Echocardiographic signs of right ventricular dysfunction, with or without deteriorating hemodynamics, were regarded as the most important criterium to start treatment with iNO in this setting. The ranking of other criteria to start iNO therapy in patients with right ventricular dysfunction is listed in Table III.

As was the case for monitoring in ARDS, echocardiography was the most universally used form of advanced hemodynamic monitoring in the treatment of right ventricular dysfunction with iNO (94%, 49 of 52). The majority of participants also monitored pulmonary artery pressures (79%, 41 of 52), central venous pressures (69%, 36 of 52) or cardiac output (derived from a pulmonary artery catheter; 69%, 36 of 52). About a third of respondents used alternatives to direct cardiac output measurements, including PiCCO.

Ten ppm and 20 ppm were most frequently reported as initial iNO dose for the treatment of right ventricular dysfunction. 40 ppm was indicated as maximum iNO dose by half of the respondents. A small minority of respondents indicated using up to 80 ppm of iNO when treating right ventricular dysfunction (Fig. 2).

Practical aspects regarding iNO therapy

A quarter of the participants (15 of 61) used iNO not only in intubated, but also in spontaneously breathing non-intubated patients. The majority of respondents routinely monitored fraction of inspired oxygen and fraction of inspired NO. Fraction of inspired NO2 and methemoglobinemia were routinely monitored by just over half of the respondents (electronic supplementary materials, Fig. 2).

Half of the respondents reported that iNO therapy is reimbursed in their country.

Table III. — Most important criteria to start iNO in right ventricular dysfunction.

Criteria	Number of respondents indicating this as most important criterium	Total sum score
Echocardiographic signs of right ventricular dysfunction	21	224
Echocardiographic signs of right ventricular dysfunction, only if hemodynamics are deteriorating	10	183
Only used if all other therapeutic measures have failed	9	144
Decrease in cardiac output	3	125
Decrease in SvO_2	1	99
Prophylactically in patients with echocardiographic signs of right ventricular dysfunction, even if hemodynamics are still adequate	3	99
Venous congestion	0	69

Weaning from iNO therapy

More than half of respondents (52%, 29 of 59) used iNO for a maximum of 72 hours, and an additional 17% (10 of 59) of respondents continued iNO therapy for up to one week. A minority (3 out of 59) of respondents continued iNO therapy until their patients were improving (electronic supplementary materials, Fig. 3). Half of the participants had a fixed strategy to prevent rebound pulmonary hypertension during weaning from iNO. The most popular agents for prevention of rebound pulmonary hypertension were phosphodiesterase type V inhibitors (35%, 10 of 29) and phosphodiesterase type III inhibitors (28%, 8 of 29), followed by prostacyclins (17%, 5 of 29) and calcium channel antagonists (10%, 3 of 29 respondents).

Alternatives for iNO

86% of respondents (53 of 62) routinely used alternative selective pulmonary vasodilators. Systemic phosphodiesterase type V inhibitors (64%, 34 of 53), inhaled prostacyclins (43%, 23 of 53) and systemic endothelin antagonists (36%, 19 of 53) were the most popular agents. Inhaled phosphodiesterase type III inhibitors were used by 26% (14 of 53) and systemic soluble guanylate cyclase stimulators and activators were used by 9% (5 of 53) of respondents.

Discussion

While inhalation of NO is a well-established strategy in managing life-threatening hypoxia and/or right ventricular dysfunction, the current clinical practice of iNO including indications, strategies and alternatives remains largely unknown. To the best of the authors' knowledge, only one international survey aiming to describe the clinical use of iNO in specific clinical settings has been published yet, however, it was performed more than 20 years ago and was restricted to Europe[6]. The present study is, therefore, the first international survey exploring the current and global clinical reality of iNO treatment for a variety of indications, giving insight in the availability, perceived indications, practical considerations and use of alternatives strategies to lower pulmonary vascular resistance.

Only a third of the respondents that fully completed the first round of background questions had iNO available in their institutions and were subsequently included for further analysis, reflecting that iNO remains an exceptional treatment modality even in a sample consisting mainly of practitioners affiliated with larger and university hospitals. This seems consistent with the European expert recommendations on iNO published in 2005, underlining that iNO is a reasonable rescue treatment for certain indications in adult patients, but should not be used as a routine treatment modality pending more robust clinical evidence of any outcome benefit[4]. This evidence is, however, still lacking.

Pulmonary arterial hypertension and right ventricular failure represented the most frequent indications for iNO use in modern clinical practice. Although evidence for mortality benefits of iNO from randomized clinical trials is lacking even for these conditions, the use of iNO undoubtedly facilitates the (perioperative) hemodynamic management of patients suffering from these conditions[3,7]. This may contribute to the popularity of iNO for these indications.

Treatment of persistent pulmonary hypertension of the newborn, which in many countries remains the only approved indication for iNO, was only the third most reported indication after pulmonary arterial hypertension and right ventricular dysfunction. However, this finding is most probably due to the extreme underrepresentation of paediatric and neonatal specialists in our study sample (only 1 respondent). Also, although amongst the generally accepted indications, use of

iNO for vasoreagibility testing in selected patients with pulmonary arterial hypertension was reported by only 14% of respondents, which might also be attributed to an underrepresentation of cardiologists in our study sample.

Interestingly, the use of iNO for the treatment of severe hypoxic respiratory failure was only the fourth most frequently reported indication. In this context, the majority of respondents treat patients with iNO only in a "last resort" setting., i.e. in the presence of a low PaO_2/FiO_2-ratio (<100 mmHg) or signs of right ventricular dysfunction, or when patients fail to respond to prone positioning or high positive end-expiratory pressure (PEEP). This tendency to use iNO only in the most severe cases represents the prudent application of the available evidence, that has not been able to prove significant improvements in morbidity or mortality with the use of iNO for ARDS[8,9,10,11,12].

A significant portion of the sampled population supported the prophylactic use of iNO during specific surgical procedures, the most frequently reported indication being cardiac surgery for patients with pulmonary artery hypertension. This is in contrast with the numerous trials that were unable to demonstrate outcome benefits of prophylactic iNO treatment[13,14,15,16,17,18,19]. Likewise, the recently published international guidelines on the perioperative management of lung transplantation do not recommend the prophylactic application of iNO[1].

This survey also highlights the importance of echocardiography in our clinical practice as echocardiography was indicated as the most important tool for advanced hemodynamic monitoring during iNO treatment. This was true for any indication, most probably because echocardiography allows the comprehensive assessment of right ventricular function and also pulmonary hemodynamics in a non-invasive (transthoracic echocardiography) or minimally invasive (transoesophageal echocardiography) manner and because echocardiography is nowadays considered a first-line diagnostic and monitoring tool[7,20]. A pulmonary artery catheter was used more often in the setting of right ventricular dysfunction than in ARDS. This could be because right ventricular dysfunction is most often encountered in cardiac surgical patients, in which pulmonary artery catheterization still belongs to the standard monitoring in many centres[21]. Less invasive alternatives to cardiac output measurement were only used by a minority of respondents, probably as these techniques still lack accuracy in patients with cardiogenic shock and do not allow the continuous monitoring of right ventricular afterload[22].

While the European expert recommendations propose the continuous monitoring of the inspired concentrations of NO, NO_2 and O_2, these recommendations do not include suggestions on hemodynamic monitoring during iNO treatment[4]. Methemoglobinemia was only routinely monitored by half of the respondents, despite the European expert recommendations suggesting to monitor methemoglobinemia at least daily. This is of particular concern when administering concentrations exceeding 20 ppm[23].

Several clinical trials have tested different concentrations of iNO for treatment of acute pulmonary hypertension and hypoxemia, establishing dose-dependent and immediate selective pulmonary vasodilatation in most patients. iNO-doses exceeding 10 ppm have not been shown to result in significantly larger decreases in pulmonary vascular resistance in ARDS or cardiac surgical patients[6,22,23]. Despite this, most respondents in our sample favoured a starting dose of 10 to 20 ppm and would not escalate the doses beyond 20 to 40 ppm. These doses are clearly higher than the recommended 10 ppm or less which are advised for long-term iNO treatment, but this might reflect the way iNO is used as a rescue therapy for patients in critical conditions. Similarly, only 66% of the respondents would stop iNO treatment after 72 hours, despite the lack of evidence that longer treatment durations offer any outcome benefit[26].

Phosphodiesterase inhibitors type V were the most frequently used alternative pulmonary vasodilators. In the setting of right ventricular dysfunction, the use of systemic vasodilators can result in a vicious circle of hypotension, leftward septal shift, right ventricular ischemia and shock[27]. In ARDS, systemic vasodilators can aggravate hypoxia by causing intrapulmonary right-left shunting due to the interference with hypoxic pulmonary vasoconstriction[28]. Nevertheless, the vast majority of respondents routinely used these alternatives to iNO either as a true alternative, or as part of a weaning strategy to prevent rebound pulmonary hypertension. Inhaled prostacyclins and inhaled type III phosphodiesterase inhibitors are a promising group of selective pulmonary vasodilators, combining some of the advantages of iNO with a significantly longer half-life, thus obviating the need for continuous administration. Furthermore, the association of iNO and inhaled prostacyclin has the potential of synergistic beneficial effects, yet this specific use of combination therapy has not been assessed in the current survey[29].

Only half of the respondents reported that iNO therapy is reimbursed in their country.

Limitations

While all members of the ESAIC anaesthesia and intensive care community were approached, the present survey had a relatively low response rate. However, considering the particular and specialised character of this topic, and the fact that many of the general membership do not routinely use this specific treatment modality, the overall return seems acceptable and is in line with a previous survey. Moreover, the COVID19-pandemic was likely a factor negatively contributing to the willingness of respondents to participate in a survey. Also, since the questionnaire was created before the COVID19-pandemic, it did not contain questions specifically regarding COVID19-related ARDS. These limitations make our results less generalizable, yet they are the best option available to us at this time to gain some insight into current practice.

Survey-based research into clinical practice has the inherent limitation of only providing insight into the respondents' perceived practice, in contrast to the actual current practice. Selection bias toward practitioners with above-average interest in iNO therapy is another unavoidable limitation of this kind of research. Attempts to more accurately describe current iNO practice would require prospective observational trials.

Conclusion

iNO remains a rescue and off-label treatment modality in adults presenting with pulmonary arterial hypertension, right ventricular failure and ARDS, among other rarer indications. Institutional guidelines are still largely lacking, resulting in widely varying practices both within and among hospitals. Further prospective trials are needed to assess accurate clinical practice of iNO (and alternative pulmonary vasodilator) therapies and a revised international and multidisciplinary consensus for modern practice recommendations.

Acknowledgements - Conflict of interest: ESAIC received an educational grant from Air Liquide (France) to convene the task force. There was no interference by industry in the development of this survey, nor in the analysis of the results.
Nandor Marczin is associated with AirLiquide as Medical Advisory Board Member.
Steffen Rex received speaking fees from Orion Pharma, a research grant from AirLiquide, and consulting fees from Messer.

Presentation: preliminary data for this study were presented as a poster presentation at the virtual Euroanaesthesia meeting, 17-19 December 2021.

References

1. Marczin N, de Waal EEC, Hopkins PMA, Mulligan MS, Simon A, Shaw AD, et al. International consensus recommendations for anesthetic and intensive care management of lung transplantation. An EACTAIC, SCA, ISHLT, ESOT, ESTS, and AST approved document. J Heart Lung Transplant 2021;40(11):1327-48.
2. Rossaint R, Falke KJ, López F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993;328(6):399-405.
3. 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 2015;49:67-79.
4. Germann P, Braschi A, Della Rocca G, Dinh-Xuan AT, Falke K, Frostell C, et al. Inhaled nitric oxide therapy in adults: European expert recommendations. Intensive Care Medicine 2005;31(8):1029-41.
5. Bigatello LM, Stelfox HT, Hess D. Inhaled nitric oxide therapy in adults--opinions and evidence. Intensive Care Med 2005;31(8):1014-6.
6. Beloucif S, Payen D. A European survey of the use of inhaled nitric oxide in the ICU. Working Group on Inhaled NO in the ICU of the European Society of Intensive Care Medicine. Intensive Care Med 1998;24(8):864-77.
7. Harjola VP, Mebazaa A, Čelutkienė J, Bettex D, Bueno H, Chioncel O, et al. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. Eur J Heart Fail 2016;18(3):226-41.
8. Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998;26(1):15-23.
9. Taylor RW, Zimmerman JL, Dellinger RP, Straube RC, Criner GJ, Davis K, Jr., et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. Jama 2004;291(13):1603-9.
10. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev 2016;2016(6):Cd002787.
11. Sokol J, Jacobs SE, Bohn D. Inhaled nitric oxide for acute hypoxic respiratory failure in children and adults: a meta-analysis. Anesth Analg 2003;97(4):989-98.
12. Adhikari NK, Dellinger RP, Lundin S, Payen D, Vallet B, Gerlach H, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. Crit Care Med 2014;42(2):404-12.
13. Ardehali A, Laks H, Levine M, Shpiner R, Ross D, Watson LD, et al. A prospective trial of inhaled nitric oxide in clinical lung transplantation. Transplantation 2001;72(1):112-5.
14. Meade MO, Granton JT, Matte-Martyn A, McRae K, Weaver B, Cripps P, et al. A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. Am J Respir Crit Care Med 2003;167(11):1483-9.
15. Tavare AN, Tsakok T. Does prophylactic inhaled nitric oxide reduce morbidity and mortality after lung transplantation? Interact Cardiovasc Thorac Surg 2011;13(5):516-20.
16. 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(6):2512-9.
17. Ramadan ME, Shabsigh M, Awad H. Con: Inhaled Pulmonary Vasodilators Are Not Indicated in Patients Undergoing Lung Transplantation. J Cardiothorac Vasc Anesth 2017;31(3):1127-31.

18. Adhikari NK, Burns KE, Friedrich JO, Granton JT, Cook DJ, Meade MO. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. Bmj 2007;334(7597):779.
19. Potapov E, Meyer D, Swaminathan M, Ramsay M, El Banayosy A, Diehl C, et al. Inhaled nitric oxide after left ventricular assist device implantation: a prospective, randomized, double-blind, multicenter, placebo-controlled trial. J Heart Lung Transplant 2011;30(8):870-8.
20. Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, et al. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. Eur Heart J Acute Cardiovasc Care 2015;4(1):3-5.
21. Judge O, Ji F, Fleming N, Liu H. Current use of the pulmonary artery catheter in cardiac surgery: a survey study. J Cardiothorac Vasc Anesth 2015;29(1):69-75.
22. Vincent JL, Rhodes A, Perel A, Martin GS, Della Rocca G, Vallet B, et al. Clinical review: Update on hemodynamic monitoring--a consensus of 16. Crit Care 2011;15(4):229.
23. Young JD, Dyar O, Xiong L, Howell S. Methaemoglobin production in normal adults inhaling low concentrations of nitric oxide. Intensive Care Med 1994;20(8):581-4.
24. Solina AR, Ginsberg SH, Papp D, Grubb WR, Scholz PM, Pantin EJ, et al. Dose response to nitric oxide in adult cardiac surgery patients. J Clin Anesth 2001;13(4):281-6.
25. Rossaint R, Falke KJ, López F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993;328(6):399-405.
26. Gerlach H, Keh D, Semmerow A, Busch T, Lewandowski K, Pappert DM, et al. Dose-response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: a prospective, randomized, controlled study. Am J Respir Crit Care Med 2003;167(7):1008-15.
27. Winterhalter M, Rex S, Stoppe C, Kienbaum P, Müller HH, Kaufmann I, et al. Effect of iloprost inhalation on postoperative outcome in high-risk cardiac surgical patients: a prospective randomized-controlled multicentre trial (ILOCARD). Can J Anaesth 2019;66(8):907-20.
28. Hill NS, Preston IR, Roberts KE. Inhaled Therapies for Pulmonary Hypertension. Respir Care 2015;60(6):794-802; discussion -5.
29. Kuhlen R, Walbert E, Fränkel P, Thaden S, Behrendt W, Rossaint R. Combination of inhaled nitric oxide and intravenous prostacyclin for successful treatment of severe pulmonary hypertension in a patient with acute respiratory distress syndrome. Intensive Care Med 1999;25(7):752-4.

doi.org/10.56126/73.2.10