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Chapter 6

Use of Inhaled Nitric Oxide in Cardiac Surgery: What is Going on?

Alfredo José Rodrigues, Patricia Martinez Evora and Paulo Roberto Barbosa Evora

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1. Introduction

In the eighties, the mere finding that acetylcholine only acts as a vasodilator in the presence of the endothelium, established its pivotal role in the physiopathology of cardiovascular diseases. Therefore, the existence of an endothelium-derived relaxing factor [1], which in 1982 was named "endothelium-derived relaxing factor" (EDRF) [2], was postulated. Using endothelial cell culture it was found that endothelium-dependent relaxation was associated with an increase of cyclic GMP (cGMP) in vascular smooth muscle, which could be inhibited by methylene blue (soluble guanylate cyclase) and hemoglobin (EDRF "scavenger").[3] With the accumulation of evidence that EDRF had characteristics similar to nitrovasodilators, Furchgott and Ignarro, [4,5] independently, proposed that EDRF was nitric oxide (NO). The research then was directed in order to determine how the endothelium itself produces the radical and presents the idea of Palmer and Moncada [6,7] postulating that L-arginine is the source of NO under the action of enzyme nitric oxide synthase (NOS).

The hypothesis that inhaled NO could cause selective vasodilatation was based on experimental models of pulmonary hypertension. [8-11] These studies have shown that concentrations of 5 to 80 ppm produced rapid and reversible pulmonary vasodilatation without systemic side effects or adverse reactions. In the lung, as elsewhere in the body, the NO formed from L-arginine in a reaction catalyzed by NO synthase induces vasodilatation through a cGMP-dependent pathway. Nitric oxide can be used by inhalation, acting selectively on those blood vessels near the alveoli. As it undergoes rapid inactivation by hemoglobin, inhaled NO can perform a selective pulmonary vasodilatation were occurring pulmonary vasoconstriction without causing systemic vasodilatation.

The existence of an NO-dependent vascular tone has led to the demonstration that its removal, resulting in "up-regulation" of receptors linked to the NO release pathway, results in increased

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sensitivity to vasodilators that act through this pathway. The pulmonary vascular bed typically has a low flow resistance. Hypertension in this area may be due to postcapillary blockage or increased flow for this system. When it persists for a long time, this situation leads to secondary changes in these vessels, where proliferation of the muscular layer, fibrosis and obliteration of light are observed. This framework, now irreversible, is associated with high morbidity and mortality. Surgical repair of heart disease should be attempted while the pulmonary vascular system is still responsive. A preoperative evaluation of responsiveness may be possible with NO inhalation. The use of systemic vasodilators can cause unwanted complications such as hypotension, aggravation of a right-left shunt and an underestimation of the real potential of the vasodilator action over the pulmonary bed. Similarly, inhalation of NO may be useful in handling situations of complex control, such as the pulmonary vasospasm observed in the postoperative period of some cardiac surgeries, reducing the right ventricle overload and improving oxygenation.

Because of the rapid inactivation by hemoglobin, and its short half-life, inhaled NO should allow selective pulmonary vasodilatation when there is a vasoconstriction secondary to endothelial dysfunction, or as a result of a potent vasoconstrictive effect.[12-14]

Nitric oxide should provide better oxygenation in the existence of balanced perfusion and ventilation, therefore, having advantages over venous administered vasodilators, which can cause hypotension and increased intrapulmonary "shunt".

The efficacy of inhaled NO in patients with endothelium NO release impairment raises the question if the endogenously release is responsible for increasing the pulmonary vascular tone.[13] NO would be released continuously under the baseline conditions, and the inhibition of this basal release could lead to an increased vascular resistance.[15] The infusion of human lungs with methylene blue alone, an inhibitor of NO-mediated vasorelaxation, leads to an increase in the pulmonary vascular resistance.[16] Thus, pulmonary endothelial damage should be considered when pulmonary vasoconstriction is a consequence of the disease (ARDS - Adult Respiratory Distress Syndrome) or a reversible side effect of treatment (cardiopulmonary "bypass").

Inhaled NO action, different from the NO intravenous action, is limited to veins and arteries of small resistance, and is unable to dilate large capacitance vessels.[17] In lungs, inhaled NO acts primarily on the arterial vessels, but can, during high venous vasoconstriction, also act in the postcapillary bed. In adults with acute lung disease, NO has a vasodilator effect mainly in the venous vascularity.[18] This increased responsiveness appears in pediatric patients with pulmonary venous hypertension, in which the NO should lead to vasodilatation with a combination of pre and post capillary vessels.

The development of right ventricular failure secondary to pulmonary arterial hypertension is a serious postoperative complication of cardiac surgery in children and adults. The selective pulmonary vasodilatation produced by inhaled NO is a therapeutic option that, in certain situations, can be crucial in managing this condition. NO binds to hemoglobin, resulting in its systemic inactivation, resulting in the preservation of coronary and systemic blood pressures (Figure 1).

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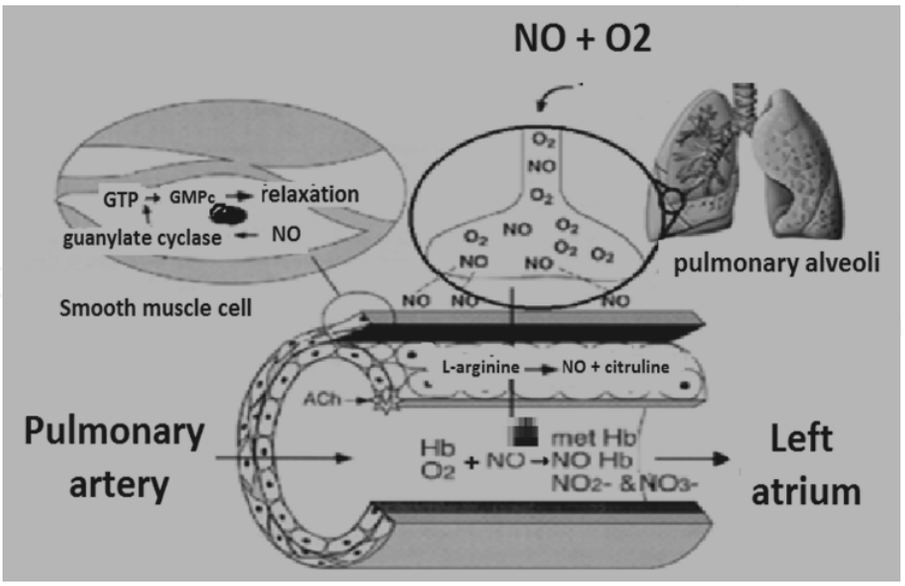

Figure 1. Schematic representation of the mechanism and site of action of inhaled nitric oxide (Adapted from Atz and Wessel [38]). Inhaled NO action, different from the NO intravenous action, is limited to veins and arteries of small resistance, and is unable to dilate large capacitance vessels. In lungs inhaled NO acts primarily on the arterial vessels but can during high venous vasoconstriction acting also in the postcapillary bed. The selective pulmonary vasodilatation produced by inhaled NO is a therapeutic option. NO binds to hemoglobin, resulting in its systemic inactivation, resulting in preservation of coronary and systemic blood pressures

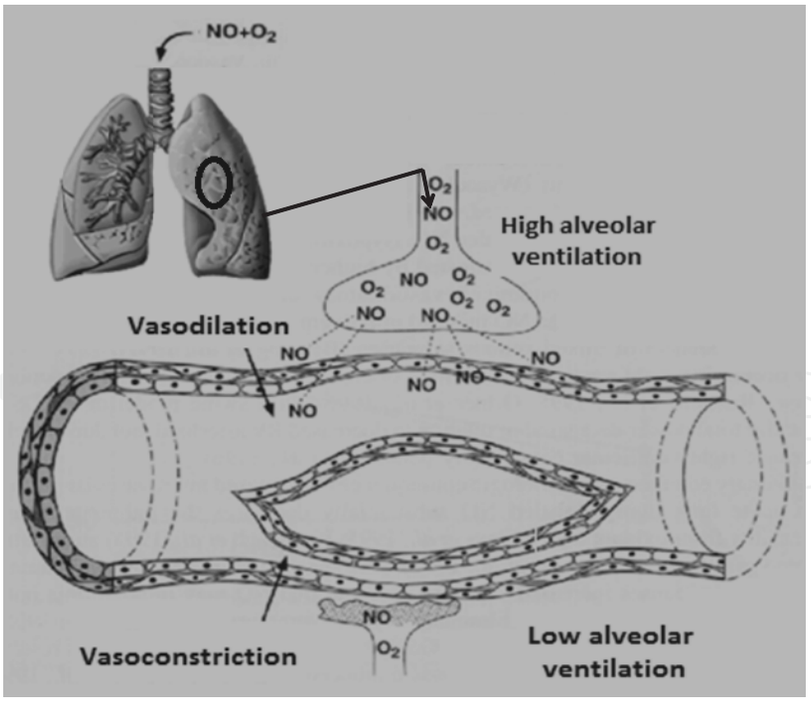

Figure 2. Schematic representation of mechanism of action in pulmonary disease (e.g.| SARA) (Adapted from Atz and Wessel [38]). In acute lung injury, inhaled NO is preferably released in areas where ventilation is high. Blood vessels are affected by the vicinity of hypoxic vasoconstriction in poorly ventilated alveoli. Inhaled NO, therefore, redirects the flow to pulmonary blood vessels dilated near well-ventilated alveoli, decreases intrapulmonary shunt and improved oxygenation

In acute lung injury, inhaled NO is preferably released in areas where ventilation is high. Blood vessels are affected by the vicinity of hypoxic vasoconstriction in poorly ventilated alveoli. Inhaled NO, therefore, redirects the flow to pulmonary blood vessels dilated near well-ventilated alveoli, decreases intrapulmonary shunt and improves oxygenation (Figure 2).

Well-defined study at INCOR in 14 adult patients with pulmonary hypertension confirmed the effect of inhaled NO, but with the caveat that pulmonary mechanics may interfere with its efficacy.[19]

2. Technical and ethical aspects

Inhaled NO in high concentrations is toxic, causing methemoglobinemia and lung injury, mainly by oxidation to NO2. International experiences have shown significant pulmonary injury vasodilatation in patients breathing low concentrations of 5-40 ppm, these levels appear not to be toxic. The 80 ppm maintained the methemoglobin levels below 3% for 3 hours. Isolated cases reported in the literature showed that the use of NO inhalation during 53 days was not associated with elevated levels of methemoglobin. Nitric oxide cannot be used intravenously because it is rapidly inactivated by hemoglobin. This makes inhaling job absolutely safe for the patient since possible excesses of the absorbed gas are "scavenged" by hemoglobin and there are subpopulations of patients with impaired ability to reduce methemoglobin.

The greatest concerns regarding the clinical use of NO are the safety of medical and paramedical staff involved in patient care due to the toxic effects of NO2. The U.S. Occupational Safety and Health Administration (OSHA) states that above 25 ppm inhaled NO is permissible in a work environment, for over 8 hours a day, with occasional increases up to 100ppm [20].

3. Critical analysis

A meta-analysis using information extracted up to 1996 from the two most prestigious banks of medical literature references (Medline and Current Contents), and data from specialized conferences, highlighted some of the key features on the use of inhaled NO. [21]

- Inhaled NO is now recognized as a valuable pharmacological tool in neonatal and pediatric intensive care medicine, surgery and cardiopulmonary disease;
- Other applications, such as chronic obstructive pulmonary disease and acute respiratory distress syndrome in adults, require careful monitoring;
- Treatment with inhaled NO is relatively inexpensive but should be used in all patients based on the paradigms of its effectiveness and potential toxicity;
- Recent discoveries of its anti-inflammatory and extrapulmonary effects open new horizons for future applications.

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A critical analysis, although with no pretension of addressing all aspects of the use of inhaled NO in cardiac surgery, should include some questions and possible answers.

Are there advantages of using inhaled NO and/or hyperventilation to control pulmonary hypertension after surgical repair of congenital heart disease?

In principle: yes. Inhaled NO and hyperventilation are both effective in reducing pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). However, the selective action of inhaled NO on pulmonary circulation offers advantages over hyperventilation because the decrease in cardiac output and increased systemic vascular resistance (SVR) are undesirable in the perioperative time. [22] It should be noted that NO in oxygen appears to be a more potent pulmonary vasodilator than oxygen alone. [23]

Is there any influence of inhaled NO on the survival of patients with secondary pulmonary hypertension?

Although inhaled NO can reduce pulmonary hypertension, it seems that this action is not associated with better survival. A randomized study is needed to determine the exact role of inhaled NO on the survival of patients with residual pulmonary hypertension after surgical treatment. [24] A randomized controlled study was carried out to test the hypothesis that inhaled nitric oxide (iNO) would improve the hemodynamic effects, and short-term clinical outcomes, of 29 patients with mitral stenosis and severe pulmonary hypertension, who underwent cardiac surgery [25]. The authors concluded that iNO immediately after surgery in patients with mitral stenosis and severe pulmonary hypertension improves hemodynamics and may have short-term clinical benefits. In addition, there are evidences that the postoperative co-administration of iNO and oral sildenafil in patients with out-of-proportion pulmonary hypertension undergoing cardiac surgery is safe, and resulting in an additive favorable effect on pulmonary arterial pressure and pulmonary vascular resistance, without systemic hypotension and ventilation/perfusion mismatch.[26]

Are there subgroups of congenital heart disease that can best benefit from the use of inhaled NO?

The answer is questionable. Studies have shown that inhaled NO causes minimal advantage over PAP or cardiac output (CO) in children after repair of the atrioventricular canal. [27]. More recently, clinical results have been demonstrating that iNO may improve hemodynamics and patient outcome after Fontan type procedures, suggesting that the use of iNO may be an effective therapy in this pediatric surgical setting. Even the use of iNO in pediatric heart transplantation has not been extensively studied. However, the limited evidence up to this date suggests that future clinical research in this setting may provide additional insight [28].

Is it possible to predict the need for the use of inhaled NO in the postoperative period of congenital and acquired heart disease?

Some factors have been associated as predictors of the use of inhaled NO: a) Age <1 year, Down syndrome, preoperative pulmonary hypertension and increased pulmonary vascular resistance. Using a multivariate model, it was possible to identify 73% of patients using inhaled NO. In a service that allows unrestricted use of inhaled NO, 50% of children undergoing surgery for congenital heart disease have made its use.[29]

Is the association of inhaled NO with prostacyclin possible?

There are some controversies. The combination of these vasodilators was not more potent than the single use of iloprost or inhaled NO for the control of pulmonary hypertension. [30] The Beraprost appears to be a therapeutical alternative to the use of inhaled NO. The combined use of both could be an alternative therapy without significant complications in the treatment of pulmonary hypertension in children. [31, 32, 33]

Is there a therapeutic option against pulmonary hypertension "rebound" after cessation of inhaled NO?

Dipyridamole could attenuate rebound pulmonary hypertension after cessation of inhaled NO in postoperative congenital heart disease. Dipyridamole may sustain elevations of cGMP induced by inhaled NO. Furthermore, the activity of phosphodiesterase could contribute to the acute pulmonary hypertension after discontinuation of inhaled NO. [34] Isolated studies suggest sildenafil as an option against PH "rebound" after iNO withdraw [35, 36].

What about long term toxicity studies?

Considering the potential toxicity of inhaled NO, there are no studies tracking the medium and long-term patients to their therapeutic use. These studies are scarce in the literature. Japanese study, reporting the follow-up of 65 children over a period of 2.0 to 4.3 years (mean 3.1 years), states that all children no longer needed to use oxygen. In addition, potential adverse effects, including the incidence of malignant tumors or chronic inflammation of the respiratory tract were not observed. [37]

Besides the pulmonary vascular resistance reduction, are there other effects of inhaled NO that may be evaluated from the therapeutic point of view?

Other actions of inhaled NO should raise interest in their therapeutic potential: Inhaled NO attenuates the proliferation of vascular smooth muscle, inhibits platelet aggregation, promotes cytoprotection for organ donors, improves the ischemic reperfusion injury, should develop angiogenesis in immature lungs and improve the ability to carry oxygen by hemoglobin in anemic falciform patients. [38] In addition, the emerging understanding of the systemic effects of iNO on inflammation opens potential therapeutic opportunities. [39]

Would the use of NO donor drugs and other drugs by inhalation, as an alternative to inhaled NO, be possible or reasonable?

At least one published work indicates that nitroglycerin spray is effective, cheap and safe to control pulmonary hypertension associated with congenital heart defects in services that do not have the resources of extracorporeal membrane oxygenation and/or inhaled NO. [40] In the Neonatal Intensive Care Unit of Ribeirão Preto Faculty of Medicine Hospital, sodium nitroprusside by inhalation has been used in extreme cases. Randomly, some infants had transient vasodilatation and became stained. In some cases, no effect was observed. Sodium nitroprusside was used in an adult patient with severe right ventricular dysfunction secondary to pulmonary hypertension associated to atrial septal defect and pulmonary thromboembolism. In postoperative pulmonary thromboendarterectomy, seven years after ASD correction, the levels of pulmonary hypertension reached 180 mmHg. Sodium nitroprusside intravenously decreased pulmonary arterial pressure but was associated with severe hypotension, although lower in magnitude than the intravenous route. It was not possible to conclude that

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the hypotension was associated to systemic absorption of nitroprusside used by inhalation. Inhaled milrinone can be an alternative to nitric oxide. A randomized clinical trial including thirty-five children below the age of 12 years who were suffering from acyanotic congenital heart disease with left-to-right intracardiac shunt and pulmonary artery hypertension (mean PA pressure > 30 mmHg) was carried out to match the acute effects of inhaled milrinone and inhaled nitroglycerin. Both inhaled drugs were effective as a valuable therapeutic option and can help reduce the high inspired oxygen concentrations needed to treat pulmonary artery hypertensive episodes in perioperative settings. [41,42]

Is there any benefit in using inhaled nitric oxide in pulmonary hypertension due to heart failure?

There are few studies that illustrate the experience with its use in congestive heart failure (CHF), which presents controversial aspects:

- In patients with CHF, the decrease in pulmonary vascular resistance is accompanied by increased values of capillary pulmonary pressure "wedge". Study of 10 patients, using 20 ppm NO inhalation, had no effect on left ventricular function, concluding that the increase of the capillary "wedge" pressure is due mainly to altered conditions of ventricular filling related to pulmonary hypertension secondary to severe CHF; [43]
- The negative inotropic effects of inhaled NO in the usual concentrations of 20 ppm are not relevant. It was determined experimentally in dogs that the increase in filling pressures seems to be secondary to the primary vasodilator effect of NO, without affecting the properties of contraction and relaxation of the left ventricle; [44.45]
- Inhaled NO would be particularly useful in the main event of isolated right ventricle failure, a less frequent situation in cases of congestive heart failure due to dilated cardiomyopathy;
- Bocchi et al., in Brazil, demonstrated that the use of inhaled NO in patients with CHF attenuated the excessive increase in tidal volume during exercise. The same authors reported the occurrence of pulmonary edema with the use of inhaled NO in patients with severe CHF. [46]

These data allow us to assert that there is no consensus for the use of inhaled NO in the treatment of pulmonary hypertension in patients with CHF. However, it can be an option in extreme and difficult to control cases, as the usual treatment. In these cases, we should be attentive to the patients worsening, and concentrations above 20 ppm are not useful. In adults with ischemic heart disease, abrupt vasodilatation may sometimes lower left ventricular filling enough to increase blood flow and dangerously increase the preload of a left ventricular function, with a possible increase of the left atrium pressure and pulmonary edema. This does not seem to be related to potential NO negative inotropic effect. [47,48,49]

Considering the reviewed aspects, which highlighted many controversies, are any conclusions possible?

One thing is certain. Arguably, although inhaled NO is a selective pulmonary vasodilator and, in no doubt, will save lives, its use has not become unanimity in a period of more than 10 years. This is certainly due to its potential toxicity and response variability (observed even in neonatology), facts that do not support the realization of large trials, which could explain many of the mentioned controversies.

In the early 90s, one of the authors (PRBE) visited cardinal U.S. clinics (Mayo Clinic, Cleveland Clinic, Johns Hopkins and Harvard) which began clinical trials with inhaled NO. A summary of these clinical observations and interviews stressed the following:

- The effectiveness of treatment in individual cases;
- The variability of response to treatment regardless of age, heart and / or respiratory disease;
- Improved therapeutic response, although transient, were observed in the most significant hypertensions and chronic lung;
- The belief that inhaled NO would be a potential therapeutic tool that could benefit transient hypertensions in neonatology and cardiopulmonary transplants;
- All physicians showed concern about NO potential toxicity, not only to patients, but also to the professional health team.
- It seems that, after decades, these observations are still present and relevant. Only one standard agreement about the use of lower doses (10-20 ppm) then originally used.

A meta-analysis of the references cited in Medline until 2002, illustrates the evolution and current role of inhaled NO in cardiac surgery. When comparing the total number of published studies/articles with the number of studies in humans, it is observed that the majority (71.36%) is related to humans. When inhaled NO is associated with pulmonary hypertension, it is observed a total number of references relative to 43.32% of the total, with prevalence of about 57.04% of human studies. When inhaled NO is associated as part of the therapeutic arsenal of ARDS, the total number of studies corresponds to 9.9% of the total, with prevalence of about 78% of studies in humans. When inhaled NO is associated as part of therapeutic heart failure, the total number of studies corresponds to 5.1% of the total, with prevalence of about 86.25% of studies in humans. [50]

Observing the *Web of Science* the data, pulmonary hypertension is still the primary target for the inhaled NO therapeutic use (44.5%). There is a decreased interest in the investigations on the applicability in ARDS, and the human studies are strongly prevalent (Figure 3).

When searching for studies, again until 2002, related specifically to therapeutic use of NO in cardiac surgery, the number of publications is about 2.5% of the total. When considering the therapeutic use of inhaled NO not only concerning cardiac surgery in general, but also including valve heart disease, congenital heart disease, heart transplant and lung transplant, the total number of communications is around 320. Of these publications, 14.7% corresponds to cardiac surgery in general, 27.6% to the heart valve, 12.5% to heart transplantation, 37% to congenital heart defects and 29.5% to lung transplants. [50]

Nowadays, the updated number of publications specifically to therapeutic use of NO in cardiac surgery is of about 3.5% of the total. Considering valve heart disease, congenital heart disease and heart transplant surgeries, the total number of communications is around 290. Of these publications, heart valve diseases corresponds to 4.8%, heart transplantation to 20.0% and congenital heart defects to 31, 4% (Figure 4).

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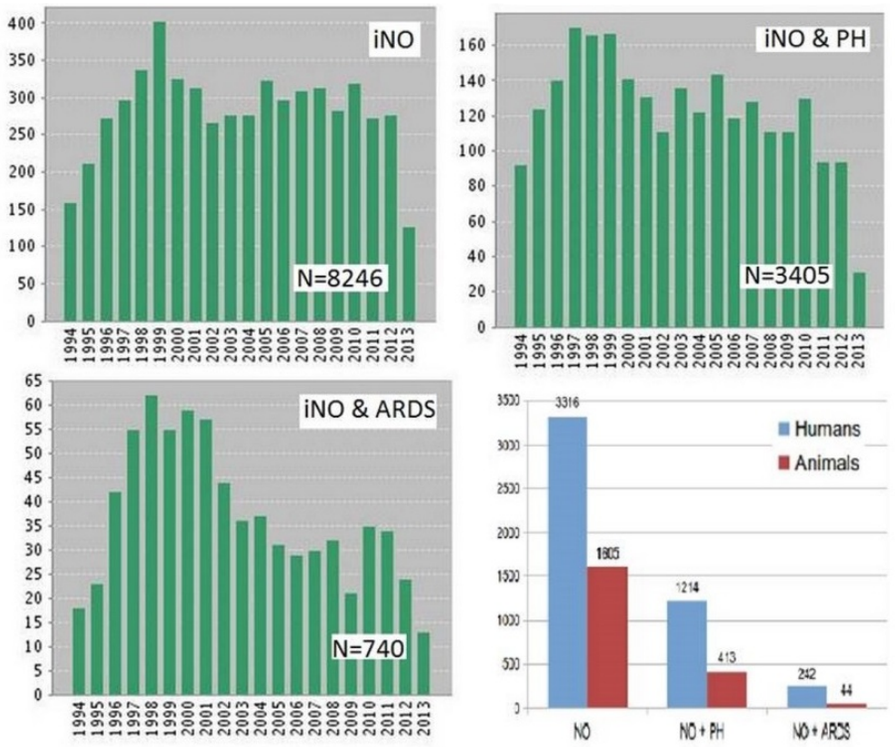

Figure 3. Graphical representation of the number of Thomson Reuters (formerly ISI) Web of Knowledge references.

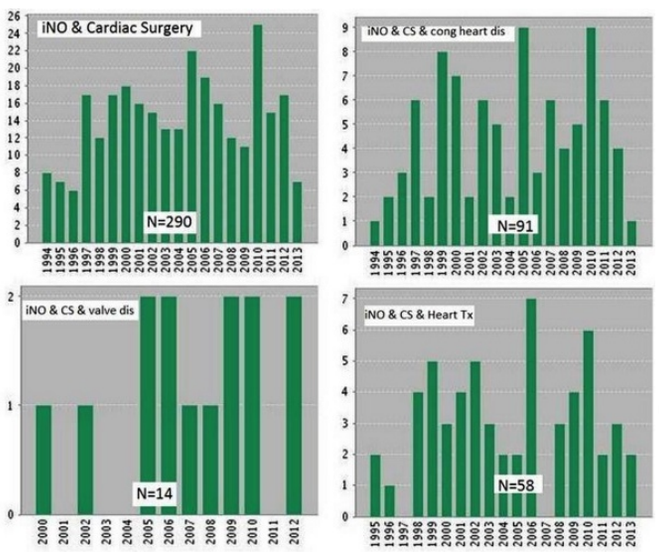

Figure 4. Graphical representation of the number of Thomson Reuters (formerly ISI) Web of Knowledge references.

In a period of 20 years (1990-2010), there was a marked drop in the number of publications regarding the use of iNO in heart transplant. This number remained below 3% for cases of coronary artery bypass graft, around 15% for publications on the use of iNO in surgeries for heart valve disease treatment (tendency to decrease) and congenital heart disease (tendency to increase) (Figure 5).

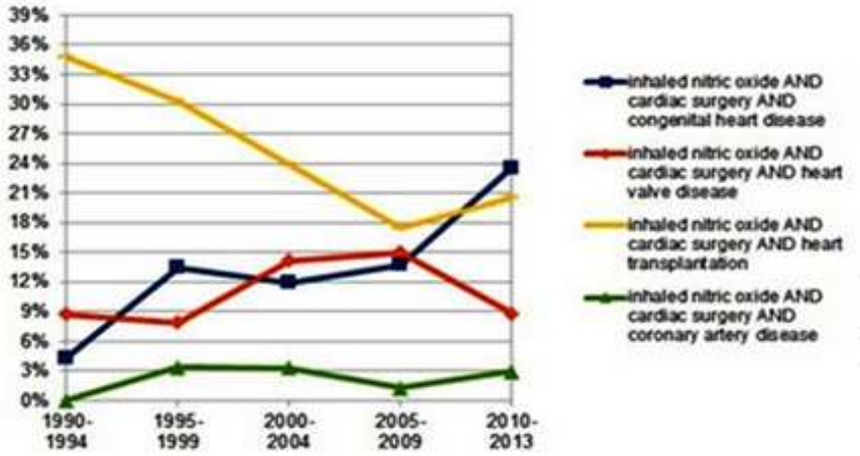

Figure 5. Graphical representation of the timeline decades of MEDLINE references

The apparent decrease of iNO use in surgeries to correct congenital cardiac defects highlights some doubts about its real usefulness. Cochrane Database System Review observed no differences in the use of iNO when compared to control in the majority of outcomes reviewed. No data were available for analysis concerning several clinical outcomes, including long-term mortality and neurodevelopmental outcome. The authors found it difficult to draw valid conclusions because of concerns regarding methodological quality, bias, sample size, and heterogeneity. [51]

These data confirm the observations and trends regarding the future therapeutic use of inhaled NO. Its use is not made unanimously, and the groups that are most benefited are those in which pulmonary hypertension is transient. Considering the relatively small number of reports, many associated with isolated cases, and a prominent prevalence of human observation, more experimental investigations are needed. Perhaps this fact is due partly to the difficulty of obtaining appropriate experimental models of pulmonary hypertension, but obviously due to the unknown about potential long-term toxic effects of inhaled NO. In the absence of trials involving large numbers of patients, and despite its potential toxicity, inhaled NO should be used, with extraordinary technical accuracy, as a therapeutic test that can save lives.

4. Concluding remarks

A Societad Iberoamericana de Información Scientific (SIIC) and a Brazilian Journal of Cardiovascular Surgery reports, in 2002, motivated the current review [50]. Updating the data so far, it can be said that the outlook for the use of inhaled NO changed little or nothing. It is worth mentioning a recent meta-analysis clinical trial for a real assessment of the problem, which was based in The Cochrane Central Register of Controlled Trials, and the reviewers support the following conclusions [51,52]:

- Inhaled NO shows no effect on mortality and improves oxygenation transiently in patients with hypoxemic respiratory failure,

- The lack of information does not allow the assessment of other clinically relevant goals,
- New trials comparing inhaled NO with some inhaled placebo will be essential to stratify the primary disease and assess the impact of other forms of combination therapy for respiratory failure
- They will need estimate, specifically, effects before any clinically relevant benefit of inhaled NO for respiratory failure can be excluded.

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References

[1] Furchgott RF & Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980, 288: 373-6.

[2] Cherry PD, Furchgott RF, Zawadzki JV, D. Jothianandan. Role of endothelial cells in relaxation of isolated arteries by bradykinin. Proc Natl Acad Sci USA 1982, 79:2106-10.

[3] Cocks T & Angus JA. Bioassay of the release of endothelium-derived relaxing factor (EDRF) from isolated endothelial cells in vitro. In: Bevan JA, Godfraind T, Maxwell RA, Stoclet JS, Worcel M, eds. Vascular neuroeffector mechanisms. Amsterdam: Elsevier, 1985:131-6.

[4] Furchgott RF. Studies on relaxation of rabbit aorta by sodium nitrite: the basis for the Proposal That the acid-activated inhibitory factor from bovine retractor penis is inorganic nitrite and the endothelium-derived relaxing factor is nitric oxide. In: Vanhoutte PM, ed. Mechanisms of vasodilatation. New York: Raven Press, 1988:401-14. Vol. IV.

[5] Ignarro LJ, Byrns RE, Wood KS. Biochemical and pharmacological properties of EDRF and Its similarity to nitric oxide radical. In: Vanhoutte PM, ed. Mechanisms of vasodilatation. New York: Raven Press, 1988:427-35. Vol. IV.

[6] Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987, 327:524-6.

[7] Palmer MR Ashton DS, Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature 1988, 333:664-6.

[8] Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 1991, 83:2038-47.

[9] Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991, 43:109-42.

[10] Snyder SH, Bredt DS. Biological roles of nitric oxide. Sci Am 1992, 266:68-77.

[11] AP Tavares Pimenta Junior AG, Evora PR. Basis for the therapeutic use of inhaled nitric oxide. Arq Bras Cardiol 1995, 64:45-52.

[12] Frostell CG, Blomqvist H, Hedenstierna G, J Lundberg, Zapol WM. Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction Causing without systemic vasodilatation. Anesthesiology 1993; 78:427-35.

[13] Wessel DL, Adatia I, Giglia TM, Thompson JE, Kulik TJ. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. Circulation 1993, 88 (5 pt 1), 2128-38.

[14] Roberts JD, Jr., Lang P Bigatello LM, GJ Vlahakes, Zapol WM. Inhaled nitric oxide in congenital heart disease. Circulation 1993, 87:447-53.

[15] Vallance P, J Collier, Moncada S. Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. Lancet 1989; 2:997-1000.

[16] Cremona G, Dinh-Xuan AT, Higenbottam TW. Endothelium-derived relaxing factor and the pulmonary circulation. Lung 1991, 169:185-202.

[17] Roos CM, Rich GF, Uncles DR, Daugherty MO, Frank DU. Sites of vasodilatation by inhaled nitric oxide vs. sodium nitroprusside in endothelin-constricted isolated rat lungs. J Appl Physiol 1994, 77:51-7.

[18] Benzing A Geiger & K. Inhaled nitric oxide lowers pulmonary capillary pressure and changes longitudinal distribution of pulmonary vascular resistance in Patients with acute lung injury. Acta Anaesthesiol Scand 1994; 38:640-5.

[19] Carmona MJ & Auler Jr. OJ. Effects of inhaled nitric oxide on respiratory system mechanics, Hemodynamics, and gas exchange after cardiac surgery. J Vasc Cardiothorac Anesth 1998, 12:157-61.

[20] Centers for Disease Control. Recommendation for occupational safety and health standard. MMWR Morb Mortal Wkly Rep 1980; 37: S7.

[21] Troncy E, M Francoeur, Blaise G. Inhaled nitric oxide: clinical applications, Indications, and toxicology. Can J Anaesth 1997, 44:973-88.

[22] Morris K, M Beghetti, Petros A, Adatia I, Bohn D. Comparison of hyperventilation and inhaled nitric oxide for pulmonary hypertension after repair of congenital heart disease. Crit Care Med 2000; 28:2974-8.

[23] KG Allman, JD Young, Carapiet D, Stevens JE, Ostman-Smith I, Archer LN. Effects of oxygen and nitric oxide in oxygen on pulmonary arterial Pressures of children with congenital cardiac defects. Pediatr Cardiol 1996; 17:246-50.

[24] Sharma R, rooted N, SK Choudhary et al. Does inhaled nitric oxide Improve survival in operated congenital disease with severe pulmonary hypertension? Indian Heart J 2001, 53:48-55.

[25] ernandes JL, Sampaio RO, Brandão CM, Accorsi TA, Cardoso LF, Spina GS, Tarasoutchi F, Pomerantzeff P, Auler JO Jr, Grinberg M. Comparison of inhaled nitric oxide versus oxygen on hemodynamics in patients with mitral stenosis and severe pulmonary hypertension after mitral valve surgery. Am J Cardiol. 2011;107:1040-5.

[26] Matamis D, Pampori S, Papathanasiou A, Papakonstantinou P, Tsagourias M, Galiatsou E, Koulouras V, Nakos G. 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.

[27] Checchia PA, Bronicki RA, Goldstein B. Review of inhaled nitric oxide in tem pediatric cardiac surgery setting. Pediatr Cardiol. 2012;33:493-505.

[28] Curran RD, Mavroudis C, Backer CL, Sautel M, Zales VR, Wessel DL. Inhaled nitric oxide for children with congenital heart disease and pulmonary hypertension. Ann Thorac Surg 1995; 60:1765-71.

[29] Laitinen PO, Rasanen J, Sairanen H. Postoperative nitric oxide therapy in children with congenital heart disease: can the need be predicted? Scand J Cardiovasc 2000, 34:149-53.

[30] Durongpisitkul K, Laoprasitiporn D, Layangool T, Sittiwankul R, Panamonta M, Mokrapong P; Thailand Multicenter Study. Comparison of the acute pulmonary vasodilating effect of beraprost sodium and nitric oxide in congenital heart disease. Circ J. 2005;69:61-4.

[31] Preston IR, Sagliani KD, Roberts KE, Shah AM, Desouza SA, Howard W, Brennan J, Hill NS. Comparison of acute hemodynamic effects of inhaled nitric oxide and inhaled epoprostenol in patients with pulmonary hypertension. Pulm Circ. 2013;3(1): 68-73.

[32] Rimensberger PC, Spahr-Schopfer I, Berner M et al. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital

heart disease: vasodilator capacity and cellular mechanisms. Circulation 2001; 103:544-8.

[33] Ichida F, ESEU K, Hashimoto I et al. Acute effect of oral prostacyclin and inhaled nitric oxide on pulmonary hypertension in children. J Cardiol 1997; 29:217-24.

[34] Ivy DD, Kinsella JP, Ziegler JW, Abman SH. Dipyridamole attenuates rebound pulmonary hypertension after inhaled nitric oxide withdrawal in postoperative congenital heart disease. J Thorac Cardiovasc Surg 1998; 115:875-82.

[35] Lee JE, Hillier SC, Knoderer CA. Use of sildenafil to facilitate weaning from inhaled nitric oxide in children with pulmonary hypertension following surgery for congenital heart disease. J Intensive Care Med. 2008;23:329-34.

[36] Nakatsu T, Nemoto S, Ikeda T, Saji Y, Nakajima H, Nishina T, Ohno N, Komeda M. Prophylactic treatment of oral sildenafil citrate for pulmonary hypertension in an infant treated with inhaled nitric oxide after open-heart surgery]. Kyobu Geka. 2005;58:1136-9.

[37] Yahagi N, Kumon K Tanigami H et al. Cardiac surgery and inhaled nitric oxide: Indication and follow-up (2-4 years). Artif Organs 1998, 22:886-91.

[38] Atz AM &Wessel DL. Nitric oxide inhalation. In: Rubanyi GM, ed. Pathophysiology and clinical applications of nitric oxide. Netherlands: Harwood Academic Publishers, 1999, 471-503.

[39] Checchia PA, Bronicki RA, Goldstein B. Review of inhaled nitric oxide in the pediatric cardiac surgery setting. Pediatr Cardiol. 2012;33:493-505.

[40] Omar HA, Gong F, Sun MY, Einzig S. Nebulized nitroglycerin in children with pulmonary hypertension secondary to congenital heart disease. W V J Med 1999; 95:74-5.

[41] Denault AY, Lamarche Y, Couture P, Haddad F, Lambert J, Tardif JC, Perrault LP. Inhaled milrinone: a new alternative in cardiac surgery? Semin Cardiothorac Vasc Anesth. 2006 ;10:346-60.

[42] Singh R, Choudhury M, Saxena A, Kapoor PM, Juneja R, Kiran U. Inhaled nitroglycerin versus inhaled milrinone in children with congenital heart disease suffering from pulmonary artery hypertension. J Cardiothorac Vasc Anesth. 2010;24:797-801.]

[43] Hayward CS, Kalnins WV, Rogers P, Feneley MP, Macdonald PS, Kelly RP. Left ventricular chamber function During inhaled nitric oxide in Patients with dilated cardiomyopathy. J Cardiovasc Pharmacol. 1999, 34:749-54.

[44] Hare JM, Shernan SK Body SC Graydon E, Colucci WS, GS Couper. Influence of inhaled nitric oxide on systemic flow and ventricular filling pressure in Patients receiving mechanical circulatory assistance. Circulation. 6 1997, 95:2250-3.

[45] E Loh, EB Lankford, DJ Polidori, EB Doering-Lubit, Hanson CW, Acker MA. Cardiovascular effects of inhaled nitric oxide in a canine model of cardiomyopathy. Ann Thorac Surg. 1999, 67:1380-5.

[46] Bocchi EA, Bacal F, Auler Junior JO, Carmona MJ, Bellotti G, Pileggi F. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. Am J Cardiol. 1994, 74:70-2.

[47] Hayward CS, Rogers P, Keogh AM, Kelly R, Spratt PM, Macdonald PS. Inhaled nitric oxide in cardiac failure: vascular versus ventricular effects. J Cardiovasc Pharmacol. 1996; 27:80-5.53

[48] Semigran MJ, Cockrill BA, Kacmarek R, Thompson BT, Zapol WM, Dec GW, Fifer MA. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol. 1994, 24:982-8.

[49] AndLoh, Stamler JS, Hare JM, Loscalzo J, Colucci WS. Cardiovascular effects of inhaled nitric oxide in Patients with left ventricular dysfunction. Circulation. 1994, 90:2780-5.

[50] Evora PRB, Viaro F, Oshiro MS, Souza DG. The utilization of inhaled nitric oxide in cardiac surgery: critical analysis and actualization. Rev. Bras. Cir. Cardiovasc, 17:221-229, 2002.

[51] Bizzarro M, Gross I. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD005055.

[52] Sokol J, Jacobs SE, Bohn D. Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Cochrane Database Syst Rev. 2003; CD002787.

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