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A European survey of the use of inhaled nitric oxide in the ICU

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Introduction

The administration of nitric oxide (NO) via inhalation has been shown to vasodilate the pulmonary circulation selectively without affecting systemic vascular tone [1, 2]. Inhaled NO has been proposed to improve oxygenation and/or reduce pulmonary hypertension in patients suffering from the acute respiratory distress syndrome (ARDS) [2], after cardiac surgery [3, 4], in congenital heart diseases [5, 6], in children with pulmonary hypertension [7], in neonatal respiratory failure [8] and in primary pulmonary hypertension [9–12]. Therefore, inhaled NO has emerged as a widely used therapy in the intensive care unit (ICU) despite a paucity of controlled studies on outcome. In pediatric and neonatal patients, multicentric trials have proved that inhaled NO could reduce mortality or requirements for extracorporeal oxygenation techniques [8, 13], but beneficial effects on outcome have not been shown in adults with ARDS [14–16].

In 1997, we conducted a study using a questionnaire evaluating the current practice among European intensivists on the indications, use, monitoring and safety of inhaled NO therapy. Our aims were to establish areas of consensus among both the opinions of the members of the Working Group and actual European practice, given the fact that recommendations (rather than fixed regulations) concerning the use of NO, even if including part of the results of this survey, would only be possible after detailed analysis of clinical studies targeted at measurements of outcome.

Material and methods

This survey was conducted as part of the activities of the Working Group on "NO in the ICU" of the European Society of Intensive Care Medicine (ESICM). This group includes 48 intensivists from 12 European countries and from USA involved in clinical and experimental developments related to NO in the ICU. To explore the current practice of inhaled NO in the ICU, a questionnaire was developed consisting of 33 questions regarding modes and doses of administration, monitoring, safety and effects on hemodynamic and gas exchange parameters (see Appendix). The questionnaire was given to members of the Working Group and sent to all members of the ESICM with an accompanying letter. A single mailing was sent on November 29, 1997, without further reminder or incentive. The results of the survey were presented to the ESICM Working Group on NO. After discussion of the results, Working Group members generated comments for the use and regulation of inhaled NO for future studies.

Binary and categorial questions were used to determine reported practice. In addition to demographic information, the questionnaire recorded year of starting the use of inhaled NO therapy, number of patients treated to date, indications and criteria for NO administration, modes of administration and monitoring, efficacy criteria and safety issues. Statistical analyses were performed using StatView software (Abacus Concepts, Inc., Berkeley, CA, 1994). Frequencies and means were computed for individual items as appropriate, and included only the persons responding to the individual items. Contingency table analyses were used to determine whether a relationship existed between the response to a given individual item and type of primary speciality, year of starting the use of inhaled NO therapy and the number of patients treated. The chi-square test was used to evaluate differences, with a probability value less than 0.05 considered as significant.

Results

Medical environment and use of NO therapy

Within 4 weeks after mailing, 310 physicians from 21 countries responded to the questionnaire. Of these, 196 (63.2%) currently use inhaled NO therapy (Fig. 1). The primary declared specialities (Fig. 2) were

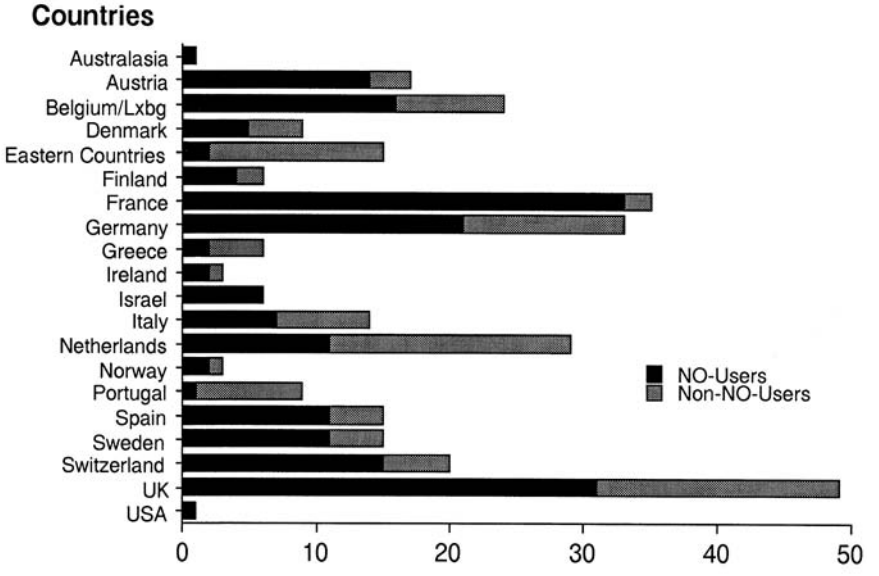

Fig. 1 Country of origin of respondents to the questionnaire. Values are number of answers

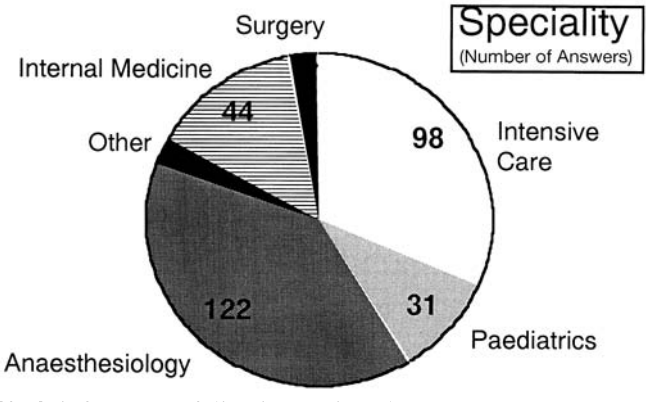

Fig. 2 Primary speciality declared by the respondents to the questionnaire. Values are number of answers

anesthesiology ($n = 122$, with 58% using NO), intensive care medicine ($n = 98$, with 71% using NO), internal medicine ($n = 44$, with 47% using NO), pediatrics ($n = 31$, with 90% using NO), surgery (7 respondents) and others (8 respondents). Chi-square analysis revealed that intensivists and pediatricians were the two specialities that were significantly most likely to use inhaled NO ($p < 0.0004$). More than half of the physicians (161 out of 310) were practising in hospitals with more than 750 beds, with a higher than expected proportion of NO-users (76%, $p < 0.0001$). Almost two-thirds of the respondents worked at university hospitals.

The distributions of the year of starting NO therapy and the numer of patients treated to date among respondents are shown in Fig. 3. The vast majority started NO therapy before 1996, and 42% of them have treated more than 30 patients. In addition to NO inhalation, besides alveolar recruitment, other techniques to improve gas exchange by the responders included prone position (used by 82% of physicians), aerosolized prostacyclin (18%), almitrine infusion (20%) and extracorporeal CO_2 removal techniques (27%).

Indications of inhaled NO therapy

The results are presented in Table 1. Not surprisingly, pediatricians mentioned ARDS (with a Murray score > 2.5) ($p < 0.0001$) and acute lung injury (ALI) ($p < 0.002$) as indications for NO therapy less frequently than non-pediatricians. For all physicians, pulmonary hypertension was considered a good indication in 80% of cases. Right ventricular failure was considered as an indication by 38% of non-pediatricians and by 16% of pediatricians ($p < 0.05$). Among pediatricians, primary pulmonary hypertension and congenital heart disease were considered as indications in 86% and 73% of respondents, respectively. Finally, NO therapy was indicated by 70% of all physicians in idiopathic pulmonary hypertension and by 77% of all physicans in transplant patients or as a test before cardiac surgery. The results were not related to the previous experience of the physicians since the answers were uniform when considering the year of starting the use of inhaled NO therapy.

Considering PaO_2 as an indicator of NO therapy, 27% of the respondents felt NO was indicated for a PaO_2/FIO_2 less than 100 mm Hg, and 32% for a PaO_2/FIO_2 between 100 and 150 mm Hg. However, 29% of the respondents did not use PaO_2/FIO_2 as a criteria for NO therapy. These results were unrelated to the primary specialities of the physicians or the year they be-

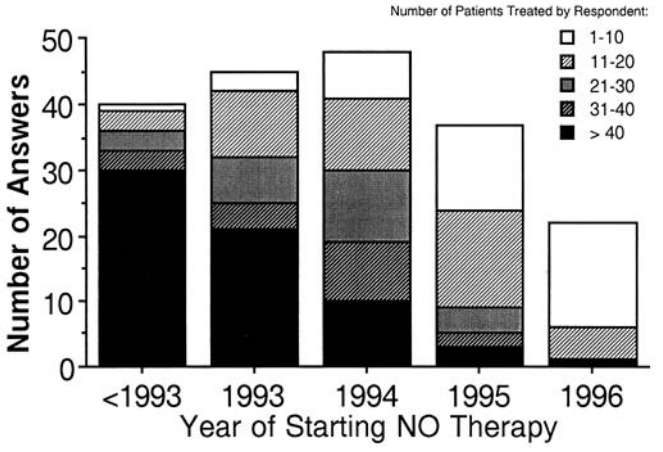

Fig. 3 Number of patients treated by the respondents to the questionnaire according to the year of starting NO therapy

gan to use NO. Considering hemodynamic data, a majority of NO-users (62%) did not consider threshold values of pulmonary artery pressure or pulmonary vascular resistance as an indication for NO therapy. The usual aims of therapy were to increase PaO_2 (97%) and reduce pulmonary hypertension/right ventricular afterload (78%). Only half of the respondents (50%) aimed to decrease the baro-volotrauma of mechanical ventilation with NO.

Modes of inhaled NO administration and monitoring

The mean duration of treatment was similar for all physicians' primary specialities and was 3–4 days in 45% of the cases and 5–6 days in 36% (Fig. 4). Less than 15% administered NO for more than a week. The mean fraction of NO given in ARDS/ALI and in pulmonary hypertension was different, with a distribution of the answers shifted towards higher doses in pulmonary hypertension (Fig. 5). The highest amount of NO given to a single patient was greater than 40 ppm for 43% of physicians. These results were influenced ($p < 0.004$) by the previous number of patients treated by the respondents: physicians who had treated 20 or fewer patients were more likely to administer a maximum dose of NO less than 20 ppm, while physicians who had treated more than 20 patients were more likely to have administered a maximum dose of NO higher than 40 ppm.

The concentration of NO in the tank used varied among users, although for non-pediatricians, 49% of respondents reported a NO concentration higher than 900 ppm (Table 2). Pediatricians usually (40%) used tanks at lower concentrations (500–900 ppm). About one-fifth used tanks with concentrations higher than 900 ppm. The site of NO administration was through the Y-piece of the ventilator for the vast majority of respondents (73%), a response not affected by the primary speciality of the physicians or by the year of start-

Table 1 Indications of inhaled NO therapy used by the respondents of the questionnaire according to the primary speciality declared. Yes/No denotes number of positive and negative answers, respectively. Percents denote percentage of positive answers within a given speciality

	Anesthesiology	Intensive care	Internal medicine	Pediatrics	Surgery	Other	Totals
Acute respiratory distress syndrome (ARDS)							
Yes/No	70/0	68/1	22/0	19/7	1/1	3/0	183/9
%	100%	98.5%	100%	73.1%			95.3%
Acute lung injury (ALI)							
Yes/No	47/19	47/15	13/8	9/17	0/2	1/0	117/61
%	71.2%	75.8%	61.9%	34.6%			65.7%
Pulmonary hypertension (PHT)							
Yes/No	53/16	57/10	13/8	23/4	2/0	4/0	152/38
%	76.8%	85.1%	61.9%	85.2%			80%
Right ventricular failure (RVF)							
Yes/No	23/38	26/37	4/16	4/21	2/0	1/1	60/113
%	37.7%	41.3%	20%	16%			34.7%
Idiopathic pulmonary hypertension (IPHT)							
Yes/No	13/46	19/35	6/14	9/16	0/1	0/1	47/113
%	22.1%	35.2%	30%	36%			29.4%
Transplant patients							
Yes/No	13/43	10/46	5/16	5/16	1/0	1/1	35/122
%	23.2%	17.9%	23.2%	23.8%			22.3%
Primary pulmonary hypertension of the newborn (PPHN)							
Yes/No	11/48	15/39	3/16	25/4	1/0	2/1	57/108
%	18.6%	27.8%	15.8%	86.2%			34.6%
Congenital heart diseases (CHD)							
Yes/No	12/44	14/41	4/16	19/7	1/0	2/1	52/109
%	21.4%	25.4%	20%	73.1%			32.3%

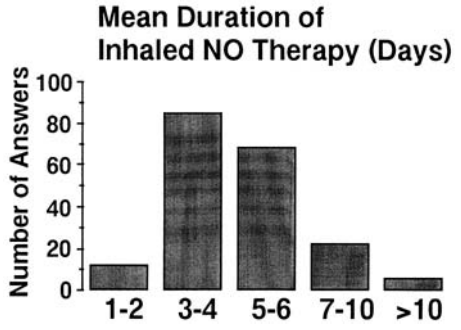

Fig. 4 Mean duration of inhaled NO therapy (days). Values are number of answers to the questionnaire

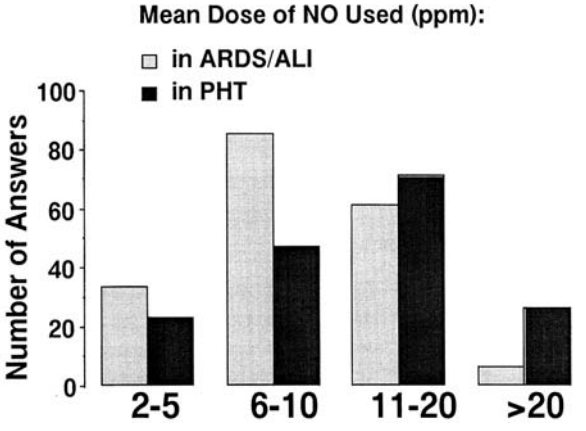

Fig. 5 Mean doses of inhaled NO (ppm) administered in acute respiratory distress syndrome/acute lung injury (ARDS/ALI) and in pulmonary hypertension (PHT). Values are number of answers to the questionnaire

ing NO therapy. Fifty-one percent of the physicians administered inhaled NO continuously throughout the respiratory cycle and 49% only during the inspiratory phase. Eighty-five percent of physicians monitored the inhaled NO concentration, mainly in the inspired circuit (77% of answers) and in a continuous mode (89% of answers). The most usual technique of monitoring was electrochemical cells (65%), although the use of chemiluminescence increased with the reported number of patients treated with NO ($p < 0.05$).

Efficacy of inhaled NO administration

On a practical aspect, the estimated number of patients not responding to NO (i.e. failing to increase PaO_2 by 10%) was distributed as a bell-shaped curve with the peak corresponding to an estimate of 10–20% of non-responders to NO (33% of answers) (Fig. 6). For the extreme answers, 16% of physicians estimated that the proportion of non-responding patients was less than

Table 2 Frequency distribution of NO in N_2 (ppm) concentrations in the tanks used for NO delivery and sites of NO administration according to the speciality of the respondents to the questionnaire and to the site (i.e. inspired or expired circuit) of NO monitoring (for the physicians using a monitoring method). Values are number of positive answers divided by total number of answers

Speciality	NO concentration in tank (ppm)				Site of NO administration		
	101 to 250	251 to 500	501 to 900	> 900	Before ventilator	Through Y piece	Catheter in tracheal tube
Anesthesiology	11/68	10/68	11/68	36/68	18/64	43/64	3/64
%	16.2	14.7	16.2	52.9	28.1	67.2	4.7
Intensive care	12/61	13/61	9/61	27/61	14/66	46/66	6/66
%	19.7	21.3	14.7	44.3	21.2	69.7	9.1
Internal medicine	0/19	3/19	6/19	10/19	3/22	18/22	1/22
%	0	15.8	31.6	52.6	13.6	81.8	4.5
Pediatrics	2/27	8/27	11/27	6/27	1/25	24/25	0/25
%	7.4	29.6	40.7	22.2	4	96	0
Surgery	0/2	0/2	1/2	1/2	0/2	2/2	0/2
Other	0/1	0/1	0/1	1/1	3/4	1/4	0/4
Totals	25/178	34/178	38/178	81/178	39/183	134/183	10/183
%	14	19.1	21.3	45.5	21.3	73.2	5.5
Site of NO monitoring							
Inspired circuit	9/115	21/115	23/115	62/115	31/113	80/113	2/113
%	7.8	18.3	20	53.9	27.4	70.8	1.7
Expired circuit	4/31	6/31	11/31	10/31	8/34	25/34	1/34
%	12.9	19.3	35.5	32.3	23.5	73.5	2.9
Totals	13/146	27/146	34/146	72/146	39/147	105/147	3/147
%	8.9	18.5	23.3	49.3	26.5	71.4	2

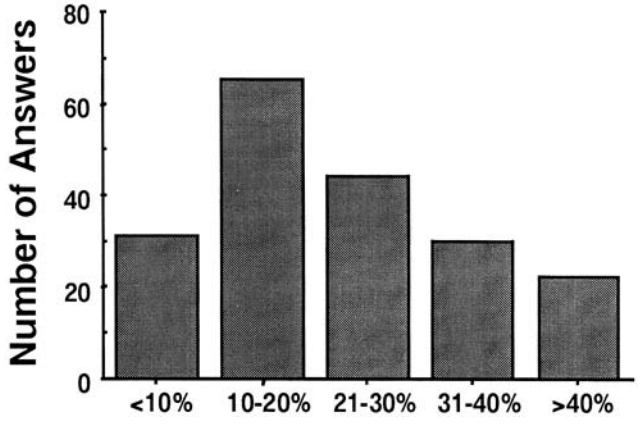

Fig. 6 Estimated percentage of patients not responding to inhaled NO therapy (i.e. failing to increase PaO_2 by 10%). Values are number of answers to the questionnaire

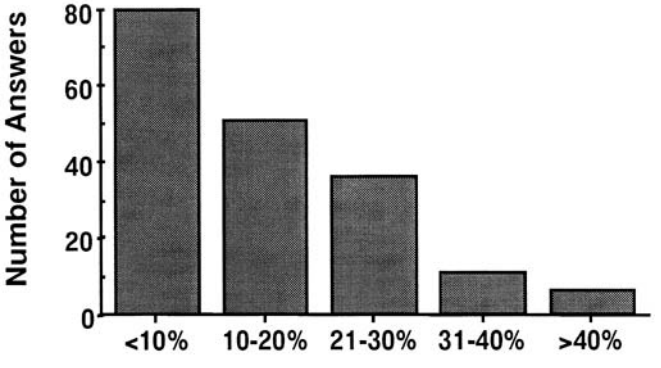

Fig. 7 Estimated percentage of failure-to-wean NO therapy. Values are number of answers to the questionnaire

10%, while 11.5% estimated that this proportion was higher than 40%. The apparent reasons for this heterogeneity are not clear and did not seem related to the year of starting NO therapy or to the medical specialities.

The most frequent answer for the FIO_2 reached for weaning from NO therapy was 0.5–0.6 (45% of answers), but the level of FIO_2 had to be lower than 0.5 for 23%. There was no statistical correlate between the preferred value of FIO_2 for weaning and the declared PaO_2/FIO_2 leading to an indication of NO therapy. Interestingly, 31% of physicians did not use this parameter for weaning, and only 37% of these also did not use the PaO_2/FIO_2 value as an index for NO indication. The vast majority of physicians used a slow wean off NO (83%) rather than a simple disconnection (16%). The estimated percentage of failure-to-wean NO therapy (requiring the re-introduction of NO therapy) reported by the physicians was relatively small: 43% estimated it to be less than 10% and 27% estimated in the 10–20% range of treatment episodes (Fig. 7).

Table 3 Declared level of recommendations/regulations regarding NO use

	Should be performed: at national level	at Europan level	Should not be performed	Totals
NO-users	34 (18%)	136 (71%)	21 (11%)	191 (100%)
Non-NO-users	13 (18%)	57 (77%)	4 (5%)	74 (100%)
Totals	47(18%)	193 (73%)	25 (9%)	265 (100%)

Safety of inhaled NO administration

The reported incidence of incidents/complications possibly related to inhaled NO was 20% for methemoglobinemia, 9% for excessive bleeding and 6% for acute pulmonary edema. There was no statistical difference related to the primary speciality of the physicians. Finally, regarding the need for recommendations/regulations, the majority of respondents estimated that such recommendations/regulations should be performed at the European level (Table 3). These results were not affected by the year of starting NO therapy, or by primary speciality. Also, 77% of NO-users (but only 40% of non-NO-users, $p < 0.0001$) declared interest in participating in a European multicentric trial.

Discussion

The recent discovery of the selective pulmonary vasodilating properties of inhaled NO has stimulated its administration to correct hypoxemia or relieve pulmonary hypertension. Furthermore, the anti-inflammatory effects of inhaled NO have been described in animal models, including decreased PMN activation or pro-inflammatory cytokines production [17, 18], in patients with ARDS [19], in neonates [20] and during lung transplantation [21]. However, inhaled NO may also worsen lung injury, especially when combined with high inspired oxygen fractions via the rapid formation of toxic NO derivatives such as nitrogen dioxide (NO_2) or peroxynitrite (ONOO) [22, 23]. Therefore, it is still unknown whether the apparent short-term beneficial effects of inhaled NO on oxygenation and reduction in pulmonary hypertension are associated with a positive effect on mortality, and no information exists on its potential long-term toxicity [24]. Following a National Heart, Lung and Blood Institute meeting in 1993, safety guidelines for studies of NO inhalation have been proposed in an attempt: 1) to minimize the amount of NO_2 generated during NO inhalation; 2) to promote the monitoring of the NO fraction administered and of methemoglobin levels; 3) to use the "lowest effective concentration of inhaled NO"; 4) to avoid sudden discontinuation of inhaled NO and 5) to have access to a supplemental

breathing circuit capable of delivering inhaled NO to allow manual ventilation during tracheal suctioning or transport [25]. Recently, based on the results of a survey obtained in 54 ICUs in the United Kingdom, Cuthbertson et al. [26] extended these recommendations, with special regard to the delivery, monitoring and scavenging of NO.

As the literature on inhaled NO therapy is rapidly expanding [27], and national regulations specifying the modalities of NO inhalation therapy besides research are at the present time only available for France, United Kingdom [26, 28], Germany, Austria and Sweden, we prepared this questionnaire to determine why and how inhaled NO is presently used, and to estimate whether a consensus on its use could be reached at the European level. The intensivists clearly declared a preference for European rather than national (or no) recommendations regarding NO use. Tentative recommendations based on evidence published in the literature cannot, as for meta-analyses, be taken as surrogate evidence for the necessity of performing large multicentric trials specifically focusing on a given question [29]. Given the inherent limitation that such a survey does not document current practice, but rather the respondents' beliefs about their practice [30], overall differences in practice among respondents to the questionnaire who used NO were relatively minor, and appeared mainly related to differences between adult and pediatric patient populations.

The large number of answers received (including onthird of respondents not even using NO) after a single mailing without any reminder or incentive could be interpreted as a sign of interest from the ESICM members. Respondents were well distributed between various specialities, with potentially good experience in respiratory critical care based on the number of patients treated and the percentage of physicians using relatively sophisticated techniques such as prostacyclin or almitrine infusion, prone position and extracorporeal CO_2 removal techniques. The vast majority of respondents had more than 2 years, experience in the use of inhaled NO and, according to the individual declarations, the total number of patients treated by the respondents of this survey was between 4290 and 5450. Respondents were apparently satisfied with inhaled NO therapy (based on percentages of patients responding to NO, failing to be weaned and the duration of treatment), with few reported incidents, and they declared a willingness to participate in a European multicentric trial. This encourages the elaboration of European recommendations for inhaled NO indications, modes of administration, monitoring and criteria for efficacy and safety, which should not, however, be interpreted as a definitive statement regarding the efficacy of NO.

The indications for inhaled NO therapy suggested by the respondents reflected the literature. Pediatricians often cited specific indications such as primary pulmonary hypertension of the newborn and congenital heart diseases. Other indications were less common for pediatricians, except for pulmonary hypertension. Among non-pediatricians, ARDS was almost unanimously cited, and ALI by three-quarters of respondents. This majority (58%) of respondents administered NO when PaO_2/FIO_2 is less than 150 mm Hg. This tendency to administer NO only to the sickest patients might be related to the potential risks associated with NO administration and/or to the unproven effect of NO administration on the outcome in patients with respiratory failure. Interestingly, one-third of respondents did not use PaO_2/FIO_2 as an index for NO administration in hypoxemic patients. Besides PaO_2 improvement, the other effects of inhaled NO, such as modulation of the pulmonary inflammation [18–20, 31], are still debated. Limitation of the deleterious consequences of baro/volotrauma, a potentially beneficial consequence of inhaled NO therapy (although still under investigation), was also an indication for initiating NO therapy in half of the respondents.

After ARDS and ALI, the third most frequent indication for NO was pulmonary hypertension, although a clear majority of respondents did not use threshold values of pulmonary artery pressure or pulmonary vascular resistance as indicators for NO inhalation. This, again, is consistent with reports in the literature on the effects of NO on the pulmonary vasculature [4, 32–38], or with the possible lack of correlation between improvement in arterial oxygenation and decrease in PVR [32, 36, 39]. Although a majority of respondents used NO as a pulmonary vasodilator, less than 40% used it in right ventricular failure. This indication may become more popular if future studies expand earlier findings of the beneficial consequences of NO on right ventricular function in patients with ARDS [39, 40] or with right ventricular dysfunction [41]. In ARDS, NO can unload the right ventricle and increase the right ventricular ejection fraction, with unchanged [39], or increased, cardiac output in responders [40]. Inhaled NO was less used in idiopathic pulmonary hypertension or in transplant patients, but this could be due to the relative rarity of these diseases. Inhaled NO has been proposed in idiopathic pulmonary hypertension [10, 12, 42], but sometimes with potentially deleterious effects [43, 44]. Increased pulmonary wedge pressure and pulmonary edema have been shown in patients with severe left heart failure [45, 46]. Other diseases, such as chronic obstructive pulmonary disease (COPD) were not proposed as an indication because of the generally accepted lack of improvement of PaO_2 for this indication [47, 48] (since areas with low VA/Q ratios could be preferentially vasodilated by NO [49]), although recent studies suggest that inhaled NO may augment oxygenation during exercise in COPD patients during exercise [50] or in combination with oxygen [51].

The duration of treatment and doses used were relatively uniform. The vast majority of respondents used NO for less than a week, a relatively short-term use that might limit the incidence of untoward effects. The doses used were relatively small compared to the doses initially described by Rossaint et al. [2], consistent with newer dose-responses studies in the literature establishing that relatively low doses of NO seem sufficient to correct hypoxemia [52, 53]. The use of higher doses in pulmonary hypertension (but still generally < 20 ppm) than in ARDS or ALI was common, consistent with different responses to NO in these diseases. Gerlach et al. [32] observed that the improvement in PaO_2 with 50% maximal response (ED50) occurred at approximately 0.1 ppm in patients with ARDS, whereas ED50 for pulmonary artery pressure reduction was approximately 2–3 ppm.

Concerning the practical aspects of NO administration, the concentration of NO in N_2 in the tanks used was not uniform. Usually, non-pediatricians use a tank containing a concentration lower than 900 ppm, whereas pediatricians usually prefer lower concentrations. This is easily explained by the fact that the pediatric population requires smaller minute ventilation than adults, and by the greater concern of toxicity (particularly methemoglobin formation [54]) than in adults. Some countries have issued special limitations for the maximum concentration of NO in N_2 in the tank to be used, especially for pediatric use. The maximum concentration of NO in the tank should probably be limited, although very high concentrations (10,000 ppm) have been used without reported incidents in 214 pediatric patients with the development of a NO controller with a fail-safe NO shut-off system and an incorporated maximum NO flow limitation [55].

Although accidental administration of high concentrations of NO (5,000 ppm) have been historically reported to cause acute pulmonary edema and significant methemoglobinemia [56, 57], the administration of therapeutic doses of NO seems to be safe in terms of NO_2 generation and methemoglobin toxicity. However, the technique of NO delivery and administration should minimize the amount of NO_2 administered to the patient and exposure to health care personnel [58]. The rate of conversion of NO to NO_2 is directly proportional to the square of NO concentration, residence time of NO in O_2, and FIO_2 [23, 59]. Nitrogen dioxide formation is also faster when the temperature is lower, but humidity does not influence NO_2 formation [60]. Gas cylinders containing NO in N_2 may also initially have a high NO_2 concentration (around 12 ppm) and should be flushed thoroughly before use [61]. Recommendations for the safe use of NO administration should include preventive measures to minimize degradation of the NO fraction administered, with delivery systems minimizing the duration of contact with O_2 given the dilution of the NO/N_2 mixture in the cylinder. The contact time between NO and oxygen can be reduced by administering NO in the respiratory circuit closer to the patient, as significantly higher rates of NO_2 formation have been described with NO administered in a prebreathing circuit blending system [7, 62, 63]. The interposition of a mixing chamber has also been proposed to prevent the variation in inspiratory peak concentrations of NO during its continuous administration [64].

For all specialists, the preferred site for NO administration was through the Y-piece of the ventilator, although one-fifth of respondents also administer NO before the ventilator. Very few ($n = 10$) administer NO through a fenestrated catheter in the tracheal tube, and this should be discouraged given the risks of direct tracheal lesions linked to high in situ concentrations of NO. Nitric oxide administration before the ventilator may lead to potential problems with a high rate of conversion of NO to NO_2, and requires the use of high precision mass flow regulators to allow a precise adjustment of the gases at the inlet gas port of the ventilator. The administration of NO in the inspiratory limb of the ventilator reduces the time contact between NO and O_2 and alleviates the need for sophisticated mass flow regulators since a precision flowmeter becomes sufficient to control the gas flow. However, it is important to note that with continuous-flow administration, NO concentrations administered are dependent upon the ventilatory settings, the most important being the I : E ratio and the addition of dead space [65]. Interestingly, half of the respondents administered NO only during the inspiratory phase of the ventilatory cycle, a technique that would limit the amount of NO administered and prevent its build-up [2, 32, 53].

A majority of physicians monitored the NO fraction administered, with regular measurements of mean inspired concentrations of NO and NOx. Electrochemical cells were the most widely used method, although experienced physicians tend to prefer chemiluminescence. These differences probably reflect the cost constraints of this method. Electrochemical methods are usually well correlated with chemiluminescence methods [63], although they may be insufficient to exclude a NO_2 toxicity because of an inability to detect measurements in the ppb-range [66]. Whatever method used for short-term monitoring, analysers should be frequently calibrated [67]. Although this question was not asked specifically in the questionnaire, the monitoring of NO therapy should also include assessment of the long-term adverse events, with regular follow-up procedures.

Very few incidences of side effects have been reported in the survey. The estimated percentage of patients failing to respond to NO therapy was relatively small, and might be related to the administration of NO in the clinical situation after a therapeutic optimization [68] including alveolar recruitment [35, 69]. However, caution should be exerted during weaning and the acciden-

tal discontinuation of therapy must be avoided. In some patients, a rebound phenomenon with acute pulmonary hypertension has been described after prolonged inhaled NO therapy [52, 70, 71] that might be secondary to a negative feedback mechanism, as inhaled NO can probably decrease endogenous NO production.

Concerning methemoglobin production following inhaled NO therapy, several case reports have described potentially deleterious increases in methemoglobin that would reduce the carrying potency of hemoglobin for oxygen [72]. Methemoglobin levels are usually not elevated following the administration of normal doses of NO [27, 73] because NO is reduced by methemoglobin reductase in the red cells [74]. Newborns may present a reduced NADH-methemoglobin reductase activity compared with adults [54], leading to possible deleterious increases in methemoglobin levels in children [7], although these are uncommon even in this population [6, 13, 75].

Finally, NO inhalation may interact with the coagulation system and increase bleeding time [76]. In ARDS patients, platelet aggregation was attenuated, but the bleeding time was found to be unchanged, even though NO fractions up to 100 ppm were used [77]. Such an "anticoagulatory" effect of inhaled NO might be beneficial in this inflammatory disease, which is characterized by the existence of microthrombi within the pulmonary microvasculature. However, this observation would suggest that caution should probably be applied regarding the use of inhaled NO in patients with bleeding tendencies, as recently reported in two patients [78].

List of participants of the working group on inhaled NO in the ICU:

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EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

Working Group on Inhaled NO in the ICU

QUESTIONNAIRE ON INHALED NO IN THE ICU

A. Medical Environment

1. You live in the following country ☐ 1

1. Australasia **2.** Austria **3.** Belgium/Luxembourg **4.** Canada **5.** Denmark **6.** Finland
7. France **8.** Germany **9.** Greece **10.** Ireland **11.** Israel **12.** Italy
13. Netherlands **14.** Norway **15.** Portugal **16.** Spain **17.** Sweden **18.** Switzerland
19 Turkey **20.** UK **21.** USA **22.** Eastern countries **23.** Other: _____

2. Your primary speciality is ☐ 2

1. Anaesthesiology **2.** Intensive Care **3.** Internal Medicine **4.** Paediatrics
5. Surgery **6.** Other: _____

3. The hospital with which you are most closely affiliated has ☐ 3

1. less than 250 beds **3.** 251 to 499 beds **3.** 500 to 749 beds **4.** 750 beds or more

4. This hospital is a ☐ 4

1. University hospital **2.** City or country hospital (regional centre) **3.** Private hospital

5. The intensive care unit (ICU) where you work has ☐ 5

1. 6 beds or less **2.** 7–12 beds **3.** 13–19 beds **4.** 20 beds or more

6. This ICU is ☐ 6

1. Medical **2.** Surgical **3.** Medico-Surgical **4.** Coronary (CCU)
5. Paediatric **6.** General

B. Practical questions about your work

7. Do you use inhaled NO? **1.** yes **2.** no ☐ 7

8. When did you start using inhaled NO?
1. before 1993 **2.** in 1993 **3.** in 1994 **4.** in 1995 **5.** in 1996 ☐ 8

9. Average number of patients treated so far:
1. 1–10 **2.** 11–20 **3.** 21–30 **4.** 31–40 **5.** > 40 ☐ 9

10. Mean duration of treatment (in days):
1. 1–2 **2.** 3–4 **3.** 5–6 **4.** 7–10 **5.** > 10 ☐ 10

11. Are your indications: **1.** yes **2.** no

ARDS (ATS definition, with Murray score > 2.5) ☐ 11
Acute lung injury ☐ 12
Pulmonary hypertension ☐ 13
Right ventricular failure (eg RV infarction) ☐ 14
Primary pulmonary hypertension of the newborn ☐ 15
Idiopathic pulmonary hypertension ☐ 16
Transplant patients/test before cardiac surgery ☐ 17
Congenital heart disease ☐ 18

12. Considering PaO_2, do you decide to administer inhaled NO if PaO_2/FiO_2 is:
1. 0–100 **2.** 101–150 **3.** 151–200 **4.** 201–300 **5.** I do not use this index ☐ 19

13. Do you consider threshold values of pulmonary artery pressure/pulmonary vascular resistance as an indication for NO therapy? **1.** yes **2.** no ☐ 20

14. Are the usual aims of inhaled NO therapy to **1.** yes **2.** no

Increase PaO_2/FiO_2 ☐ 21
Decrease baro-volotrauma of mechanical ventilation ☐ 22
Reduce pulmonary hypertension/right ventricular afterload ☐ 23

15. In your experience, what is the percentage of patients not responding to NO (i.e. failing to increase PaO_2 by 10%)? ☐ 24
1. < 10% **2.** 10–20% **3.** 21–30% **4.** 31–40% **5.** > 40%

16. Which is the usual amount of NO given (ppm) in ARDS/Acute lung injury? ☐ 25
1. 1 **2.** 2–5 **3.** 6–10 **4.** 11–20 **5.** > 20

17. Which is the usual amount of NO given (ppm) in pulmonary hypertension? ☐ 26
1. 1 **2.** 2–5 **3.** 6–10 **4.** 11–20 **5.** > 20

18. Which is the highest amount of NO (ppm) ever given in a selected patient? ☐ 27
1. 10 **2.** 11–20 **3.** 21–30 **4.** 31–40 **5.** > 40

19. Would you administer inhaled NO: ☐ 28
1. Continuously throughout the respiratory cycle **2.** Only during the inspiratory phase

20. Which is the concentration of NO (ppm) in the delivery tank used? ☐ 29
1. 1–100 **2.** 101–250 **3.** 251–500 4. 501–900 **5.** > 900

21. Which is the site of NO administration used? ☐ 30
1. Before the ventilator **2.** Through the Y-piece **3.** Fenestrated catheter inside the tracheal tube

22. Do you monitor the inhaled NO concentration given? **1.** yes **2.** no ☐ 31

23. If you do monitor inhaled NO therapy, which is the technique used? ☐ 32
1. Electrochemical cells **2.** Chemiluminescence **3.** Mass spectrometry

24. Where do you monitor? ☐ 33
1. Inspired circuit **2.** Expired circuit

25. What is the frequency of the monitoring? ☐ 34
1. Continuously **2.** Every hour **3.** Every 2 hours **4.** Every 6 hours **5.** Daily

26. Do you wean the patient from NO when: ☐ 35
1. $FiO_2 < 0.5$ **2.** $FiO_2 = 0.5 - 0.6$ **3.** I do not use this index for weaning

27. How do you wean the patient from NO? ☐ 36
1. Just by disconnecting NO **2.** Down titration, slowly decreasing NO dose

28. In your experience, what is the percentage of failure-to-wean NO therapy (imposing to re-introduce NO therapy)? ☐ 37
1. < 10% **2.** 10–20% **3.** 21–30% **4.** 31–40% **5.** > 40%

29. In your clinical practice in ARDS, besides alveolar recruitment, do you use the following therapies in addition to NO inhalation? **1.** yes **2.** no

Prone position	☐ 38
Aerosolised prostacycline	☐ 39
Almitrine infusion	☐ 40
Extracorporeal CO_2 removal techniques	☐ 41

30. Did you observe the following incidents/complications in your practice that you think were possibly related to inhaled NO? **1.** yes **2.** no

Methemoglobinemia	☐ 42
Excessive bleeding	☐ 43
Acute pulmonary oedema	☐ 44
Other (please specify):	☐ 45

31. Did your country's medical health services issue recommendations/regulations regarding the use of inhaled NO? **1.** yes **2.** no ☐ 46

32. Do you think such recommendations/regulations should be performed at the:
1. National level **2.** European level **3.** Should not be perfomed ☐ 47

33. Would you be interested in participating in a European multicentric trial? **1.** yes **2.** no ☐ 48
If yes, please write your complete address (+ fax, phone & E-mail) below.

Additional comments/suggestions on inhaled NO utilisation, or on this questionnaire:

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Many thanks for your interest and the time you spent to answer this questionnaire.

Please return this document to

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B-1070 BRUXELLES

November 1996