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# Current Practices and Attitudes Regarding Use of Inhaled Nitric Oxide in the NICU

## Results From a Survey of Members of the National Association of Neonatal Nurse Practitioners

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### ABSTRACT

**Background:** Excessive supplemental oxygen exposure in the neonatal intensive care unit (NICU) can be associated with oxygen-related toxicities, which can lead to negative clinical consequences. Use of inhaled nitric oxide (iNO) can be a successful strategy for avoiding hyperoxia in the NICU. iNO selectively produces pulmonary vasodilation and has been shown to improve oxygenation parameters across the spectrum of disease severity, from mild to very severe, in neonates with hypoxic respiratory failure associated with persistent pulmonary hypertension of the newborn.

**Purpose:** An online survey was conducted among members of the National Association of Neonatal Nurse Practitioners to gain insight into the level of understanding and knowledge among neonatal nurse practitioners (NNPs) about optimizing supplemental oxygen exposure and the use of iNO in the NICU setting.

**Results:** Of 937 NNP respondents, 51% reported that their healthcare team typically waits until the fraction of inspired oxygen level is 0.9 or more before adding iNO in patients not responding to oxygen ventilation alone. Among respondents with 1 or more iNO-treated patients per month, only 35% reported they know the oxygenation index level at which iNO should be initiated. Less than 20% of NNPs reported perceived benefits associated with early initiation of iNO for preventing progression to use of extracorporeal membrane oxygenation or reducing the length of hospital stay, and about one-third of respondents reported they believe early iNO use minimizes hyperoxia.

**Implications for Practice:** More education is needed for NNPs regarding the negative effects of oxidative stress in neonates.

**Implications for Research:** Additional clinical trials investigating the most beneficial strategies for avoiding neonatal hyperoxia are warranted.

**Key Words:** hypoxic respiratory failure, inhaled nitric oxide, National Association of Neonatal Nurse Practitioners, neonatal intensive care unit, persistent pulmonary hypertension of the newborn, survey

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An estimated 35,000 term and near-term infants born each year in the United States experience hypoxic respiratory failure severe enough to require mechanical ventilation,<sup>1</sup> and approximately 8000 experience respiratory failure associated with persistent pulmonary hypertension of the newborn (PPHN).<sup>2,3</sup> PPHN is a syndrome resulting from the failure of normal pulmonary vascular adaptation at birth, which leads to elevated pulmonary vascular resistance and severe hypoxemia.<sup>2</sup> Supplemental oxygen is one of the most frequently administered therapies in the neonatal intensive care unit (NICU) for newborns with hypoxia-related pulmonary disease<sup>4,5</sup> because oxygen therapy is known to enhance dilation of the pulmonary vasculature and to improve tissue oxygenation.<sup>6,7</sup> However, overexposure to oxygen is toxic.<sup>8,9</sup> The presence of hyperoxia (fraction of inspired oxygen [FiO<sub>2</sub>] level >0.21 [room air]) increases oxidative stress, resulting in the generation of toxic reactive oxygen species, which can damage various biologic molecules.<sup>6</sup>

A number of strategies for avoiding hyperoxia when administering oxygen to neonates have been investigated. These strategies include the initial use of room air, instead of 100% oxygen, for resuscitation with upward titration as needed to achieve appropriate oxygen saturation levels,<sup>10</sup> as well as the implementation of modified protocols for reduced oxygen use based on oxygenation targets.<sup>11</sup> Another strategy for avoiding hyperoxia in neonates receiving oxygen therapy is the use of pulmonary vasodilators such as inhaled nitric oxide (iNO), sildenafil, prostacyclin, milrinone, or bosentan.<sup>6,12</sup> Exploratory studies of enteral and intravenous administration of sildenafil, a phosphodiesterase 5 inhibitor, have shown sildenafil treatment to be associated with significant improvement in oxygenation parameters in infants with hypoxic respiratory failure with PPHN.<sup>13,14</sup> Case reports of aerosolized prostacyclin, an endothelial-derived systemic and pulmonary vasodilator, have suggested that this agent also improves oxygenation in infants with PPHN.<sup>15-18</sup> Data from case reports<sup>19,20</sup> and a small exploratory study<sup>21</sup> suggest that intravenous milrinone, a phosphodiesterase 3 inhibitor, may be useful for improvement in oxygenation in neonates with PPHN,<sup>19-21</sup> but more studies are needed. Finally, results from case reports and a single-center prospective, randomized, placebo-controlled study suggest that bosentan also improves oxygenation in the setting of PPHN.<sup>22-24</sup> iNO acts as replacement therapy for the low levels of NO in the setting of PPHN.<sup>6</sup> Unlike oral or parenterally administered vasodilator drugs, iNO is delivered directly into the lungs, where it selectively produces pulmonary vasodilation without affecting the systemic vasculature.<sup>12</sup> In the United States, iNO is indicated for use in conjunction with ventilatory support and other appropriate agents for treatment of term and near-term (>34 weeks' gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.<sup>25</sup> The use of iNO has been shown to significantly improve oxygenation and reduce the need for extracorporeal membrane oxygenation in neonates with hypoxic respiratory failure associated with PPHN.<sup>26-28</sup> In addition, data from pivotal studies suggest that iNO therapy improves oxygenation parameters in hypoxic respiratory failure across the spectrum of disease severity, from mild to very severe.<sup>29</sup> The most common adverse reaction associated with the use of iNO is hypotension.<sup>25</sup>

Despite the fact that supplemental oxygen is ubiquitously used in neonatal units throughout the world,<sup>4</sup> there appears to be a dearth of knowledge regarding optimal therapeutic use of supplemental oxygen and the importance of meeting oxygen needs in neonates while minimizing risk of oxygen toxicity.<sup>10,30,31</sup> Therefore, an online survey, sponsored by Mallinckrodt Pharmaceuticals (Bedminster, New Jersey), was conducted among members of the National Association of Neonatal Nurse Practitioners to gain insight into

the level of understanding and knowledge among neonatal nurse practitioners (NNPs) about optimizing supplemental oxygen exposure and the use of iNO in US NICU settings. Results from the survey will be used to inform the content of future educational initiatives designed to enhance NNPs' knowledge about appropriate use of oxygen and iNO in their practice as informed members of a collaborative healthcare team.

## DESIGN AND METHODS

This was a self-report online survey that consisted of 89 questions accessed by electronic links provided by the National Association of Neonatal Nurses and the National Certification Corporation. The survey included questions designed to assess the knowledge levels and perceptions of NNPs regarding oxygen toxicity and the relationship between neonatal oxygen levels and early use of iNO in the NICU. Kantar Health (New York City, New York) conducted the survey during March and April 2014. The survey was not designed as a research study and did not require institutional human subjects review board approval.

Screening questions were included in the beginning of the survey to ensure that respondents were currently practicing direct patient care in an NICU and had at least 1 year of NICU practice experience. Respondents were not required to complete all sections of the survey, nor were they required to answer all survey questions. The iNO section of the survey included questions about how hypoxic respiratory failure and PPHN are diagnosed at the respondent's institution, attitudes and concerns regarding oxidative stress associated with excess exposure to oxygen therapy, availability of iNO and extent of its use, and typical clinical scenarios in which iNO is prescribed. The questions included in the iNO section of the survey and the number of respondents who answered each question are shown in Table 1.

## RESULTS

A total of 1300 NNPs participated in the survey, and 948 answered questions in the section of the survey that focused on the use of iNO. Not all questions were answered by every respondent, and respondents were allowed to skip any questions they did not wish to answer. The number of respondents who answered each question in the iNO section of the survey ranged from 492 to 948.

Overall, 86% (812/944) of respondents reported that iNO was available in their NICU. On average, among those who had access to iNO, each personally cared for approximately 2 iNO-treated patients per month. When asked about the preferred method for diagnosing hypoxic respiratory failure with PPHN in their NICU, 69% of 948 NNPs reported that diagnosis relies on echocardiographic evidence

TABLE 1. Survey Questions About Respondents' Experiences With iNO

Survey Question (Total Number of Respondents)	Response Options
1. What proportions of your HRF/PPHN patients are diagnosed through each of the following? (n = 948)	a. ___% Echocardiographic evidence b. ___% Differential saturation (pre- and postductal oxygen saturation) c. ___% Clinical evidence d. ___ Other (please specify): _____
2. Does your NICU have access to iNO? (n = 944)	a. Yes b. No
3. In a typical month, how many patients do you personally order iNO for? (n = 803)	___ # patients I order iNO for
4. Which of the following best describes your ability to order iNO in your primary NICU? (n = 673)	a. My NICU has a strict protocol in place determining when iNO may be ordered b. My decision to order iNO is generally or always reviewed by a neonatologist c. There are no/few restrictions on my ability to order iNO d. Other (please specify): _____
5. In a typical month, approximately what percentage of your HRF/PPHN patients at each severity level (however you personally define these severity levels) do you <i>personally</i> prescribe iNO for? (n = 676)	___% of neonates with mild HRF/PPHN who are prescribed iNO and % of those who are not prescribed iNO ___% of neonates with moderate HRF/PPHN who are prescribed iNO and % of those who are not prescribed iNO ___% of neonates with severe HRF/PPHN who are prescribed iNO and % of those who are not prescribed iNO ___% of neonates with very severe HRF/PPHN who are prescribed iNO and % of those who are not prescribed iNO
6. At what OI level do you typically initiate iNO to your HRF/PPHN patients? (n = 588) For your reference, the OI is calculated as follows: $OI = FiO_2 \times \text{mean airway pressure} / PaO_2$	___ OI level at which I typically initiate iNO (OI range provided was 5-50) ___ Don't know
7. At what $FiO_2$ level do you typically add iNO if an HRF/PPHN patient is not responding to just oxygen ventilation? (n = 628) <i>Please select only 1 response.</i>	a. <0.4 b. 0.4 c. 0.5 d. 0.6 e. 0.7 f. 0.8 g. 0.9 h. 1.0 (100%) i. Don't know
<i>This question was asked only if the response to the previous questions was 1.0 (100%).</i>	
8. Typically, how long do you run $FiO_2$ at 1.0 (100%) for your neonatal HRF/PPHN patients before adding iNO? (n = 277)	a. <1 h b. Between 1 and 2 h c. Between 2 and 3 h d. Between 3 and 6 h e. Between 6 and 12 h f. Between 12 and 24 h g. Between 24 and 48 h h. >2 d i. Don't know
9. At what $FiO_2$ level do you typically initiate differential saturations? (n = 593) <i>Please select the best response.</i>	a. <0.4 b. 0.4 c. 0.5 d. 0.6 e. 0.7 f. 0.8 g. 0.9 h. 1.0 (100%)

(continues)

TABLE 1. Survey Questions About Respondents' Experiences With iNO (Continued)

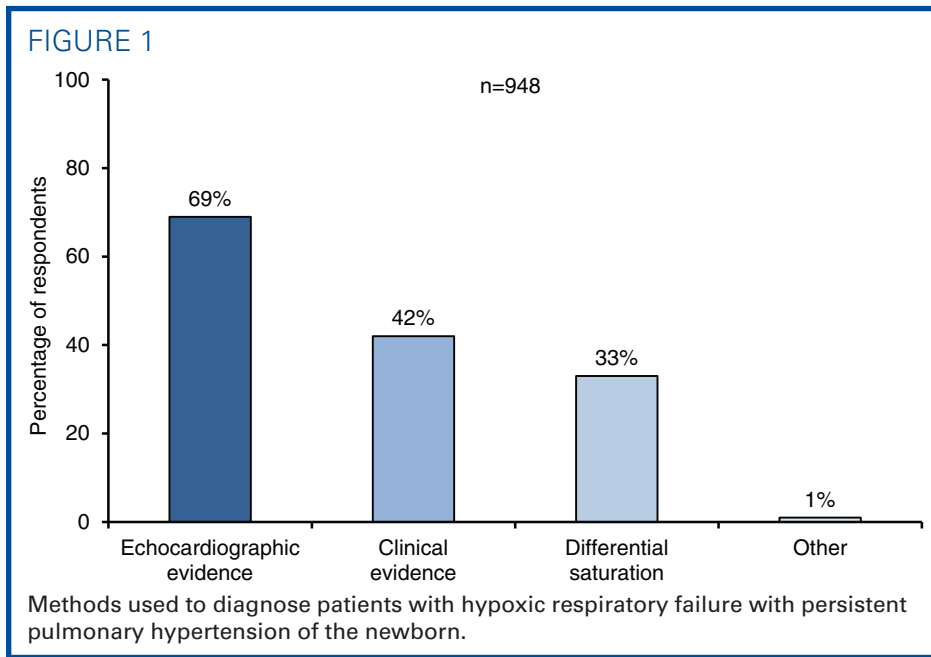
Survey Question (Total Number of Respondents)	Response Options
<p>10. Please indicate how much you agree or disagree with each of the following statements, using a 7-point scale where 1 = "strongly disagree" and 7 = "strongly agree."</p> <p><i>Please select only 1 response for each statement.</i></p> <p>a. Initiating iNO at lower OI levels prevents progression to more severe HRF/PPHN (n = 524)</p> <p>b. Initiating iNO at lower OI levels allows me to avoid unnecessary oxygen toxicity (n = 517)</p> <p>c. Initiating iNO at lower OI levels minimizes ventilator-induced lung injury (n = 512)</p> <p>d. Initiating iNO at lower OI levels leads to fewer total days on oxygen (n = 508)</p> <p>e. Due to cost, I initiate iNO at higher OI levels than I would otherwise prefer (n = 507)</p> <p>f. Over the past 12 mo, I have been initiating iNO therapy at lower OI levels in the course of treatment for my HRF/PPHN patients (n = 505)</p> <p>g. Initiating iNO at OI levels below 20 prevents progression to ECMO (n = 496)</p> <p>h. Initiating iNO at OI levels below 20 leads to shorter overall length of stay (n = 492)</p> <p>i. I am concerned about oxidative stress in neonates after 5 min of exposure at an <math>FiO_2</math> of 1.0 (100%) (n = 676)</p> <p>j. I am concerned about oxidative stress in neonates after 30 min of exposure at an <math>FiO_2</math> of 1.0 (100%) (n = 676)</p> <p>k. I am concerned about oxidative stress in neonates after 60 min of exposure at an <math>FiO_2</math> of 1.0 (100%) (n = 676)</p> <p>l. I am concerned about oxidative stress in neonates after 120 min of exposure at an <math>FiO_2</math> of 1.0 (100%) (n = 676)</p> <p>m. I am concerned about the formation of reactive oxygen species due to excess oxygen exposure (n = 497)</p> <p>n. Early use of iNO minimizes hyperoxia (high <math>FiO_2</math> levels) (n = 502)</p>	<p>Answers were given on a 7-point numeric rating scale where 1 = "strongly disagree" and 7 = "strongly agree"</p>

Abbreviations: ECMO, extracorporeal membrane oxygenation;  $FiO_2$ , fraction of inspired oxygen; HRF, hypoxic respiratory failure; iNO, inhaled nitric oxide; NICU, neonatal intensive care unit; OI, oxygenation index;  $PaO_2$ , partial pressure of arterial oxygen; PPHN, persistent pulmonary hypertension of the newborn.

(Figure 1). Among the 588 NNPs who cared for at least 1 iNO-treated patient in a typical month, 65% (382/588) reported that they do not know the oxygenation index level at which iNO should be initiated; among the 35% (203/588) of the respondents who said they do know the appropriate oxygenation index level, the mean oxygenation index level at initiation of iNO was reported to be 25. Fifty-one percent of respondents reported that their healthcare team typically waits until the  $FiO_2$  level is at least 0.9 before adding iNO in patients not responding to oxygen ventilation alone (Figure 2). Among the 277 NNPs who reported a practice of waiting until the  $FiO_2$  level reaches 1.0 before adding iNO, 71% reported their patients are typically allowed to be exposed to an  $FiO_2$  level of 1.0 for at least 1 hour before iNO is added (Figure 3).

Differential oxygen saturation was usually initiated at an  $FiO_2$  level of 0.5 and 0.6 according to 31% and 18% of 593 respondents, respectively, who have 1 or more iNO-treated patients per month. Few respondents recognized a need for earlier initiation of iNO therapy; 61 of 505 (12%) respondents agreed with a statement indicating a tendency toward initiation of iNO at lower oxygenation index levels over the past 12 months in their practice.

The survey also asked NNPs about their perceptions regarding iNO, oxidative stress, and excess oxygen exposure. Few respondents reported seeing a benefit with initiating iNO at lower oxygenation index levels (Figure 4). Overall, 33% or fewer respondents strongly agreed with statements of benefit regarding early initiation of iNO in

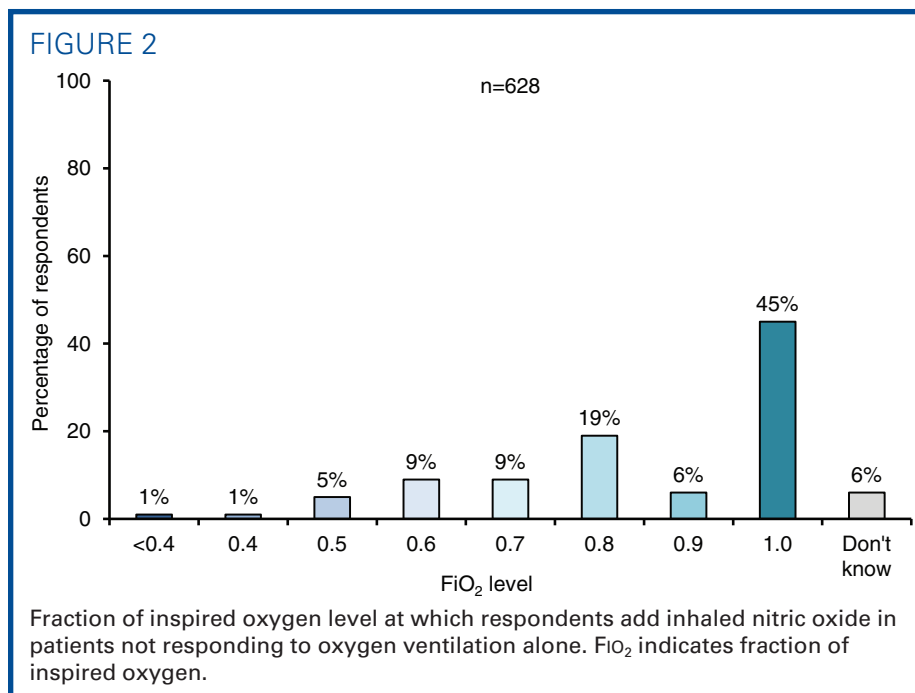


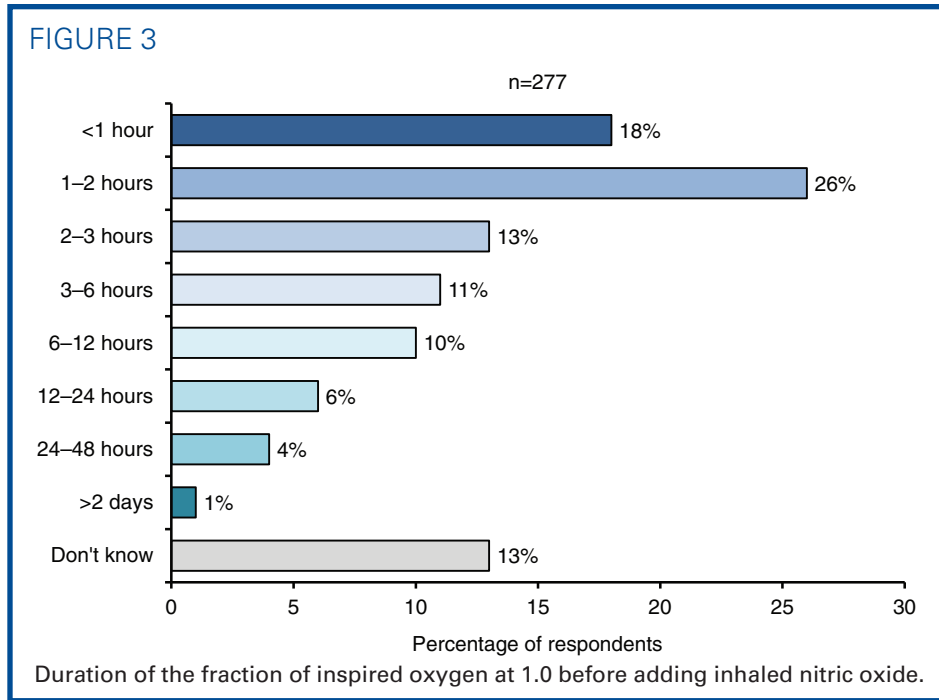
preventing progression of hypoxic respiratory failure with PPHN, avoiding oxygen toxicity, minimizing ventilator-induced lung injury, and reducing total days on oxygen. Eighteen percent or fewer respondents agreed with statements regarding the benefits of early initiation of iNO for preventing progression to use of extracorporeal membrane oxygenation or reducing the length of hospital stay. Forty-six percent of respondents reported being concerned about oxidative stress before 1 hour of  $FiO_2$  of 1.0 (Figure 5). Although

60% of 497 NNPs who responded reported that they were concerned about reactive oxygen species formation due to excess oxygen exposure, only 37% of 502 respondents believe that early iNO use minimizes hyperoxia.

**DISCUSSION**

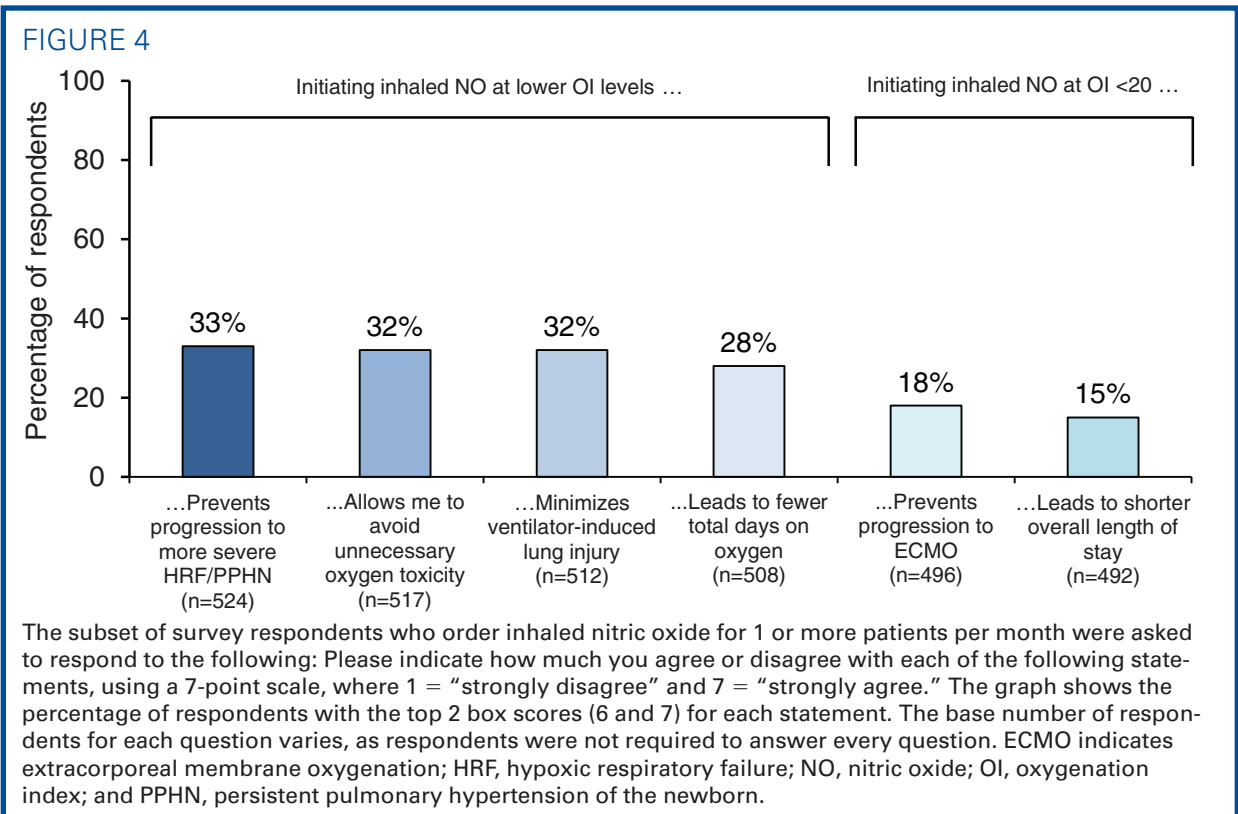
The results of this survey suggest that while iNO is widely available (86% of respondents had access) and was administered to, on average, 1 or 2 patients per

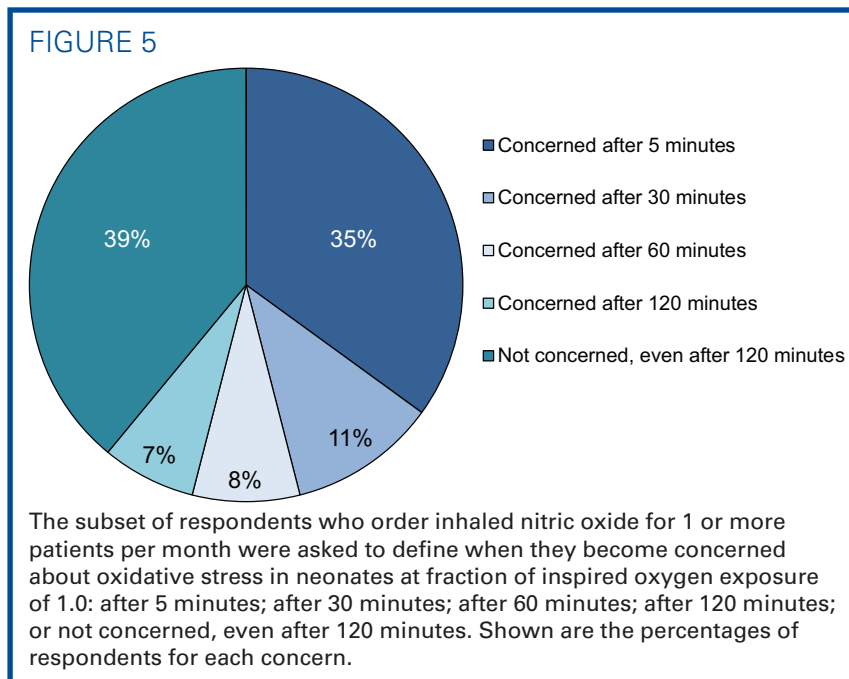




month, there appears to be a perceived lack of benefit associated with iNO use. Many NNPs (65%) reported that they were unfamiliar with the oxygenation index level at which initiation of iNO should be considered, and about half reported their patients are typically allowed to be exposed to high oxygen levels ( $FiO_2 \geq 0.9$ )

for an hour or more before the addition of iNO is considered. Overall, despite the published evidence supporting the potential benefits associated with iNO use, few respondents reported they believed early initiation of iNO would be of benefit in avoiding oxidative stress or oxygen toxicity, preventing progression of respiratory





failure, preventing ventilator-induced lung injury, preventing progression to the use of extracorporeal membrane oxygenation, or reducing duration of hospital stay. Of particular interest is that 39% of respondents reported they were not concerned about oxidative stress in neonates at  $\text{FiO}_2$  of 1.0 even after 120 minutes. These results are consistent with those from a previous survey of 4453 neonatal healthcare providers, which showed that an alarming proportion of respondents recognized educational deficits regarding neonatal oxygenation and the function of oxygen saturation monitors.<sup>32</sup>

It should also be noted that the majority of respondents reported they did not know the oxygenation index level at which iNO should be initiated; those who did know reported that the appropriate level for iNO initiation is an oxygenation index of more than 25. Indeed, traditional practice has been to initiate iNO at an oxygenation index of 25 or more, based on criteria used in clinical studies of iNO that were conducted during the 1990s.<sup>27,28</sup> However, later studies have shown that earlier initiation of iNO may be more beneficial for improvement in oxygenation and attenuating progression to severe hypoxic respiratory failure than later initiation, and patients with lower oxygenation index levels at iNO initiation may be more likely to have a complete response to iNO (Table 2).<sup>29,33-35</sup> Given that premature infants are particularly susceptible to oxygen toxicity,<sup>36,37</sup> and the known risks of toxicity associated with overreliance on the use of supplemental oxygen,<sup>5,38,39</sup> consideration of early initiation of iNO (ie, before patients reach moderate to severe hypoxic respiratory failure) may help balance supplemental oxygen needs and improve patient outcomes.

## IMPLICATIONS FOR PRACTICE

Therapeutic oxygen is an important component of treatment of hypoxic respiratory failure in neonates. However, neonatal healthcare providers must understand that excessive supplemental oxygen exposure (eg, prolonged use of 100% oxygen) can cause oxidative stress and result in hyperoxia, which can damage lung tissue and pulmonary vasculature, or cause hyperoxemia, which can result in systemic damage. Early intervention with a pulmonary vasodilator may help avoid hyperoxia.

The majority of NNPs responding to the online survey expressed concern about the formation of reactive oxygen species due to excess oxygen exposure; however, only a small proportion of respondents reported early use of vasodilators to minimize hyperoxia risk in their practice setting.

On the basis of the observations from this survey, we believe that implementation of strategies to minimize oxygen exposure in neonates who require oxygen therapy, educational initiatives that focus on the negative effects of hyperoxia, and heightened awareness regarding the importance of early implementation of pulmonary vasodilators to minimize hyperoxia can lead to meaningful improvement in patient outcomes. Although NNPs in some states may be able to independently prescribe iNO, in most cases, the decision to treat the neonate is made through the collaborative efforts of the neonatal healthcare team.<sup>40,41</sup> Practical knowledge regarding the potential risks associated with overexposure to supplemental oxygen, as well as the potential benefits associated with early initiation of iNO (when appropriate) can

TABLE 2. Overview of Studies Assessing Benefits Associated With Early Use of iNO

Study Citation	Design	Population	Treatment Groups	Outcomes of Interest	Key Results
Gonzalez et al <sup>33</sup> (2010)	Prospective, randomized, unblinded study	Neonates $\geq 35$ weeks' GA with moderate HRF (OI = 10-30) and PH	Early iNO group: iNO initiated at 20 ppm + MV (n = 28) Control group: MV with 1.0 Fio <sub>2</sub> (n = 28)	Improvement in oxygenation; attenuation of development of severe HRF (OI >40)	Early iNO group: Mean OI significantly decreased from 22 at baseline to 15 at 48 hours ( $P < .01$ vs control); 7/28 (25%) developed severe respiratory failure (OI >40; $P < .05$ vs control) Control group: Mean OI remained significantly increased from 22 at baseline and remained significantly higher through 48 h; 17/28 (61%) developed severe respiratory failure (OI >40)
Konduri et al <sup>34</sup> (2004)	Prospective, randomized, double-blind study	Neonates $\geq 34$ weeks' GA with moderate HRF (OI $\geq 15$ and <25) and need for MV	Early iNO group: iNO initiated at 5 ppm (n = 150) Control group: Simulated iNO (n = 149)	ECMO and/or death before hospital discharge or 120 d of postnatal age, whichever was sooner (primary outcome measure); change in Pao <sub>2</sub> ; change in OI	Early iNO group: 16.7% (25/150) achieved primary outcome ( $P = .53$ vs control); 73% had >20 mm Hg increase in Pao <sub>2</sub> ( $P < .001$ vs control); 7% progressed to OI >40 ( $P = .056$ vs control) Control group: 19.5% (29/149) achieved primary outcome; 37% had >20 mm Hg increase in Pao <sub>2</sub> ; 14% progressed to OI >40
Konduri et al <sup>35</sup> (2013)	Post hoc subgroup analysis of data from the 2004 Konduri et al <sup>34</sup> study	Neonates $\geq 34$ weeks' GA with moderate HRF (OI $\geq 15$ and <25) and need for MV	Early iNO group: iNO initiated at 5 ppm (n = 150) Control group: Simulated iNO (n = 149)	Factors associated with ECMO/death and progression to HRF (OI $\geq 30$ )	Early iNO group: 16.7% progressed to OI $\geq 30$ ( $P = .002$ vs control); 25% progressed to composite outcome of OI $\geq 30$ and/or ECMO/death ( $P = .02$ vs control); OR (95% CI) for ECMO/death in iNO patients initiated at OI <20 was 0.25 (0.08-0.67) and those with iNO initiated at OI = 20-25 Control group: 32.2% progressed to OI $\geq 30$ ; 38% progressed to composite outcome of OI $\geq 30$ and/or ECMO/death
Golombek and Young <sup>29</sup> (2010)	Retrospective pooled analysis of data from 3 pivotal iNO studies	Neonates $\geq 34$ weeks' GA with HRF stratified by severity of HRF at baseline (mild = OI $\leq 15$ ; moderate = OI >15 to $\leq 25$ ; severe = OI >25 to $\leq 40$ ; very severe = OI >40)	iNO group: iNO initiated at 20 ppm (n = 260) Control group: 100% oxygen, iNO 0 ppm, or nitrogen gas (n = 264)	Improvement in oxygenation, as reflected by change in Pao <sub>2</sub>	iNO group: Mean increase in Pao <sub>2</sub> from baseline was 55 mm Hg after 30 min ( $P < .001$ vs control); mean Pao <sub>2</sub> increased significantly from baseline across all severity strata ( $P < .001$ for comparison vs baseline in each severity subgroup) and was significantly higher than controls across all severity strata ( $P < .01$ for each comparison vs control subgroup) Control group: Mean increase in Pao <sub>2</sub> from baseline was 14 mm Hg after 30 min

Abbreviations: ECMO, extracorporeal membrane oxygenation; GA, gestational age; HRF, hypoxic respiratory failure; iNO, inhaled nitric oxide; MV, mechanical ventilation; OI, oxygenation index; Pao<sub>2</sub>, partial pressure of arterial oxygen; PH, pulmonary hypertension; ppm, parts per million.



Summary of Recommendations for Practice and Research	
<b>What we know:</b>	<ul style="list-style-type: none"> <li>Excessive supplemental oxygen exposure can lead to negative consequences for the neonate.</li> <li>Neonatal nurse practitioners in neonatal intensive care units (NICUs) often are responsible for managing oxygen supplementation for newborns.</li> </ul>
<b>What needs to be studied:</b>	<ul style="list-style-type: none"> <li>Further investigation of specific approaches to avoid hyperoxia while achieving adequate oxygenation in neonates requiring oxygen therapy</li> <li>Further investigation of the specific impact of pulmonary vasodilators, such as inhaled nitric oxide on oxygen use and related efficacy and safety outcomes</li> </ul>
<b>What we can do today:</b>	<ul style="list-style-type: none"> <li>Implement strategies in the NICU to minimize oxygen exposure in neonates requiring oxygen therapy, thereby improving patient outcomes.</li> <li>Educate neonatal healthcare practitioners regarding the negative effects of hyperoxia.</li> <li>Stress the importance of early implementation of vasodilators to minimize hyperoxia.</li> </ul>

help NNPs better engage and collaborate with their colleagues to advocate for minimizing the risk of oxygen toxicity and optimizing iNO use in the NICU.

To further deepen the understanding of the role of oxygen therapy and vasodilators in the treatment of PPHN, a more formal education process for the bedside clinician and NNPs can include discussions of the body's NO pathway, mechanism of action of iNO and its selective pulmonary vasodilation properties, and effects of reactive oxygen species on major organs. Use of iNO causes pulmonary vasodilation by the entrance of inspired air into the alveoli.<sup>42</sup> The NO molecule is diffused into the vascular smooth muscle adjacent to the pulmonary arterioles, where it activates soluble guanylate cyclase.<sup>42</sup> The vasodilatory effects of iNO are limited to the arterioles adjacent to the alveoli, where it penetrates and selectively dilates the pulmonary vasculature.<sup>42</sup>

In addition to echocardiographic findings, calculating the oxygenation index at the bedside is a quick, easy, and widely accepted tool (Oxygenation index =  $FiO_2 \times \text{Mean arterial pressure} \times 100$ , divided by  $PaO_2$ ) to look at severity of the disease process (mild: 0-15; moderate: 15-25; severe: 25-40; very severe: >40).<sup>33</sup> Diseases commonly associated with oxygen supplementation and oxidative stress are outlined in the study by Kayton et al.<sup>43</sup>

It is imperative for NNPs to understand the disease process of PPHN leading to hypoxic respiratory failure, as well as the effects of oxidative stress when reactive oxygen species exceed the capacity of antioxidant mechanism.<sup>44</sup> Educating the bedside clinician and NNPs can be achieved in a formal classroom setting or through continuing education offerings, simulation laboratories, and case study presentations.

Interpretation of results from our survey may be limited by potential confounding factors that are inherently associated with any survey. As reported in the "Design and Methods" section, respondents were not required to complete all sections of the survey, nor were they required to answer every question within a given section of the survey. While

respondents had confirmed they had at least 1 year of practice experience in providing direct care to newborn patients, it was not possible for us to compare or stratify the survey results by respondents' NICU level of care or years of experience. Despite these limitations, the survey provides valuable information that will inform future educational initiatives for NNPs.

## CONCLUSION

The survey results reported here imply that more education regarding the negative effects of hyperoxia and reactive oxygen species, as well as implementation of strategies to minimize oxygen exposure and optimize the use of iNO, is needed. This practical knowledge will enable NNPs and other neonatal nurse specialists to engage and collaborate with their colleagues on the neonatal healthcare team to advocate for better oxygen balance in their critically ill patients.

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