Review Article

Oxygen for newborn resuscitation: a narrative review

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Background and Objective: Supplemental oxygen was used for newborn resuscitation for the first 200 years after its discovery; however, over the last 50 years the safety of this practice has been called into question. Discovery of hypoxanthine, which is produced under anaerobic conditions and when oxidized produces free radicals, called into question the safety of supplemental oxygen following a hypoxic period, especially intrauterine hypoxia. The goal of this review is to examine the bench to bedside transition of this field of research and how it led to practice change regarding neonatal resuscitation in the delivery room.

Methods: In order to synthesize key findings for the objectives of this review, we searched literature published up to August 31, 2021 using PubMed with the following keywords: "Hypoxanthine", "Hypoxia", and "Oxidative stress"; with a second search including the terms "Neonatal", "Resuscitation", "Oxygen", "Room air".

Key Content and Findings: The early neonatal hypoxanthine studies coincided with an increased appreciate for oxidative injury that happens following hypoxia-reperfusion, such as neonatal resuscitation following intrauterine asphyxia. Based on 10 feasibility and safety studies in infants mostly >35 weeks gestation, resuscitation with air proved to be superior to 100% O_2 in mortality which led to a change in the standard of care. The physiology that causes a preterm infant to require resuscitation at birth is not the same as term infants; therefore, these infants require oxygen supplementation during resuscitation although unavoidable oxidative stress from this necessary oxygen exposure does occur.

Conclusions: Today it is recommended to start with air in the delivery room if term or near-term newborn infants need positive pressure ventilation (PPV) immediately after birth. This discovery may prevent up to half a million newborn deaths annually. For premature infants <35 weeks gestational age supplemental oxygen may be needed; however, the optimal initial oxygen concentration for the most immature infants is not known.

Keywords: Neonatal; resuscitation; hypoxanthine; oxygen; room air

Received: 08 December 2021; Accepted: 11 April 2022; Published online: 18 April 2022.

doi: 10.21037/pm-21-110

View this article at: https://dx.doi.org/10.21037/pm-21-110

Introduction

Oxygen, literally meaning "acid former", was first described as an element in 1772 and named as such 3 years later by Lavoisier. Although Priestley, in his original article on oxygen in 1774, cautioned about the possible toxic effects of pure oxygen (1), it quickly became a ubiquitous medical treatment, including in newborn care. Oxygen was used during newborn resuscitation for about 200 years before the first critical appraisal of its safety occurred. With the introduction of the Apgar score in 1953, oxygen use became ubiquitous as many centers used it to "pink

Table 1 The search strategy summary

Items	Specification
Date of search	August 31, 2021
Databases and other sources searched	PubMed
Search terms used	"Hypoxanthine", "Hypoxia", and "Oxidative stress"
	"Neonatal", "Resuscitation", "Oxygen", "Room air"
Timeframe	Published up to August 31, 2021
Inclusion criteria	Study type: review, systematic review, clinical trial, and randomized controlled trials
	Language restrictions: none
Selection process obtained, etc.	All the authors conducted the selection after discussion
Any additional considerations, if applicable	Author familiarity with this field allowed for the inclusion of 3 publications from Romania not available through PubMed

up" the newborns in order to achieve a higher score (2). Moreover, there was a prevailing dogma that if oxygen was not available for newborn resuscitation, an attempt with air would be futile and was often withheld. Into the 1990s, the American Heart Association guidelines for newborn resuscitation stated "there is no reason to be concerned giving pure oxygen a brief period after birth" (3) despite articles emerging to question the necessity and safety of this practice starting as early as the late 1970s (4). Pure oxygen continued to be recommended as the primary gas in newborn resuscitation guidelines until first revised by the World Health Organization (WHO), in 1998, which endorsed the use of room air (5) subsequently followed 12 years later by similar guidelines from International Liaison Committee on Resuscitation (ILCOR) in 2010 (6). The goal of this review is to explore the biochemical background and neonatal trials that lead to this change in practice. We present this article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-110/rc).

Methods

We conducted two literature searches using online database PubMed (*Table 1*), specifically for papers related to the hypoxanthine molecule in response to hypoxic conditions, as well as the fractional inhaled concentration of oxygen (FiO_2) used for the initiation of neonatal resuscitation. The key search terms included for the first search were "Hypoxanthine", "Hypoxia", and "Oxidative stress"; for the second search terms included were "Neonatal", "Resuscitation", "Oxygen", "Room air". In our search, all neonatal literature included for the discussion in the manuscript publications were divided into term/near-term, including infants ≥35 weeks gestational age at birth, and preterm, including infants <35 weeks gestational age at birth.

Biochemical and experimental background

The focus on a single molecule, hypoxanthine, initiated the research cascade to transition from oxygen to air for newborn resuscitation. Hypoxanthine itself is an inert purine metabolite formed as a byproduct of adenosine triphosphate (ATP) breakdown under anerobic conditions. However, in subsequent aerobic conditions, the oxidative cascade needed to clear hypoxanthine from the body produces oxygen free-radicals, such as superoxide (O_2*) when it is oxidized to uric acid through xanthine as an intermediary (*Figure 1*).

Biochemically, this oxygen consumption assessing the hypoxanthine level, can be measured via this cascade to indirectly quantify the oxygen deficit previously experienced by a cell or organism. In 1973, clinically leveraging this reaction to reflect the degree of intrauterine asphyxia was a novel concept. Saugstad and Rooth were the first to apply this chemical reaction to quantify the hypoxanthine concentration in body fluids which reflects the anoxic intrauterine environment experienced during intrauterine asphyxia. In the process, refining an assay that only required 0.2 mL of blood or bodily fluid to provide an oxygen consumption read out (7).

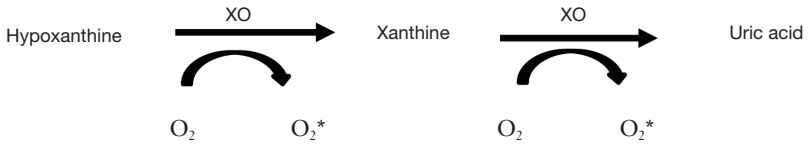

Figure 1 Hypoxanthine is oxidized to uric acid, via xanthine in the presence of XO. As a byproduct, superoxide radicals are generated. XO, xanthine oxidase; O_2, oxygen; O_2*, superoxide.

The first studies to test the clinical applicability of hypoxanthine used cord blood levels of this purine in birth asphyxiated infants to reflect the degree of hypoxic experienced in their intrauterine environment. Infants with signs of intrauterine hypoxia (low Apgar score, fetal bradycardia <100 beats per minute or meconium-stained fluid) had cord plasma levels of hypoxanthine that were 5 times higher than control infants (8). Subsequent animal studies, with various hypoxemic and experimental conditions, showed that hypoxanthine sensitively reflects hypoxia across several tissue types such as plasma, cerebrospinal fluid, or skeletal muscle (9-12). The phenomenon of increased hypoxanthine in response to low partial pressure of oxygen (PaO_2) was not limited to systemic hypoxemia, but also occurred in response to impaired tissue oxygen delivery in a hemorrhagic shock model (13).

Although the hypoxanthine data was an intriguing measure of hypoxia, concerns regarding pure oxygen therapy for neonatal resuscitation did not arise until this data was examined in concert with other free radical work going on within the field at the time. Some years earlier, McCord and Fridovich had demonstrated that xanthine is a potential free radical generator when oxidized to uric acid (14). This fundamental observation, which these authors themselves did not relate to clinical conditions, made some of us question that perhaps it may be detrimental to administer high FiO_2 concentrations especially in situations with high hypoxanthine concentrations (15). Concurrent to this work was the discovery of a significant burst of O_2* or hydroxyl ions (a reactive oxygen species), downstream of hypoxanthine, in various hypoxia-reoxygenation models (16-19). Perhaps this was the answer to the so-called oxygen paradox, an enigmatic and unexplained phenomenon, described in the 1950's that oxygen aggravates injury following an episode of hypoxia (20)? Later this concept was further developed by McCord's group and named "ischemia-reperfusion injury" (17,19). We consequently warned against the use of high oxygen concentrations in a post hypoxic situation (8,15). As more information began to emerge about the risk of free radical production and activation of reactive oxygen species by metabolites, such as hypoxanthine, there was burgeoning interest in determining the optimal FiO_2 for neonatal resuscitation in order to limit unintended harm due to oxidative stress.

Using air to resuscitate animals

In order to transition from the use of oxygen to air for resuscitation, two factors needed to be addressed: feasibility and harm; the evidence for both are examined here. When examining these studies, air will be used to designate groups exposed to 21% FiO_2 and oxygen for groups exposed to 100% FiO_2.

Although there was mounting evidence that oxygen, especially following a period of hypoxemia, could be detrimental, the question remained: would room air even work for neonatal resuscitation? The first work we are aware of, was carried out in the 1960s, when Campbell *et al.* demonstrated, in anoxic newborn rabbits, that positive pressure ventilation (PPV) with air was as effective during resuscitation as ventilation with oxygen (21). Hutchinson subsequently studied the use of air versus oxygen for ventilation in premature lambs subjected to an induced hypopnea/apnea model. Although the heart rate recovery was equivocal between the groups, the air group had a quicker return to baseline for minute ventilation, pH and partial pressure of carbon dioxide ($PaCO_2$) (22). Weaver *et al.* demonstrated these techniques could be applied outside of the laboratory to improve survival of livestock (23). Twenty years later, the Martin group demonstrated that 100% oxygen resuscitation in rodents delays the onset of sustained spontaneous respiratory effort as measured by diaphragmatic electromyography (24). In the 1990's, we and others lead a series of studies using mostly a newborn piglet model to demonstrate that it was possible to resuscitate with air as efficiently as with oxygen (25,26). Follow-up studies examined if reoxygenation with oxygen versus air would induce differential oxygen delivery between various

organs. Nong *et al.* found no difference in oxygen delivery to vital organs although the PaO_2 was higher in the oxygen group (27). Additional studies specifically focused on the brain found greater early oxygen delivery in the forebrain in the air resuscitated group, but this difference was not sustained at 20 minutes. Moreover, there were no differences in cerebral blood flow between the air or oxygen groups (28).

Simultaneous to the physiologic studies, there was emerging evidence that hyperoxia and high oxygen exposure could induce oxidative stress. Therefore, the oxygen versus air resuscitation paradigm began to shift from: is air resuscitation possible, to is oxygen resuscitation harmful? Several groups, including ours, used the piglet model of perinatal asphyxia followed by resuscitation with varying FiO_2 to test this concern. We found higher levels of matrix metalloproteinases (enzymes responsible for tissue injury and inflammation), lower antioxidant capacity, and extracellular glycerol (a sign of tissue hypoxia) (29). Feet *et al.* and Cheung *et al.* found similar recovery when resuscitation was performed with air or an additional sub-ambient oxygen (FiO_2 18%) group. These studies indicated that the reoxygenation with oxygen appears sub-optimal and the use of sub-ambient oxygen offers no further benefit, when compared with air (30,31).

Temesvári *et al.* did not find differences in blood oxidative stress markers or cerebral histopathology between air and oxygen groups; however, they did find behavioral deficits in the oxygen group (25). In non-inferiority studies using rodents, Nong *et al.* demonstrated a dose effect on the accumulation of intracellular calcium that favored lower oxygen tension (27). Finally, when an oxidant scavenger, N-acetylcysteine, is administered concurrent to oxygen for resuscitation, myocardial and kidney oxidized glutathione (GSSG) and the ratio of oxidized to reduced glutathione (GSSG:GSH) levels were returned to the levels seen in the air resuscitated group supporting that oxidative stress cascades are induced by oxygen resuscitation (28).

Clinical studies in full term infants

The first study to challenge the dogma that oxygen is necessary for newborn resuscitation was published in 1993, as a monocentric pseudo-randomized investigation from Delhi, India. Eighty-four full-term infants with birth depression were evenly divided between the intervention groups: air versus oxygen for resuscitation. Both groups started with relative bradycardia that responded quickly, within 60 seconds, to either intervention. The 1-minute Apgar scores were not different between the groups; unexpectedly, the 5-minute Apgar scores were higher in the air group than the oxygen group. Neonatal mortality did not differ between the groups (32). This sentinel study demonstrated that infants could be successfully resuscitated with air.

The second study, the Resair 2, was an international, multicenter follow-up to our 1993 Delhi study. Independent of the intervention, the heart rate increased by 20 bpm after 30 seconds of PPV; as a physiologic note, this 20-bpm response to 30 seconds of ventilation has since become the gold standard for evaluating the effectiveness of PPV during ventilation. One minute Apgar scores were significantly higher in the air than the oxygen group. Although the median Apgar score was not different at 5 minutes, there were significantly more infants in the oxygen group with an Apgar score <7. This is likely due to the novel finding that median time to first breath and cry occurred 24 seconds earlier in the air group. Moreover, there was also a strong tendency, although not significant difference, in neonatal mortality favoring air as an intervention (33). Beyond confirming that air ventilation is feasible for resuscitation, it introduced the potential that air may have physiologic and outcome benefits. Based on these first two studies the WHO updated their guidelines for newborn resuscitation in 1998 to recommended initiating resuscitation with air (5).

Outcomes for several randomized studies from Spain shifted from feasibility to evaluating clinical parameters such as onset of spontaneous respiration, mortality, and oxidative stress. The collective six-year experience from a unit in Spain reported outcomes of Apgar scores at 1 and 5 minutes of life and mortality (34). The group demonstrated that onset of cry was significantly earlier in the air than the oxygen group by 48 seconds (35). Interestingly, a non-asphyxiated control group was included to evaluate for the oxidative stress related to birth suppression in addition to the intervention (35-38). Compared to the non-asphyxiated group, infants that required any resuscitation had higher oxidative stress at birth demonstrated by elevated cord blood levels of GSSG, and related enzyme activity of glutathione peroxidase (GPx), glutathione-s-transferase (GSH-S-T), glutathione reductase (GR) and superoxide dismutase (SOD). Reduced glutathione (GSH) concentrations were elevated in both asphyxiated groups and decreased similarly over the first 15 minutes of life. However, at 15 minutes of life, the oxygen resuscitated group had ongoing elevation of GSSG, SOD, GPx, GSH-S-T, GR enzyme activity

(34,35,37,38).

A third randomized study from Vento's group evaluated end organ stress. The study redemonstrated a prolonged period of generalized oxidated stress 48 hours after oxygen resuscitation. Kidney and myocardial injury were specifically assessed by urinary N-acetyl-glucosaminidase (NAG) and plasma cardiac troponin (cTnT) respectively. Similar to the markers of systemic oxidative stress, both of these indicators remained elevated at 48 hours of life (36). At baseline, infants have lower total amount of antioxidants and the corresponding enzymes; as well as the fact that the enzymes that they do have are less effective than those in adults. This produces a perfect storm where a neonates' antioxidant system can quickly be overwhelmed when exposed to high levels of free radicals or reactive oxygen species which leads to direct tissue injury, changes in metabolism and even potentially DNA damage (39).

Oxidative stress has been associated with epigenetic changes in gene expression that can increase lifelong risks for disease (40,41). Collectively, the oxidative stress studies seem to indicate that resuscitation with oxygen may actually cause undue harm beyond the immediate neonatal period.

Two additional studies from India transitioned to examining in addition to mortality, the clinical outcome of hypoxic ischemic encephalopathy (HIE), a common morbidity often seen in infants who require resuscitation at birth (42,43). Ramji *et al.* found that the duration of resuscitation was 1 min shorter with air compared to oxygen. There was no difference in HIE; however, mortality was lower in the air group (42). On the other hand, in a significantly smaller study, Bajaj *et al.* found no difference in the primary outcome of either HIE and/or death before discharge (43). The absence of an effect on HIE rates more likely reflects that the antecedent of this pathology is often before the resuscitations began. Only one of these studies found an impact on mortality favoring air; although this change was dramatic at 30%, the lack of findings in the second study could be related to the smaller number of patients included in this cohort.

Three additional publications out of Romania, one an original science study (44) and 2 published abstracts from society meetings (one a duplicate between an international and European meeting) were published in 2006-7 (45-47). Only the abstracts were available in English; however, the author provided information directly to one of the authors of this analysis. In brief, these findings seem to affirm the other international findings of no difference in HIE or hemodynamics with air resuscitation.

Despite the longstanding use of oxygen for neonatal resuscitation, all told the preponderance of evidence in favor of air resuscitation only required approximately 2,150 infants and less than a dozen studies to change practice guidelines (*Table 2*). To our knowledge no more randomized studies have been carried out in term or near-term infants investigating air versus oxygen for newly born infants needing PPV at birth. We do not anticipate any future studies, as resuscitation recommendations have changed, and there is no longer equipoise for term infants regarding the question of air versus oxygen due to the evidence of oxidative injury and increased mortality with high oxygen. However, 6 meta-analyses and systematic reviews have been published of which two where in the Cochrane format (Table S1).

The first review by Davis *et al.* was published in the *Lancet* in 2004 (48), followed by Cochrane reviews by the same authors in 2004 and 2005 including more or less identical data in all three studies (49,50). These authors reported a reduction in mortality in favor of air resuscitation although they were not able to demonstrate a significant difference in neurodevelopmental outcomes. In 2005 and 2008, Saugstad *et al.* published two additional systematic reviews (51,52) that found the same benefit regarding survival and a trend toward decreased HIE, although this was not significant. Finally, a systematic review was published in 2019 by Welsford *et al.* including infants ≥35 weeks (53) which demonstrated a significant reduction in mortality when air is used for resuscitation. In this review, the I^2 heterogeneity assessment was <40% for the included studies indicating a relative homogeneity of the populations and likely little impact on the combined results on the forest plots (53,54). The early reviews included only 4 or 5 of the studies in the field (48-51); only the reviews from Saugstad [2008] and Welsford included all of the studies discussed in this manuscript (52,53). These systematic reviews are based on the same studies and therefore give relatively similar results with approximately a 30% reduction in mortality in those initiated with air versus oxygen.

Clinical studies in preterm infants

As opposed to the full-term population, determining the ideal starting oxygen concentration for resuscitating preterm infants has been a more elusive, likely due to the heterogeneity of this population over the gestational age spectrum. In addition, this clinical situation is unique from

Table 2 Publications examining the use of air rather than 100% for neonatal resuscitation (term and near-term infants)

Study	Study design	Patients, n, BW (g) (SD), GA (w) (SD)	Primary study outcomes
Ramji *et al.* (32)	qRCT	A: 42, 2,410 (540), 38.4 (±1.9)	Feasibility, 1-, 5-Apgar scores
		O_2: 42, 2,410 (660), 38.1 (±2.6)	
Saugstad *et al.* (Resair 2) (33)	qRCT	A: 288, 2,600 (r: 1,320–4,078), 38 (r: 32–42)	Heart rate response, first breath/cry, 1-, 5-Apgar scores, mortality
		O_2: 321, 2,560 (r: 1,303–3,900), 38 (r: 31–41.5)	
Vento *et al.* (34)	qRCT	A: 300, 3,380 (318), 38.6 (1.7)	Mortality, onset of spontaneous respiration, blood gases, 1-, 5-Apgar scores and ROS
		O_2: 237, 3,190 (245), 40.2 (0.8)	
Vento *et al.* (35)	Blinded	A: 19, 3,380 (318), 38.6 (1.7)	First cry, sustained respiratory effort, 1-, 5- and 10-Apgar scores; ROS at 72 hours and 28 days
		O_2: 21, 3,190 (245), 40.2 (0.8)	
Vento *et al.* (36)	Blinded	A: 17, 3,320 (180), 39.6 (1.6)	Kidney and myocardial injury
		O_2: 22, 3,110 (90), 39.2 (1.2)	
		C: 22, 3,280 (140), 38.5 (0.9)	
Vento *et al.* (37)	Blinded	A: 15*	First cry, sustained respiratory effort, 1-, 5-Apgar scores; ROS at 5 and 15 minutes of life
		O_2:17	
		C: 14	
Vento *et al.* (38)	Blinded	A: 55, 3,160 (240), 38.9 (1.6)	Systemic ROS
		O_2: 51, 3,220 (168), 40.5 (1.1)	
		C: 22, 3,310 (190), 39.5 (1.9)	
Ramji *et al.* (42)	qRCT	A: 210, 2,400 (563), 37.9 (2.9)	Total duration of resuscitation, mortality and HIE
		O_2: 221, 2,529 (629), 38.1 (2.6)	
Bajaj *et al.* (43)	qRCT	A: 107, 2,461 (602), 38.3 (2.8)	HIE or death before discharge
		O_2: 97, 2,319 (614), 37.4 (3.5)	
Toma *et al.* (44)	RCT	A: 20, 3,536, 39	HIE or mortality
		O_2: 24, 3,530, 39.2	
Toma abstracts (45-47)	Unknown	A: 2,684 and 3,172, 36 and 38.8	HIE, mortality and 12–15 months follow up
		O_2: 2,468 and 3,200, 35.3 and 38.8	

*, individual BW and GA not reported other than "no significant difference present". qRCT, quasi-randomized control trial; RCT, randomized control trial; BW, birthweight; GA, gestational age; A, air for resuscitation; O_2, 100% oxygen for resuscitation; C, non-asphyxiated reference group; r, range; ROS, reactive oxygen species; HIE, hypoxic ischemic encephalopathy.

term infants who often require resuscitation at birth because of perinatal asphyxia which is generally not an antecedent for preterm infants requiring resuscitation. According to the 2015 ILCOR neonatal resuscitation guidelines, it is strongly recommended that preterm infants <35 weeks' gestation should be stabilized with a lower (21–30%) and not higher (>65%) initial oxygen at the onset of resuscitation (55). The guiding clinical principle for many of these investigations were time to achieving the target oxygen saturation range outlined in the ILCOR or Neonatal Resuscitation Program guidelines, as well as oxidative stress and neonatal morbidities.

The outcome assessed in the preterm feasibility studies was the achievement of target oxygen saturations. One of the first studies to examine this found that whether starting at 30% or 100% oxygen both groups were ultimately titrated a FiO_2 ~45% by 5 to 7 minutes of life. In addition, there weren't significant differences in the oxygenation

saturations (SpO_2) during the neonatal transition period (56). Others found a similar need to titrate the FiO_2 for both groups to around 40–50% over the first 5–10 minutes of the resuscitation without differences in the SpO_2 during and after the resuscitation (57-60). Oei *et al.* demonstrated in a cohort of 768 newborn infants <32 weeks gestation, from 8 randomized studies, independent of starting resuscitation with a high or low FiO_2, that a failure to achieve SpO_2 of 80% by 5 minutes increased the risk of death but not intraventricular hemorrhage (IVH) or bronchopulmonary dysplasia (BPD) (61). Compared to term infants, premature infants have an even more immature antioxidant systems with lower total antioxidants available as well as less efficacious enzyme activity. Therefore, this population is at greater risk for oxidative injury related to free radical metabolites following high oxygen exposure which are hypothesized to contribute or compound many of the common comorbidities of prematurity (39,62). The Targeted Oxygen for the Resuscitation of Preterm Infants and their Developmental Outcomes (TO2RPIDO) assigned <32-week infants to resuscitation starting with either air or oxygen which could be titrated based upon pre-ductal oxygen saturations. Infants in the oxygen group had higher SpO_2 and significantly elevated advanced oxidative protein products at 12 hours of life; however, there were no differences in the other oxidative stress markers that were assessed (non-protein-bound iron and isoprostanes) (60). Groups have found increases in reactive oxygen species, hydroperoxide, as well as decreased ability to recycle antioxidant, measured by the ratio of the redox potential to total hydroperoxide, when preterm infants are resuscitated with oxygen versus air (58,63). On the other hand, others have reported no difference in GSH concentrations (the most abundant intracellular antioxidant), non-protein-bound iron, (a potential reactive oxygen species) and urinary oxidative stress markers (8-hydroxy-2-deoxyguanosine/2-deoxyguanosine ratio (8-OhdG/2dG); ortho-tyrosine/phenylalanine ratio (O-Tyr/Phenyl); 3-chlortyrosine; 3-nitro-tyrosine) at 1 or 6 days of life based on the resuscitation gas used (59). However, Vento's group who has been the most prolific for studying oxidative stress related to neonatal resuscitation definitively demonstrated increased GSSG:GSH levels on day 1 and 3, as well as increased urinary elimination of several oxidative byproducts (O-Tyr/Phenyl, 8-OhdG/2dG ratio on days 1 and 7; isoprostane metabolites and isofurans on day 1) when using oxygen. Interestingly, they took these results further and were able to correlate GSSG levels on day 3 and urinary isofuran, o-tyrosine, and 8-hydroxy-2'-deoxyguanosine levels on day 7 with development of BPD (57).

Important clinical outcomes for preterm infants are chronic comorbidities such as respiratory and neurodevelopmental impairments. Vento *et al.* first demonstrated a decreased need for mechanical ventilation, total oxygen days and BPD in infants whose resuscitation is initiated with lower oxygen concentrations (57). Kapadia *et al.* similarly found in a small cohort of <34-week infants that starting resuscitation with air versus oxygen required less 'rescue ventilation' with high frequency, less total ventilator days and a decreased incidence of BPD (58). However, neither group looked at long-term developmental outcomes or post hospital mortality. On the other hand, Boronat *et al.* did investigate these longer-term outcomes and found no difference in survival or neurodevelopment (via Bayley-III) at 24 months between initiating resuscitation with either 30% or 60–65% FiO_2 (64). Similarly, Rook *et al.* found no difference in long term respiratory outcomes or survival (59).

Welsford *et al.* also published a separate systematic review regarding infants <35 weeks GA (65). They found ten randomized controlled studies and 4 cohort studies with a composite of close to 5,700 infants. There were no statistically significant benefits of or harms from starting with lower compared with higher FiO_2 in short-term mortality. In this systematic review, no differences in HIE or long-term outcomes were found between the groups.

Discussion

After 200 years of newborn resuscitation with oxygen, it took 30 years from when the first experimental study and 17 years from when the first clinical study was published until ILCOR changed from recommending 100% oxygen to air when initiating resuscitation of term or near-term infants (6). The data seems to be quite robust indicating a 30% reduction in mortality in those resuscitated with air versus oxygen to support this change. For example, this degree of risk reduction means, in year like 2000, where there were an estimated 4 million births complicated by asphyxia and subsequently 1 million asphyxiated-associated deaths, this represents a potential annual reduction in newborn deaths by approximately 300,000.

For premature infants the data are less clear, however, data support to start resuscitation with air down to 32 weeks GA. Between 28–31 weeks GA it is not clear whether 21% or perhaps 30% oxygen should be used, and for those <28 weeks it definitely seems to be a need

to start with supplemental oxygen. How much is a matter of discussion; however, our recent data suggest starting with 30% O_2 (66). For all GAs, FiO_2 should be changed according to development of SpO_2, and we recommend targeting a SpO_2 of 80–85% within 5 minutes in all infants, especially in the immature ones.

Despite these data, supplemental oxygen may be needed for subgroups of term and near-term infants, for instance those with lung involvement may need extra oxygen. As always, the interventions need to be tailored to each patient's needs and, ideally, altered based on prenatal risk factors.

The demonstration of elevated hypoxanthine concentrations in umbilical cord blood after asphyxia followed by the understanding that hypoxanthine is a potential oxygen free radical generator has been translated to a dramatic reduction in neonatal mortality (67). The concept of room air resuscitation also paved the way for new resuscitation programs such as Helping Babies Breathe (68); although these changes introduced new challenges as oxygen blenders are not always available in resource limited settings (69). The introduction of such programs may potentially save another 2–300,000 lives annually. Based on our understanding of one molecule, hypoxanthine, the journey from bench to bedside represents one of the most successful interventions to guide the evolution of neonatal resuscitation (67,70,71).

Conclusions

It took 200 years of practice to understand that resuscitation of term and near-term newborn infants with oxygen is detrimental. This practice is an example of inadvertent harm that occurs when therapies, either historical or new, are used ubiquitously without randomized trials. We now know many infants should have been resuscitated with air which could have prevented the death of millions of newborn. Current recommendations for newborn infants <32 weeks gestation recommend initial FiO_2 should be 0.21–0.30 and for those <29 weeks one should start with at least 30% oxygen; however, time will tell if this is the optimal initial FiO_2 for these infants.

Acknowledgments

Funding: This work was supported by the National Institutes of Health (No. HL140152 to MER).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Pediatric Medicine* for the series "Oxygen in the Newborn". The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-21-110/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-21-110/coif). The series "Oxygen in the Newborn" was commissioned by the editorial office without any funding or sponsorship. ODS served as the unpaid Guest Editor of the series and serves as an unpaid Associate Editor-in-Chief of *Pediatric Medicine* from January 2022 to December 2023. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pm-21-110
Cite this article as: Robbins ME, Saugstad OD. Oxygen for newborn resuscitation: a narrative review. Pediatr Med 2023;6:28.

Supplementary

Table S1 Metanalyses published comparing the outcome of death when using air versus 100% oxygen for neonatal resuscitation

Author	Decreased mortality with air (95% CI)	Number of studies [n = total patients]
Davis *et al.*, 2004 (48)	RR 0.71 (0.54–094)	5 [1,302]
Tan *et al.*, 2004 (49)	RR 0.71 (0.54–0.94)	5 [1,302]
Tan *et al.*, 2005 (50)	RR 0.71 (0.54–0.94)	5 [1,302]
Saugstad *et al.*, 2005 (51)	OR 0.57 (0.42–0.78)	5 [881]
Saugstad *et al.*, 2008 (52)	RR 0.69 (0.54–0.88)	10 [2,133]
Welsford *et al.*, 2019 (53)	RR 0.73 (0.57–0.94)	10 [2,164]

CI, confidence interval; RR, relevant risk; OR, odds ratio.

https://dx.doi.org/10.21037/pm-21-110