

# Normoxemic Resuscitation in the Delivery Room

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The 2005 Guidelines of the International Consensus Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science (Neonatal Resuscitation Section; part 7) have introduced substantial modifications in the use of supplementary oxygen in comparison with the previous 2000 Guidelines<sup>1,2</sup>. Thus, the current Guidelines do not recommend a specific oxygen concentration for initiating resuscitation as opposed to the previous guidelines which recommended 100% oxygen (sic): *“There is insufficient evidence to specify the concentration of oxygen to be used at initiation of resuscitation”*<sup>1,2</sup>. Thus, the use of supplementary 100% oxygen for the initiation of ventilation can no longer be regarded as the standard of care. In addition, the guidelines indicate that, even if heart rate does not improve after adequate ventilation, the priority should be to secure cardiac output by chest compression, since there is no evidence that modifying the inspired oxygen concentration will improve prognosis<sup>1</sup>. Finally, the present guidelines caution against adjusting the oxygen supply to pulse oximetry because reliable values of oxygen saturation following birth are lacking<sup>1</sup>. These statements serve only to confirm the uncertainty that surrounds specific aspects of neonatal resuscitation. In the present editorial, we propose to clarify the pathophysiologic sequence of events following the use of excess oxygen with the aim of facilitating decision making by health professionals faced with an asphyxiated neonate.

Evidence accumulated in recent years has shown that room air is at least as effective, if not more so, than 100% oxygen in resuscitating asphyxiated newborn infants above 1.000 g of birth weight<sup>3-7</sup>. Moreover, meta-analyses of these studies have shown reduced mortality in room-air resuscitated infants<sup>8,9</sup>, and follow-up of the surviving infants at 2 years of age showed no differences in neurological sequelae between the two groups<sup>10</sup>. The combined available evidence prompted the International Liaison Committee on Resuscitation (ILCOR) to modify

the standard of care in relation to the use of supplementary oxygen in delivery room resuscitation of newborn infants<sup>2</sup>.

Several studies were published after the ILCOR meeting in January 2005 and were therefore not included in the formulation of the current Guidelines. A study performed by an independent group of researchers (other than the authors) has confirmed the safety of room air for resuscitating asphyxiated newborn infants<sup>11</sup>. Secondly, a comprehensive meta-analysis including the full information present in the databases of the investigators who performed the previous clinical studies<sup>3-7</sup> demonstrated reduced mortality in room-air resuscitated infants compared with those resuscitated with pure oxygen<sup>12</sup>. In another study, which used specific biochemical markers, increased damage to organs such as heart and kidney in the first days of life was observed when pure oxygen was used as compared to room air<sup>13</sup>. In fact, a statistically significant correlation between markers of oxidative stress (reduced/oxidized glutathione [GSH/GSSG] ratio) and of cardiac [cardiac troponin T (cTnT)] and renal damage (N-acetyl-glucosaminidase) was found<sup>13</sup>. Finally, a further study underscored the importance of cardiac frequency as a simple and reliable means of evaluating response to resuscitation, as well as the high sensitivity and specificity of pulse oximetry in predicting outcome<sup>14</sup>.

In the last 10 years, hundreds of infants have been effectively resuscitated with room air in clinical trials globally<sup>12</sup>. Although not all of these infants suffered from severe asphyxia, all of them needed positive pressure ventilation to overcome postnatal respiratory depression. The use of room air significantly shortened the duration of resuscitation by several minutes<sup>8,9,12</sup>. The mean volume of excess oxygen that each infant resuscitated with 100% oxygen received as compared to those resuscitated with room-air amounted to around 115 ml per kilogram of body weight<sup>7</sup>. Most of these newborn infants did not

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have pulmonary disease and therefore the oxygen supplied with positive pressure could freely reach the alveolar surface. Although it is well known that the alveolar lining fluid contains a substantial concentration of antioxidants, especially extracellular superoxide dismutase and GSH, this antioxidant defense barrier has proven insufficient to scavenge the burst of oxygen free radicals produced during the hypoxic-reoxygenation process characterizing asphyxia. Thus, in previous studies, the GSH/GSSG ratio was significantly diminished in infants resuscitated with 100% oxygen as compared to those resuscitated with room-air, indicating the presence of oxidative stress<sup>5</sup>. Moreover, the use of 100% oxygen during resuscitation caused hyperoxemia as measured in arterial blood gases performed during resuscitation, while partial pressure of oxygen remained within the physiologic range in room-air resuscitated neonates<sup>7</sup>. Thus, a significantly decreased GSH/GSSG ratio and activation of the glutathione redox enzymes were found in pure oxygen resuscitated infants as compared to room-air resuscitated infants<sup>14</sup>. In addition, there was a significant correlation between the concentrations of GSSG and arterial partial pressure of oxygen, indicating that hyperoxemia led to a pro-oxidant status<sup>7</sup>.

Do these findings have a clinical correlate, or are they simply biochemical data with only theoretical implications? A recent prospective randomized clinical study blinded for the gas source reported that markers of cardiac (cTnT) and renal damage [N-acetyl-glucosaminidase (NAG)] were increased in plasma and urine respectively in severely asphyxiated newborn infants after birth<sup>13</sup>. However, infants ventilated with pure oxygen had significantly higher concentrations of cTnT and NAG during the first days of life than those resuscitated with room air and, remarkably, there was a significant correlation between markers of cardiac and renal damage and GSSG<sup>13</sup>. Our studies have described a sequence of pathophysiologic events in the human neonate derived from the administration of excess oxygen after a prolonged hypoxic-ischemic event. The use of 100% oxygen delays the onset of spontaneous respiration thus prolonging the duration of positive pressure ventilation. As a consequence, a cascade of events is triggered: hyperoxemia, production of oxygen free radicals, oxidative stress and increased tissue damage. We hypothesize that this sequence of events could explain the increased mortality observed in newborn infants resuscitated with pure oxygen<sup>8,9,12</sup>.

The principal clinical repercussion of all of the above is that excess oxygen supplementation to tissues after an asphyxia episode should be unequivocally avoided. The 2005 Guidelines are skeptical about the reliability of continuous pulse oximetry as a guide to determining oxygen needs during resuscitation<sup>1</sup>. However, faced with a dilemma on the need or otherwise for oxygen supplementa-

tion, monitoring of arterial oxygen saturation (SaO<sub>2</sub>) using continuous oximetry, and especially the use of oximeters that incorporate signal extraction technology, is still the most reliable method of adjusting individual oxygen needs during resuscitation. Interestingly, in a large group of asphyxiated patients, we found that SaO<sub>2</sub> at 1 min of life gave the highest sensitivity and specificity regarding death in the first week of life<sup>15</sup>. Moreover, the receiver operating curve (ROC) for SaO<sub>2</sub> at 1 min as a predictor of death in the first week of life gave the highest area under the curve (0.84) compared with other indicators such as heart rate at different times, Apgar score, and hypoxic ischemic encephalopathy grade II/III<sup>15</sup>. However, as stated by the ILCOR, further studies are required to determine the normal SaO<sub>2</sub> curves of infants of distinct gestational ages in the first minutes of life. These normality curves would guide the need for oxygen in individualized cases, thus helping to avoid excess oxygen supplementation and its deleterious consequences.

A substantial number of editorials have analyzed studies that have compared room-air resuscitation versus 100% oxygen<sup>16-21</sup>. The main criticism of these studies concerns randomization and the small number of infants recruited. However, all authors agree on the difficulty of performing such studies and on the urgent need for a large, multicenter, randomized clinical trial. As stated by Prof. Tarnow-Mordy, performing a classical randomized clinical trial with the aim of reducing mortality or brain damage from 24% to 21% with a power of 80% and a two-sided  $\alpha$  of 0.05, would require 7000 asphyxiated neonates<sup>16</sup>. This approach is nowadays impossible to put into practice. However, as proposed by Prof. R J Martin, there are other alternatives, which are feasible and highly informative<sup>21</sup>. Thus, a non-inferiority trial (a specific concentration of oxygen is as good as 100% oxygen) could be performed. Another possibility would be to use titrated oxygen supplementation controlled by pulse oximetry initiated immediately after birth, setting a small margin of equivalence and high power to minimize the chances of incorrectly concluding that a new approach is equivalent to 100% oxygen when in fact it is inferior<sup>20</sup>. Either of these alternatives, and even others that could be designed by competent epidemiologists, would allow a valid and informative prospective randomized study with a population of around 700 newborn infants to be performed, which is perfectly feasible and highly desirable.

In the future it is highly probable that newborn infants will be monitored by a new generation pulse oximeters, which will allow us to accurately determine SaO<sub>2</sub> in the newborn infant immediately after birth. Resuscitation should then be guided according to normal SaO<sub>2</sub> development. Until then we will have to rely on the response of heart rate to positive pressure ventilation and the SaO<sub>2</sub> values described in recent scientific literature.

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