**III. Respiratory and Ventilator Management**

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**I. What are the goal values for PaCO2 and PaO2 on ABGs?**

With regard to CO2, the goal may be values within the normal range (40-55 mmHg Note: although higher PaCO2 may be appropriate for certain infants with significant ventilator requirements). Infants who have suffered a hypoxic-ischemic insult will have resultant changes in metabolism that lead to less CO2 production. Also, CO2 may be low secondary to respiratory compensation for the initial metabolic acidosis. Hypothermia may reduce CO2 production as well[1]. These factors combined lead to less ventilator support needed to obtain a desirable CO2.

Hypocapnia has also been shown to be harmful in this population. Low CO2 leads to decreased cerebral perfusion and decreased oxygen release from hemoglobin. Current research has also determined it to be associated with death and poor neurodevelopmental outcome in infants with HIE [2].

Hyperoxia has also been shown to have a detrimental effect on these infants. Hyperoxia leads to increased oxidative stress and increased free radical production. It can be especially toxic in the setting of reperfusion and attenuate brain injury[3] . Further, hyperoxia has been associated with death and poor long-term outcomes post asphyxia [2]. We therefore recommend goal PaO2 values of 50-100 mmHg.

Infants who suffer from birth depression and resultant HIE often undergo vigorous resuscitation at birth. As a result, they may have hyperoxia and hypocapnia from birth. After initial asphyxia the cardiopulmonary function often improves rapidly necessitating less support. We recommend obtaining a post resuscitation ABG, and using a conservative ventilator strategy.

*Recommendations:*

1. Keep PaCO2 in the range of 40-55 mmHg (Note: these are suggested ranges and may need to be modified for individual patient care based on the bedside clinicians exam and the patient’s underlying pathophysiology). If the neonate is self hyperventilating to a lower level, assure that mechanical ventilation is not contributing to further decreases in CO2 by lowering support as much as clinically indicated.
2. Keep PaO2 in the range of 50-80 mmHg to prevent hyperoxic injury.
3. Avoid over ventilation by starting with a conservative initial ventilator rate (For example 30 breaths per minute. This suggestion should be modified based on the clinical presentation.)
4. ABG post resuscitation, manage ventilator to obtain goal PaO2 and PaCO2

*Level of Evidence:* IV- Case Series and Expert opinion based on current review of the literature.

**II. What parameters are recommended for FiO2 and oxygen saturations?**

As outlined above, hyperoxia is particularly harmful in this population. Current guidelines recommend the use of room air for the initial resuscitation of term infants. Infants resuscitated with room air have higher Apgar scores at 5 minutes, higher heart rates at 90 seconds of age, and took their first breath 30 seconds earlier than those who received 100% oxygen [4].

*Recommendations:*

1. Initiate resuscitation with room air (follow the Neonatal Resuscitation ProgramTM guidelines 6th edition for delivery room management)
2. When oxygen is required, use the least amount of FiO2 needed to maintain saturations > 92%

*Level of Evidence:* IB- RCT and Expert opinion based on current review of literature.

**III. What defines a patient who may be a candidate for ECMO?**

Infants who suffer from severe HIE often meet ECMO support criteria secondary to pulmonary hypertension with or without meconium aspiration and/or hypoxic respiratory failure. Recent literature has examined the practice of continuing hypothermia therapy while undergoing ECMO with good results [5]. One practice management that may be initiated as ECMO becomes likely is nitric oxide (NO). The use of NO, even at low dosing (5 ppm), can decrease the use of ECMO by as much as 35% when the oxygen index is > 25 [3]. However, despite the use of NO, ECMO is often still the required therapy in this population. A recent survey to the directors of ECMO programs showed that there is significant variability in how neonates are selected for ECMO once severity of illness criteria has been met. In this survey, 48% of the responders stated they would not offer ECMO to infant’s with severe HIE[6].

*Recommendations:*

1. In the experience of the network sites, hypothermia may be continued safely during ECMO.
2. Early discussion of the ECMO criteria for infants with severe HIE should be established. The discussion should include multiple disciplines (neonatology, pediatric surgery, ethics committee).
3. May consider rewarming slowly by 0.20C to see if the pulmonary vascular resistance relaxes with mild increases in the temperature. The clinician may consider proceeding straight to ECMO if the baby is very early in the hypothermia course or rewarming to a target range which is still considered neuroprotective, 350C. Conversely, the clinician may consider rewarming fully if the neonate is close to the end of the 72 hour cooling period in an attempt to avoid ECMO.

*Level of Evidence*: IV- Case Series and Expert opinion based on current review of the literature.

**IV. How should temperature correction factor into the interpretation of blood gases?**

Hypothermia affects blood gas parameters such as pH and CO2; at lower temperatures pH increases and CO2 decreases [7]. Most blood gas instruments contain a temperature-controlled sample chamber specified to be 37oC, referred to as α-stat method. In the α-stat method, uncorrected values are used to keep the pH and CO2 close to the 37oC reference value. Alternatively, in the pH-stat method, the measured pH is corrected to the actual body temperature of the patient. For example, during hypothermia (core temperature 33°C), pH will rise to 7.5 and PCO2 will decrease 34 mm Hg (6). At this point it is unclear whether the α-stat or pH-stat method should be used for the ventilator management of the asphyxiated neonate undergoing hypothermia [7].

*Recommendation:*

1. Recognition that blood gas values will vary depending on the method used in calibration; the clinician may consider alternative ventilator strategies to obtain goal blood gas values.

*Level of Evidence:* V- Expert opinion based on current review of literature.

**V. Should patients be extubated during the cooling or rewarming process?**

*Recommendation:*

Based on case reports it appears to be a safe practice if the infant meets all the parameters needed for safe extubation. These infants represent a unique population and awareness of their high-risk status must be considered: airway protection (if diminished gag reflex), seizure activity, and apnea associated with the cooling and/or rewarming process

*Level of Evidence:* V- Expert opinion based on current review of literature.

**VI. What are the recommendations regarding ventilator management?**

As discussed previously, initial ventilator settings should be conservative, with moderate pressures and respiratory rate.  Initial PEEP should also be conservative.  Overdistension of the lung may increase PVR and reduce venous return, therefore impairing peripheral and cerebral perfusion.  Finding the optimal balance between sufficient MAP to allow lung recruitment and its potential negative effects on circulation may often require multiple chest radiographs and echocardiography [3].

*Level of Evidence:* V- Expert opinion based on current review of literature.

**VII. What are the recommendations regarding the use of nitric oxide (iNO)?**

As discussed in the section on ECMO, iNO can effectively improve oxygenation in the asphyxiated newborn, with or without evidence of PPHN.  It may also be used, even at smaller doses, to aid in the weaning of FiO2 if the patient is on high settings.  In previous studies, oxygen used has diminished after the initiation of iNO therapy.  If infants are on high FiO2 and ventilator settings consideration should be given to starting NO therapy [8].

*Level of Evidence:* V- Expert opinion based on current review of literature.

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