# Oxygen to the newborn—too little or too much?

This special series of *Pediatric Medicine* (*PM*) is about oxygenation of the newborn. World leading experts are presenting the most updated knowledge and information in this field. Today we know that oxygenation of the newborn represents a double edged sword. Too little may lead to hypoxia with a number of potential negative effects and too much oxygen may lead to oxidative stress and injury to tissues of several organs. Contemporary newborn medicine therefore deals with the dilemma to find the optimal balance between not giving too little and not too much. Already in 1774, when Joseph Priestly described oxygen as an element he realized oxygen may be toxic. However, it was the French chemist Antoine Lavoisier who a few years later understood the role of oxygen in combustion. When he was beheaded in 1794, during the French revolution, the world lost one of its best brains ever.

The role of oxygen therapy in the newborn is to:

(I) Provide sufficient oxygen to the tissues and avoid anaerobic metabolism;

(II) Prevent hypoxic pulmonary vasoconstriction;

(III) Promote brain and somatic growth;

(IV) Minimize adverse effects.

These, sometimes conflicting goals, illustrate the delicate balance between too little and too much we have to define (1-3). The epidemic leading to retrolental fibroplasia and blindness in the 1940's illustrates this. Even today the blindness caused by too much oxygen in premature infants represents a global health problem. Up to quite recent time this balance in oxygenation has been ignored. In 1992 the American Heart Association published guidelines for newborn resuscitation with the now infamous statement: "there is no reason to be concerned giving pure oxygen a brief period after birth" (4). Today we know there were reasons to be concerned. As we point out in this series of PM and elsewhere, much of the experimental and clinical studies related to newborn oxygenation which were carried out from around 1990 and onwards were based on the studies of one single molecule "hypoxanthine" (5-7).

Since 2010 it has been established that term or near term newborn infants in need of positive pressure ventilation (PPV) immediately after birth should be given air instead of oxygen (8). This paradigmatic shift in understanding and practice is estimated to prevent up to half a million newborn deaths annually, due to a reduced mortality applying air instead of pure oxygen combined with the effort to rescue so-called fresh stillbirths with air ventilation (7,9,10). Another advantage with air resuscitation compared to resuscitation with 100% $O_2$ is that the newborn takes its first breath approximately 30 seconds earlier when PPV is provided by air (9-11). New resuscitation programs such as the *Helping Babies Breathe* developed by the American Academy of Pediatrics are based on this new recognition of applying air (12). However, there are still gaps in our knowledge regarding resuscitation and many of these are discussed in this series of PM.

Sankaran, Rawat, and Lakshminrusimha discuss optimal oxygen use during cardiopulmonary resuscitation including chest compressions. They summarize important physiological aspects of chest compressions. There are limited clinical data to guide us about the optimal $FiO_2$ during chest compressions. Sankaran *et al.* argue, however, convincingly that 100% oxygen should be applied during the compressions. It is, however, important to wean directly to air as soon as sinus rhythm is established (13).

Oxygenation of premature infants, and especially the most immature ones during PPV is another matter of discussions and arguing. Oei and co-workers have the recent years presented the most fundamental new knowledge in this field through randomized studies and questionnaires. This group was the first to demonstrate that immature infants <28 weeks gestational age need more than air if they need PPV at birth (14). However, how much supplemental oxygen is still not known. What we have learnt from this group is the importance of an optimal development of the oxygen saturation of premature infants the first 5–10 minutes after birth. The most optimal outcome is found if $SpO_2$ reaches 80% within the first 5 minutes (15). By analyzing the same cohort of premature infants, Kapadia *et al.* have shown that bradycardia the first minutes after birth reflects poorer outcome. In fact, the combination of not reaching $SpO_2$ of 80% and bradycardia (<100 bpm) more than 2 minutes during the first 5 minutes after birth, increases risk of death 18-fold (16). In this series of PM Sotiropoulos, Kapadia, Ramachandran, and Oei summarizes why it is so important to control oxygen saturation and heart rate during the first 10 minutes of life. They also discuss the optimal techniques to monitor oxygenation and heart rates (17).

Padilla-Sanchez *et al.* were pioneers to demonstrate that delayed cord-clamping accelerates the increase of $SpO_2$ the first

minutes after birth (18). In this series in PM Padilla-Sanchez together with Baixauli-Alacreu, Solaz-Garcia, Lara-Canton, and Vento in Valencia, Spain present updated reference ranges for $SpO_2$, heart rate and respiratory function the first minutes after birth (19). These are important in order to guide the neonatologists in their attempts to stabilize the newly born child in the delivery room.

The oxygenation of premature infants beyond the delivery room is summarized by Schmidt and Kirpalani (20). Also in this period of life, we don't know the optimal oxygenation for the most immature infants. However, the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) study, of which one of the principle investigators was Barbara Schmidt, has provided us with more knowledge so we can give recommendations (21). $SpO_2$ should be kept between 91–95%, or 90–94% according to the NICE and European Consensus guidelines respectively (22,23). Both recommend tight alarm limits in order to avoid oxygen fluctuations. It seems that not only low oxygen but also oxygen peaks are detrimental. Schmidt and Kirpalani in their article argue that each neonatal unit should adjust these guidelines according to the morbidity and mortality profile of the unit. Neonatal intensive care units with high risks of death and severe necrotizing enterocolitis will benefit more from higher target saturations than units where the risks of these outcomes are low. Similarly, neonatal intensive care units with a high risk of severe retinopathy will experience more harm from higher target saturations than units where the risk of severe retinopathy is low. This represents a step forward towards personalized medicine (20).

Sun, Rong, and Zhang present an overview of oxygen therapy in China. These therapies are now adjusted to international guidelines, however, still there is a lack of important equipment such as pulse oximeters and blenders (24). This article sheds lights on why there has been a dramatic reduction of neonatal mortality and morbidity in a short time period in China. Low and middle income countries could gain experience from this Chinese success story.

However, in spite of all the progress, there are a number of unknown factors regarding newborn oxygenation. The future generations of neonatologists do not lack new research topics and projects on the way to optimize oxygen care of the newborn. It is recommended to create international study groups and systematize and coordinate efforts, in order to reduce neonatal mortality and morbidity even further. The present series of *Pediatric Medicine* may be a starting point and tool to achieve that.

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