Neonatal resuscitation research: closing the gap

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In 1966, Harold Abramson edited the first edition of the textbook "Resuscitation of the newborn infant".(1) Abramson was a professor of pediatrics at New York Medical College and chairman of the special committee on infant mortality. In his preface he describes neonatal resuscitation as a problem "as old as mankind, yet not satisfactorily solved".(1) Although he authored and edited many chapters, he admitted that "there is very little knowledge in neonatal resuscitation, due to a lack of understanding in the physiology of fetus and neonate, lack of techniques and reluctance to initiate studies. This has led to dogmatic practices, the acceptance of procedures not well founded and representation of unsubstantiated impressions and beliefs carried down through the years from textbook to textbook in scissor and glue pot fashion and from one practitioner to another".(1) Although some interventions are largely based on dogma, have been extrapolated from adult medicine or are based on animal models with questionable relevance, they remain in resuscitation algorithms and recommendations from prominent resuscitation organizations like the International Liaison Committee on Resuscitation.(2, 3) While some 50 years have passed since Abramson's textbook and our knowledge, although fragmentary, has increased, it is perhaps not a surprise that some of the interventions mentioned by Abramson's remain in resuscitation treatment recommendations.

For many years the healthcare burden associated with neonatal medicine was underestimated and a "disconnect" between the scientific and clinical research meant that the continuous and ongoing need for improving care was largely fulfilled by clinical studies. However, the connection between scientific and clinical research has improved, which has increased awareness among clinicians as to the unique physiological challenges all infants must face to survive after birth. Indeed, infants at birth are unlike any other human patients, and when newborns cannot meet the physiological challenges required to transition to newborn life, clinicians need to intervene. However, the available equipment and interventions used in the delivery room lag far behind the resources and evidence-based practices that are available in the intensive care unit. This discrepancy is striking, given that postnatal transition represents a highly vulnerable period for newborn infants. This reflects a "gap in knowledge", which likely results from the difficulties in conducting clinical studies in the delivery room, developing appropriate preclinical animal models to study fetal-to-neonatal transition and accurately replicating the scientific knowledge gained from preclinical models into clinical studies.(4) In this commentary we will shortly discuss the considerable efforts that have been made to close this gap in knowledge, as well as the outstanding barriers to progress in neonatal resuscitation research.

Our understanding of the physiology underpinning the transition from fetus to neonate has accelerated in recent decades, (5-7) driving an increased focus on optimizing management of infants at birth to improve clinical outcomes. Over the last decade, research in perinatal transition and neonatal resuscitation has increased exponentially, with the number of publications almost doubling each year. The relevance of animal models has improved and clinicians have benefited from observing in detail the physiological processes during transition and the effect of interventions in animals who are going through transition.(4) Advances in technology has also made it possible to measure some physiological parameters in human infants at birth, which has confirmed the similarity between humans and animals in the underlying physiological processes. Results from such well-designed animal studies represent an integral part of a knowledge pipeline that is necessary to correctly inform clinical studies.

Following the initiative of Professor Colin Morley from the Royal Women's Hospital, Melbourne, and Professor Neil Finer, University of California San Diego Medical Centre, California, several research groups undertook observational studies during stabilization or resuscitation at birth.(8-10) An abundance of knowledge has been generated by observing and measuring the transition of newborns

and how they respond to the support they are given. The combination of improved animal models and human observational data works in a bi-directional way. The clinical observations not only confirm the experimental data, but they also raise a series of new scientific questions to be answered in a controlled experimental setting. This approach has already nullified several long held but unproven assumptions and dogmas about the mechanisms of transition and led to advocating new interventions in guidelines. The information provided can form the scientific basis for robust study protocols for large national and international clinical studies.

Another reason that clinical studies in this field are scarce is due to the complexities of obtaining parental consent for their newborn's participation in scientific research. Prospective consent is challenging to obtain due to time constraints or ethical inappropriateness immediately prior to birth. This consent process excludes the sickest infants from clinical trials, reducing the generalizability of studies that employ antenatal consent.(11) This barrier is recognized in national and international legislation and regulations for medical scientific research with humans, which allow retrospective consent in exceptional situations and under strict conditions.(12, 13) Retrospective consent for neonatal resuscitation studies is gradually being used by several centers but remains a topic of discussion.(14) While medical research can greatly improve the care of newborns at birth, there is a balance between the indirect benefits of conducting clinical research while respecting the autonomy of individual patients and parents.

One challenge confronting this field is defining the population of interest. The recommendation for interventions for asphyxiated term infants and preterm infants are currently combined into a common neonatal resuscitation guideline and compromised infants are thus approached in a similar way.(15) This seems odd as there is an increasing awareness that these are two distinctly different groups of infants with their own pathophysiological origin for the problems they experience during the fetal-to-neonatal transition. Most preterm infants are not apneic and do not need resuscitation.(16, 17) The focus here should be on supporting them in their adaptation during transition. While several clinical trials have compared different modes of respiratory support, observational studies, using physiological measurements, have shown this may not be very efficient.(17-19) For example, mask leak, airway obstruction due to a closed larynx and induction of a diving reflex all adversely affect respiratory support and there has been a widespread misunderstanding of the importance for spontaneous breathing.(20, 21) While studies are now examining a combination of more efficient strategies, there is now sufficient awareness of the differences in approaches needed for near term asphyxiated infants versus prematurely born infants, that perhaps the time has come to consider separate guidelines for term and preterm infants.

The timing of cord clamping after birth is another good example of how clinicians need to rethink the "one size fits all" approach for providing newborn assistance at birth. It has taken us a long time to acknowledge that immediate cord clamping was introduced as a questionable solution for a maternal problem (postpartum haemorrhage), despite having a demonstrable adverse effect on neonatal outcome (reduction in birth weight). However, while we now understand that postponing cord clamping is beneficial for almost all newborn infants, it is possible that we will repeat the same mistakes by basing our decision for when to clamp on the minute hand of the clock, rather than on the infant's physiology.(22) We need to question whether this is simply because a clock is easier to read than the infant's physiology. Experimental studies have made it clear that the moment of cord clamping should be defined by the physiological changes that occur during transition.(23, 24) As the time-point of establishing these changes differs for each infant, the moment of cord clamping should not be defined by a fixed time but should be individualized according to the infant, which inevitably leads to a variation in clamping times.(25, 26) In addition, both the benefit and defining the best moment of cord clamping

are different for each transitional problem, whether it is due to asphyxia, prematurity or a congenital abnormality. Scientific and clinical data for this physiology-based cord clamping has been provided and currently large RCTs are underway.

Last but not least, there is the issue of choosing the primary outcome for clinical resuscitation studies. When the evidence for possible treatments at birth is evaluated for recommendation in guidelines, the chosen outcome is important. Most interventions investigated after birth birth are short-acting and are designed to benefit the infant as it passes through the very short time-window we call transition. However, proximal benefits may not be appreciated when assessing longer term outcomes- which are susceptible to multiple subsequent interventions. Indeed, while delivery room interventions directly influence the (patho)physiology at transition, which is quantifiable, the scientific community prioritizes primary outcomes that are measured at a much later time point.(27) We need to question where this logic comes from. Is it handed down from adult medicine where the interacting physiological changes are considerably less multi-dimensional? Although decreasing mortality, as well as short- and long-term morbidities is what we all (researchers, doctors and parents) hope to achieve, demonstrating this in trials investigating interventions at birth remains very difficult. Fortunately, mortality rates among many populations of interest are low; thus, mortality may not be the appropriate outcome. High risk patients such as very preterm infants receive intensive care for a long period; mortality and morbidity outcomes are therefore determined by the integration of many factors and by a huge variety of interventions during the NICU course. To overcome the huge level of "noise" that these influencing factors generate, trials require very large sample sizes to demonstrate whether a single, short duration intervention performed right at birth has a positive effect. At best, these trials are time and cost consuming and lead to very slow progress in improving the care of infants at birth. At worst they cause progress to stagnate. A potential alternative is to sequentially identify the best interventions at birth by measuring the direct effects on physiological parameters. This approach may allow for interventions that best influence the perinatal transition to be "bundled" together into a large trial that has the potential to be more effective and efficient in demonstrating differences in important clinical outcomes.

The importance of this research field and the need for further development was recognized by the European Society for Paediatric Research (ESPR) and in 2019 an official section "neonatal resuscitation" has been launched (www.espr.eu). Most members of this section already participated in a platform, named "the European Scientific Collaboration in Neonatal Resuscitation; ESCNR", which was established in 2010. The aims of the neonatal resuscitation section of ESPR are to: 1) exchange and discuss new ideas ("from hunch to hypothesis") and 2) facilitate collaborations between researchers ("from protocol to partnership"). It is important to emphasize that the focus of this section is on science and clinical research and not to evaluate or provide an alternate interpretation of the resuscitation guidelines. The neonatal resuscitation section of ESPR does not yet have a fixed research agenda, but we hope to contribute to advancing research in the unique setting of the delivery room while addressing the outstanding issues discussed.

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