Prof.dr. A.B. te Pas

The Equilibrist

Universiteit
Leiden
The Netherlands

Discover the world at Leiden University

The Equilibrist

Inaugural speech delivered by

Prof.dr. A.B. te Pas

at the acceptance of the Chair in Pediatrics,

in particular the perinatal transition and neonatal resuscitation

Leiden University,

on 11 February 2019

Universiteit
Leiden
The Netherlands

Rector Magnificus, respected members of the audience,

I am proud and grateful to stand here before you, commencing my new post as Professor of Paediatrics with the study field "perinatal transition and neonatal resuscitation". Neonatology – specialising in the care of seriously ill newborns and preterm infants – is both wonderful and challenging, and in my opinion extremely valuable. Not only because we are entrusted with caring for fragile young lives, but also because we deal with very vulnerable parents. Parents who have been looking forward to the magical moment of birth for months, when their joyful expectation suddenly turns to fear for their child's future. This is the moment they need us. They must hand over their child to doctors, complete strangers, at a time when – as every parent knows – they long to hold their baby close and protect it from the outside world. This is what makes neonatology so special. When our care succeeds, our profession is a thing of beauty.

At the deepest level, being a neonatologist is much like being a tightrope walker – an equilibrist. Our therapeutic work is a constant, subtle balancing act to keep seriously ill newborns or premature babies in a place of safe equilibrium. Whether it's in the oxygen delivery, artificial respiration, or medication, a little too much or not quite enough can make all the difference. Every day we perform this balancing act as a team. Offering the optimal treatment within such narrow margins is an art. Acting within these narrow margins, but also exploring them through research, is a major challenge with an important goal: maximising the chances of survival and minimising the risks of damage.

Neonatology is relatively young specialism. The first neonatal intensive care units (the NICUs) were established last century, in the fifties, but real progress has only taken place in the last twenty five years. Scientific research and technological innovations have focused on improving care at NICUs. As a result, the survival rate of neonates has considerably improved. In the last decade, however, we have become aware that perinatal transition is an extremely critical phase and that our actions in neonatal stabilisation or resuscitation can cause damage. [1] This is why we need more research, including clinical studies, to offer the right care.

With my new study and teaching assignment I enter a virtually unexplored terrain where so much can be gained towards increasing survival chances and reducing the risk of permanent damage in neonates. So I am very grateful to the Executive Board of Leiden University and to the Board of Directors at LUMC, both for daring to take a pioneering role by creating this chair and for placing their confidence in me. I want to take this opportunity to continue and expand current research to ensure the best possible start to early life, not only for the children themselves but also for the parents, who look forward to a happy future with a healthy child.

In this lecture I'd like to tell you about how I believe the therapeutic balancing act of this research project can be realised. For this, I will review topics such as two breakthroughs in clinical scientific research, the importance of animal research, the issue of retrospective consent, new technologies, learning and education. I also want to mention the brand new single care room at the Leiden department of Neonatology. Yes, I know my colleagues have been a bit nervous about that part – but I have a vision that I'd like to share with you. And finally, let's look to the future with a dream of what an ideal form of care could look like. But first, for those of you who aren't familiar with this field, I'd like to briefly explain some of the terminology of perinatal transition and neonatal resuscitation.

Perinatal transition and neonatal resuscitation

Before a foetus can survive outside the womb it has to go through enormous physiological changes: this transition is called perinatal transition. In fact, this is the biggest and

most abrupt physiological change that each of us will ever experience: birth is the moment a foetus becomes a neonate, literally meaning 'newborn'.

The lungs and heart, in particular, go through an important transition. At birth, the neonate clears the lungs of fluid with a few strong breaths and fills them with air.[2] The blood flow to the lungs increases enormously, and because of this they can regulate the gas exchange. [2] This is the moment parents know so well, when they hear their baby cry for the first time. Because the neonate no longer depends on gas exchange via the placenta, the umbilical cord can be cut. Disconnected from the placenta, the heart then has to adjust to a drastic change in blood circulation.[3]

Most perinatal transitions go very smoothly. Still, about ten percent of all neonates who are born every day are not able to get through this stage without assistance.[4] The help we offer to get the respiration and blood circulation going is called stabilisation or, in life-threatening situations, resuscitation. The main reasons for stabilisation and resuscitation are preterm birth and asphyxia - oxygen deficiency around the time of birth.

Babies who are born too early - premature babies – tend to experience problems with the transition. In the Netherlands, approximately 12,000 neonates are born prematurely each year, and around 15 million worldwide.[5] We speak of preterm birth when the baby is born earlier than 37 weeks, and of extreme preterm birth at earlier than 32 weeks. These extremely premature births are usually unable to complete the transition independently because their organs are immature. This means that, in order to survive, they are dependent on intensive specialist help and care at the NICU from birth. When they survive, there is also a risk of life-long health problems or the development of disabilities in later life. So, it is enormously important to improve these interventions in problematic perinatal transitions.

Fortunately, we have made great progress in this field in the past decade thanks to scientific research. I will now highlight two scientific breakthroughs, followed by my own ambitions for further research.

Two scientific breakthroughs

To optimise the treatment of neonates who need help making the transition, scientific knowledge is gathered through experimental animal research. Successful findings are then translated to the clinic, where we look for clinical evidence to support our hypotheses. These clinical findings in turn raise new questions that we then try to answer through further animal research.

Much has already been achieved with this bidirectional research approach. This has led to important new insights into the physiological mechanisms and processes involved in the transition, leading to real improvements in the care of newborns and changes in the clinic. Recently we made two important discoveries that could significantly improve care: first, the function of the vocal cords during the transition, and secondly stabilisation on the umbilical cord.

The function of the vocal cords during the transition

Most premature babies need help to start breathing properly. Using a ventilator that takes on the function of breathing, we gently deliver breaths through a mask placed over the baby's nose and mouth. Because we now understand that the lungs are very vulnerable at birth, we know that giving mask ventilation is a very delicate procedure: too much ventilation and oxygen delivery can lead to lung and brain damage, but so can too little.

While looking for ways to optimize this balance, we discovered that, contrary to what was assumed, most premature babies actually do try to breathe for themselves.[6-9] However, their

breaths are often so weak that they are barely perceptible to the naked eye. We also discovered that the vocal cords play an important role in the transition, one that has been overlooked up to now.

The vocal cords of the foetus are closed before birth and sometimes open briefly during respiratory movements. Research shows that during the first few minutes after birth the vocal cords of premature babies remain closed, until breathing has started.[10] Because of this the lungs cannot be aerated with artificial ventilation, unless the vocal cords open briefly with a spontaneous breath.[8,11,12] This shows that the vocal cords also go through a critical transition, which makes it crucial to review our vision of ventilation in premature births.[4]

It means that medical intervention should not focus on controlling breathing through artificial ventilation, but rather on stimulating and supporting the spontaneous - and often hardly perceptible - breathing when the vocal cords open automatically, so that the lungs can be aerated.[4,13] This is the way we can make mask ventilation more effective, and it also means that we're less likely to have to resort to intubation, a riskier and more demanding form of assisted ventilation where a breathing tube is placed inside the lungs, passing over the vocal cords.[4,13]

LUMC can already boast of excellent research results showing the effectiveness of various methods to stimulate breathing.[14-17] The next step in the research will be to develop an optimal strategy to support spontaneous breathing.[13] Finally, this will culminate in a study to find the most balanced combination of the two methods of breathing stimulation and support.

This approach could be a huge game changer, because we expect that it will help premature infants through the transition far more effectively than the current method.

Stabilisation on the umbilical cord

The second breakthrough - a great example of translational, bi-directional research involving multiple disciplines - is stabilisation on the umbilical cord. With a healthy baby the umbilical cord is only cut a few minutes after birth, because this leads to higher blood levels directly after birth and less likelihood of iron deficiency in later life. But in a problematic transition the cord is cut immediately as a matter of urgency, so that resuscitation or stabilisation on the resuscitation table can begin as soon as possible.

Experimental animal research, however, has shown that in a difficult transition the newborn naturally remains stable while waiting for the lungs to be aerated.[18,19] As with healthy babies, blood circulation in the lungs can then get going. Not only does the oxygen content in the blood improve, but circulation also remains stable, even after cutting the umbilical cord, as it becomes less dependent on blood circulation from the placenta.[18,19] In other words, these findings from animal research suggest that it is better not to cut the umbilical cord immediately in premature infants, but to stabilise and resuscitate them while still attached, so the natural physiological processes of transition can take place.

This meant that we faced a practical problem in the clinic, however. Our resuscitation tables were not built to provide life-saving care without cutting the umbilical cord. So, in close collaboration with the Department of Clinical Technology and the Department of Obstetrics, a new resuscitation table has been designed to overcome this problem. Within two years we have moved from a cardboard model to a fully-fledged prototype: the Concord, meaning 'with the umbilical cord'.[20] A strong piece of work. Thanks to the foundation of the Concord Neonatal BV company, the Concord can now be available to all neonatology centres in the Netherlands, and there has also been great interest from abroad.

Once the practical problem had been solved with the Concord Table, we realised we also needed a cultural change on the floor. With the introduction of the Concord, teams from neonatology, obstetrics, and – for caesarean sections – operating theatre, found themselves working in the same space and had to collaborate closely.[20] At LUMC this has gone very smoothly and with great success. In the Erasmus Medical Centre in Rotterdam, too, there was a lot of enthusiasm for the new method: when a newborn was chosen to receive care with the Concord Table, paediatricians and obstetricians gave each other a high five.

Meanwhile, the first clinical study with premature infants shows exactly the same positive effects on the oxygen level and the blood circulation as the animal studies when the umbilical cord is only cut after the lungs have been aerated.[21] For once, the results of animal experimentation and clinical research go hand in hand: something a researcher can hardly dare dream of. This has convinced us that we're on the right track and can continue to roll out the new method.

One further side effect of the Concord is very important to me, so I don't want to leave it unmentioned: with umbilical cord stabilisation, direct contact between mother and child also becomes possible. When I first saw this, it made a profound impression on me.

LUMC recently started a large national study. All ten neonatal centres in the Netherlands will participate, and we hope to show that stabilisation on the umbilical cord significantly improves the care of premature children.

Using umbilical cord stabilisation, we also plan to do further research on infants who need assistance through the transition for reasons other than preterm birth. Particularly those with perinatal asphyxia, who are born in a bad condition due to lack of oxygen, are expected to benefit from stabilisation on the umbilical cord.[22] The same applies to newborns with diaphragmatic hernia, a congenital hole in the diaphragm resulting in breathing difficulties at birth.[23] Animal research has already shown that both these patient groups can benefit. We therefore have high expectations that a study on umbilical cord stabilisation with the Concord table for newborns with diaphragmatic hernia will soon start at the specialist department at the Erasmus Medical Centre in Rotterdam.

The importance of animal research

The scientific breakthroughs I've described are possible thanks to animal research. As is well-known among medical professionals, evidence-based medicine means that doctors base their interventions on the best available evidence, so they can apply the most effective therapy.

The problem here, however, is that in medical science all research is not valued equally: data obtained from a randomised, controlled clinical examination or meta-analyses are regarded as the highest, purest form of evidence, while data obtained from animal experimental research as the lowest and weakest.[24] If clinical evidence is lacking, scientific evidence from animal studies is often not included in guideline development. In my opinion, this is wrong. Contrary to common understanding, based on unproven assumptions, dogmas or traditions, both animal research and clinical studies lead to scientific knowledge and evidence. And scientific knowledge should underlie our actions.[24]

A condition, of course, is that the animal models used are very similar to human newborns. This is the case in neonatology. Research with newborn rabbits and lambs are long-established animal models that have been proven to translate (patho) physiological changes of the lungs, blood circulation and brain into the human newborn.[24] The greatest advances in neonatology are thanks to these animal models. For example, animal experimental research has shown that by administering antenatal steroids[25] and surfactants[26,27], the chances of survival in human newborns increased considerably.

In my view, animal studies should also form the basis of clinical studies. After all, the more convincing the results of animal research, the greater the chance of a successful randomised, controlled clinical trial. Data obtained from animal experimental research should therefore not be considered as 'low and weak evidence'. Rather, as a highly-valued and indispensable link in bi-directional research, it should be valued in our aim to raise neonatology to a higher level through clinical studies.

Animal research into perinatal transition is now quite advanced, and as a clinical scientist I am very grateful to work so closely with physiologists and physicists who have developed two animal models unique to neonatology. The first model uses the synchrotron, a particle accelerator that generates special X-rays that can be used to image the lungs, blood circulation and vocal cords of premature rabbits.[10,28,29] This makes it possible to view and measure in detail what happens to certain physiological processes during the transition and the effects of intervention. The second model involves research in which measuring instruments are placed in unborn lambs to study all physiological changes and to measure the effect of interventions during the transition.[18,19]

These two animal models are complementary: what we cannot measure with one model, we measure with the other. The bi-directional research approach with these models has proved to be very successful – and, in saying this, I again want to underline the importance and value of animal research. It has already nullified several long held but unproven assumptions and dogmas about the mechanisms of transition and led to new intervention guidelines.

For the sake of clarity, I would like to say that I am not in favour of the direct translation of data from animal research into large clinical studies. The findings from animal research can best be verified via an intermediate step with human neonates. That intermediate step, which the Neonatology department of LUMC is now known for, means that a specially developed resuscitation monitor registers the physiological parameters of the newborn during birth.[30,31] Of course, these measurements are taken in a safe, non-invasive way and don't disturb the newborn. The data we collect with this monitor provide a lot of clinical information that, together with the data from animal research, forms the scientific basis for a well-thought-out study protocol for large national and international clinical studies.

In view of this, I believe that we should take a critical approach to the current undervaluing of animal research in perinatal transition and neonatal resuscitation. Animal research, together with clinical information obtained through the intermediate step, should be the scientific basis for setting up large clinical studies. Animal research should be the guiding principle when drafting guidelines when clinical research is lacking. After all, how is it scientifically justifiable to intervene on the basis of guidelines based on unproven assumptions or dogmas?

Clinical research and parental consent

As I said in the introduction, little clinical research has been done into perinatal transition and neonatal resuscitation, probably because clinical studies with this group of newborns are difficult. This is because the participation of a child in scientific research always requires prior permission from the parents: prospective consent. The problem with clinical research into perinatal transition and neonatal resuscitation is that there may not be time to obtain prospective consent because the newborn is in a life-threatening situation.

Even when there is time to ask for permission in advance, it may be considered inappropriate from an ethical point of view to approach the parents. They are experiencing an extraordinary amount of emotional and physical stress because of the sudden realisation that their baby is likely to be born

prematurely.[32-34] However, requesting retrospective consent – in other words, obtaining their permission afterwards - is also considered ethically inappropriate. For the scientific advancement of neonatology, in which clinical evidence is regarded as the highest and purest evidence, this yields a classic catch-22 situation that makes solid clinical research virtually impossible.[32,35]

However, this catch-22 is recognised in national and international legislation and regulations for medical scientific research with humans, and it's overcome by allowing retrospective consent in exceptional situations.[36-39] Naturally, this is subject to extremely strict conditions. For example, the patient must be in an emergency situation, the treatment must benefit the patient, and there must be a minimal risk and minimal burden in comparison with the standard treatment.

Despite the fact that our legislation provides for retrospective consent in clinical medical research, in our case with newborns, retrospective consent remains a topic of discussion – not only nationally, but worldwide.[40] At the Neonatology department at LUMC, we take this discussion seriously. After all, in our studies we mainly depend on retrospective consent and believe that it is our responsibility to shed some light on this problem. It is also essential to communicate clearly to prospective parents that medical research in this field can greatly improve the care of newborns. That is why, in collaboration with LUMC's Medical Ethics department, a PhD candidate has been appointed to conduct research into the question of how parents feel about their baby participating in a study when they were only approached for permission afterwards.

This research is still in progress, but it is already clear that involving parents who have been through this can add important value to developing protocols for studies that require retrospective consent. We are also looking for ways to create social awareness, especially among future parents, about the importance of medical research in newborns for improving care.

Education and training

Academic hospitals strive for improvements in neonatal care through university education and training as well as through research. The topic of perinatal transition and neonatal resuscitation is part of the curriculum of Medical Studies and Paediatrics course in Leiden. While there's a great deal of education and training on this available at LUMC, I'd like to highlight two learning methods that make the Paediatrics course unique in this field.

Firstly, in the neonatal resuscitation training in our Paediatrics course we include the mask technique. Adequate control of mask ventilation is the cornerstone of effective stabilisation and resuscitation. We have shown that this is no easy task, and that inadequate mask ventilation can destabilise the subtle balancing act we perform.[6,41] With this in mind, in 2011, in collaboration with the Advanced Life Diagnostics company, a so-called 'resuscitation monitor' was developed, which gives immediate feedback on the effectiveness of the caregiver's mask technique during training.[31] In view of the need for an appropriate mask technique and for the sake of learning efficiency, we recommend integrating this training in national neonatal resuscitation courses.[42]

Secondly, we have introduced weekly audits at the NICU of the LUMC. This means that we record what we do while stabilising newborns via the resuscitation monitor, and then review these images with the whole team at regular intervals.[43] We give each other feedback on how we acted in critical situations, without blaming or shaming. We can all learn from this in terms of education, information and care improvement. For example, these are the moments when we share thoughts about how we could improve technical interventions to implement guidelines in the best way possible. Recent research has shown that this method has a very positive effect on the quality of stabilisation and reporting.[44] This underlines the importance of peer learning in professional development.

Now that I have reached the NICU of the LUMC in this speech, I will stay there to bring single room care to your attention.

Single room care

Newborns in a critical state will end up at the NICU. Until recently they were all together in one room. After a major renovation, our unit has been transformed into a department with single room care, which means that every newborn has his or her own room. It is almost impossible to explain how much this privacy is appreciated by parents. Single room care, which fits in with the concept of 'family-oriented care', allows parents to be with their newborn child day and night, to play a role in day-to-day care, and to be able to talk to healthcare providers about their child's condition and medical treatment. Incidentally, for our nursing and medical team, this method of family-oriented care is nothing new: we have stood and continue to stand for family-oriented care for many years, and we attach great value to it. I am deeply happy with this new single room care for families.

However, in my opinion, one thing we have overlooked is the impact of single room care on the workload for the nursing team. Unlike the previous situation, when several newborns were together in one room, nurses can no longer check on the condition of several babies at a glance. So, I find it worrying that single room care has led to a significantly higher workload for the nursing team. It takes them a lot of effort to offer family-oriented care in this new situation at the same high level as before. The ideal solution for single room care would be one-on-one nursing - one nurse per newborn. However, this solution is very costly and also difficult to realise considering the current shortage of nursing staff in the healthcare sector.

This is why it remains important to look for other solutions to reduce the nursing staff's workload, while at the same time keeping the health of newborns in optimal balance. Here, new technologies can offer a solution.

New technologies

The arrival of new technologies, whether or not in combination with artificial intelligence, has made much manual work at the NICU redundant in the last twenty years and has improved care. In other words, the use of new technologies is a perfect way not only to reduce work pressure, but also to offer the most balanced, effective treatment to newborns within very narrow therapeutic margins.

A well-known example of this is the globally used servo-controlled incubator, which regulates the temperature in the incubator automatically. Ventilation equipment is also becoming increasingly sophisticated with built-in software which contains algorithms to accurately determine the correct degree of ventilation to the newborn.

A wonderful new technology, one that works in a more sophisticated way than manual care, is automatic oxygen titration in hypoxia. During hypoxia, the oxygen content in the blood is too low. Many premature infants suffer from this, and it often happens more than once.[45] As a matter of urgency, nurses then had to deliver extra oxygen manually and - if the oxygen level returned to normal – reduce the level manually to prevent hyperoxia, too much oxygen to the blood.[46] Both hypoxia and hyperoxia are proven to be harmful to premature babies.[47]

At the NICU in the LUMC, our research has shown that through automatic oxygen titration, premature babies retain the correct oxygen levels in the blood more often and for longer.[48] This is why our NICU is now one of the first clinics in the world that allows all sick newborns to benefit from this new technology. Automation provides a win-win situation here: it reduces the workload and facilitates the most balanced care within a very narrow, therapeutic margin.

The same applies to a new technology that can be used in cases of apnea. Apnea occurs frequently in premature infants because, as a result of an immature respiratory centre, the baby "forgets" to breathe.[49] In addition to administering oxygen, the nurse will have to stimulate breathing by, for example, gently rubbing the skin. This manual stimulation can be taken over by a vibratory mechanism that intervenes automatically - and therefore faster - in the event of a threatening apnea.[50] Animal research into this automated method has been successfully completed and the hope is to clinically test the first prototype next year.

Meanwhile, the time has come for research that uses artificial intelligence to develop algorithms that can predict a future health incident of any kind - hypoxia, apnea, infection, etc. - based on all the measurements and data we collect, also called big data. This would offer the opportunity to intervene in time to prevent the health condition of the newborn from becoming unbalanced and ending up outside the desired therapeutic bandwidth.

Incidentally, technology does not have to be extraordinarily advanced or complex to identify major health issues. In collaboration with Pediatric Cardiology of LUMC, we recently completed a major study in which all obstetricians in the region of Leiden, Haarlem and Amsterdam were given a oxygen saturation meter, a device that easily measures the oxygen level in the blood. This proved to be an extremely simple method of detecting potentially life-threatening conditions - such as heart defects, infections or lung problems - at an early stage, allowing intervention before severe symptoms develop.[51] With this simple technology, the health of newborns in the home situation can be much better monitored.

Nevertheless, a word of caution is required in the midst of all this optimism. Mother nature is very complex and it will be a great challenge to deal with this complexity in the development of medical technologies. In addition, the use of new technologies also means that healthcare professionals need new skills: they have to be able to operate the technology, understand it, and recognise any glitches and artifacts. The transition to automated technological care will therefore mean that technical physicians must be added to the neonatal team. But above all, we must realise that technology does not make man superfluous: the clinical view remains necessary.

A Dream for the Future

As promised, I want to take a moment to share a dream with you. In my dream of the future, the doctor performs a "hands-off stabilisation" and only approaches the newborn when absolutely necessary, so that the bonding process between mother and child is not disturbed. In the delivery room, the Midwifery and Neonatology teams are both ready for the birth of a baby after twenty-five weeks of pregnancy. There is a relaxed atmosphere, because the medical teams now know that they can effectively assist the baby in initiating breathing. The mother has received medication just before the birth to stimulate the baby's breathing as soon as it is born.

Immediately after the birth, the neonatologist will put a pair of nasal prongs – barely noticeable – in place so the newborn's own breathing is supported by additional air and the lungs become aerated. In the meantime, the baby is wrapped in a special blanket to prevent cooling down and placed on an ingenious mat that regularly emits vibrations that automatically stimulate the baby's breathing. While being given all the necessary care, the baby is lying calmly on the Concord table, the umbilical cord still connected to the placenta, so that the circulatory system and heart rate remain nice and stable.

Only when the natural physiological processes of the transition have got off to a good start, the cord is cut and the baby can lie beside the mother in an ingenious incubator that keeps it in an optimal state of health using the most advanced technologies.

In this dream, the neonatologist, as equilibrist, provides the best possible care within the narrow therapeutic margins, so the baby has every chance of a fully healthy future.

And now, back to reality, I want to conclude with a word of thanks.

A Word of Thanks

Reaching a milestone in your career is a fortunate combination of circumstances that is partly due to your own commitment, and partly to that of others. This is why I am grateful to many people around me for giving me help, support or space. I hope that I have expressed my gratitude before this, and frequently, so this doesn't come as a surprise. To all of you who know what I'm talking about, I say from the bottom of my heart: thank you!

Executive Board of Leiden University, Board of Directors of the LUMC, and Edmond Rings in particular, this appointment is a great honour.

Colleague Professor Enrico Lopriore, my capo, my respect for you has continued to grow over the years, and now I can also respect your unconventional way of leadership. *Gallina vecchia fa buon brodo*. Literal translation: you can make good broth from an old chicken. Figurative meaning: good quality can't hide itself.

Colleagues of the Neonatology department, the truth is simple: without you I would not be here. With this inaugural lecture I have a lot to celebrate, but simply having you as my colleagues is reason for a celebration in itself. Providing the best care for newborns is what binds us together, but caring for each other and giving each other all we can makes us as strong as a team. Working with you feels like a warm bath, as we say in Dutch.

Nursing team and doctor's assistants of Neonatology, there is no technology in the world that can replace your dedicated care and commitment. Physician Assistants, there is very little I do not entrust you with.

Romy Berkhout, research has become much easier since you started as a research nurse. Wendy Matthijssen, I can't afford it, but you are the perfect personal assistant.

I am grateful for the exceptionally fruitful collaboration with the Department of Obstetrics, Pediatric Cardiology, Ethics and Law, Technical Development and colleagues in neonatology at other hospitals.

The natural-born optimism of neonatologist Ronny Knol and obstetrician Frans Klumper, and the problem solving ability of technical engineer Alex Vernooij have been essential elements in getting to this point in our research in cord clamping.

Pediatric Cardiologist Arno Roest and Nico Blom, our collaboration was "crossing organs" and this has paid off. I am also convinced that this collaboration will lead to fewer consultations of Pediatric Cardiology in the NICU with the conclusion: "the problem is not cardiac"

Colleague-professor Steffen Pauws, a man of few words but a lot of data: everyone talks about 'big data', and so do we, but we do it with a clear research plan. I look forward to making it happen.

I have had many supervisors who taught me the tricks of the trade and who also gave me the trust and the freedom to develop into the researcher I am today. Jan Maarten Wit and Frans Walther, thanks for the opportunities and guidance you have offered. Colin Morley, Peter Davis and Stuart Hooper, for me the three wise men did not come from the East but from Down Under. The three of you are my great examples. Except Stuart, you are not: you are my greatest example.

Behind every successful professor are smart students and graduate students. To everyone I have supervised, whether clinically or scientifically, I hope that I managed to pass on what I appreciated so much from my own trainers and supervisors: an infectious enthusiasm and curiosity. Think about that the next time I tell you 'that you knock it off in an afternoon'.

My Father, Mother and Sister: you were the first to understand that I prefer make my own decisions about how to get from A to B, and to appreciate the detours. Meanwhile, others around me have understood that too. Thank you for giving me this freedom, and for your trust.

Leyla and Diba, it is impossible to express in words how wonderful it is to be your father. You are the best thing that has ever happened to me, except for your mother.

Sara, you call my laptop my silver princess, but it's you who are my true princess. That's an incredible thing for someone who is not a prince himself. But my love for you is of royal proportions.

I have spoken.

Reference list

1. Polglase GR, Miller SL, Barton SK, et al. Respiratory support for premature neonates in the delivery room: effects on cardiovascular function and the development of brain injury. Pediatr Res 2014;75:682-8.
2. Hooper SB, te Pas AB, Kitchen MJ. Respiratory transition in the newborn: a three-phase process. Arch Dis Child Fetal Neonatal Ed 2015;101(3):F266-71.
3. Hooper SB, Binder-Heschl C, Polglase GR, et al. The timing of umbilical cord clamping at birth: physiological considerations. Matern Health Neonatol Perinatol 2016;2:4.
4. Foglia EE, Te Pas AB. Effective ventilation: The most critical intervention for successful delivery room resuscitation. Semin Fetal Neonatal Med 2018;23:340-6.
5. Blencowe H, Cousens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health 2013;10 Suppl 1:S2.
6. Schilleman K, van der Pot CJ, Hooper SB, Lopriore E, Walther FJ, te Pas AB. Evaluating Manual Inflations and Breathing during Mask Ventilation in Preterm Infants at Birth. J Pediatr 2013;162(3):457-63.
7. O'donnell CP, Kamlin CO, Davis PG, Morley CJ. Crying and breathing by extremely preterm infants immediately after birth. J Pediatr 2010;156:846-7.
8. van Vonderen JJ, Hooper SB, Hummler HD, Lopriore E, te Pas AB. Effects of a sustained inflation in preterm infants at birth. J Pediatr 2014;165:903-8.
9. Huberts TJP, Foglia EE, Narayen IC, van Vonderen JJ, Hooper SB, Te Pas AB. The Breathing Effort of Very Preterm Infants at Birth. J Pediatr 2018;194:54-9.
10. Crawshaw JR, Kitchen MJ, Binder-Heschl C, et al. Laryngeal closure impedes non-invasive ventilation at birth. Arch Dis Child Fetal Neonatal Ed 2018;103:F112-F9.
11. van Vonderen JJ, Hooper SB, Krabbe VB, Siew ML, te Pas AB. Monitoring tidal volumes in preterm infants at birth: mask versus endotracheal ventilation. Arch Dis Child Fetal Neonatal Ed 2015;100:F43-F6.
12. van Vonderen JJ, Lista G, Cavigioli F, Hooper SB, te Pas AB. Effectivity of ventilation by measuring expired CO2 and RIP during stabilisation of preterm infants at birth. Arch Dis Child Fetal Neonatal Ed 2015;100:F514-8.
13. Martherus T, Oberthuer A, Dekker J, et al. Supporting breathing of preterm infants at birth: a narrative review. Arch Dis Child Fetal Neonatal Ed 2019;104:F102-F7.
14. Dekker J, Hooper SB, van Vonderen JJ, Witlox R, Lopriore E, Te Pas AB. Caffeine to improve breathing effort of preterm infants at birth: a randomized controlled trial. Pediatr Res 2017;82:290-6.
15. Dekker J, Martherus T, Cramer SJE, van Zanten HA, Hooper SB, Te Pas AB. Tactile Stimulation to Stimulate Spontaneous Breathing during Stabilization of Preterm Infants at Birth: A Retrospective Analysis. Front Pediatr 2017;5:61.
16. Dekker J, Hooper SB, Martherus T, Cramer SJE, van Geloven N, Te Pas AB. Repetitive versus standard tactile stimulation of preterm infants at birth - A randomized controlled trial. Resuscitation 2018;127:37-43.
17. van Vonderen JJ, Narayen NE, Walther FJ, et al. The administration of 100% oxygen and respiratory drive in very preterm infants at birth. PLoS ONE 2013;8:e76898.
18. Bhatt S, Alison BJ, Wallace EM, et al. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol 2013;591:2113-26.
19. Polglase GR, Dawson JA, Kluckow M, et al. Ventilation onset prior to umbilical cord clamping (physiological-based cord clamping) improves systemic and cerebral oxygenation in preterm lambs. PLoS One 2015;10:e0117504.
20. Knol R, Brouwer E, Vernooij ASN, et al. Clinical aspects of incorporating cord clamping into stabilisation of preterm infants. Arch Dis Child Fetal Neonatal Ed 2018;103:F493-F7.

21. Brouwer E, Knol R, Vernooij ASN, et al. Physiological-based cord clamping in preterm infants using a new purpose-built resuscitation table: a feasibility study. Arch Dis Child Fetal Neonatal Ed 2018.
22. Polglase GR, Blank DA, Barton SK, et al. Physiologically based cord clamping stabilises cardiac output and reduces cerebrovascular injury in asphyxiated near-term lambs. Arch Dis Child Fetal Neonatal Ed 2018;103:F530-F8.
23. Lefebvre C, Rakza T, Weslinck N, et al. Feasibility and safety of intact cord resuscitation in newborn infants with congenital diaphragmatic hernia (CDH). Resuscitation 2017;120:20-5.
24. Hooper SB, Te Pas AB, Polglase GR, Wyckoff M. Animal models in neonatal resuscitation research: What can they teach us? Semin Fetal Neonatal Med 2018;23:300-5.
25. Liggins GC. Premature delivery of foetal lambs infused with glucocorticoids. J Endocrinol 1969;45:515-23.
26. Enhorning G, Robertson B. Lung expansion in the premature rabbit fetus after tracheal deposition of surfactant. Pediatrics 1972;50:58-66.
27. Enhorning G, Grossman G, Robertson B. Effect of tracheal deposition of surfactant on air expansion of lungs--study on premature rabbit fetuses. Arch Dis Child 1973;48:162.
28. Hooper SB, Kitchen MJ, Siew ML, et al. Imaging lung aeration and lung liquid clearance at birth using phase contrast X-ray imaging. Clin Exp Pharmacol Physiol 2009;36:117-25.
29. Lang JA, Pearson JT, te Pas AB, et al. Ventilation/perfusion mismatch during lung aeration at birth. J Appl Physiol (1985). 2014;117(5):535-43
30. van Vonderen JJ, Roest AA, Siew ML, et al. Noninvasive measurements of hemodynamic transition directly after birth. Pediatr Res 2014;75:448-52.
31. van Vonderen JJ, van Zanten HA, Schilleman K, et al. Cardiorespiratory Monitoring during Neonatal Resuscitation for Direct Feedback and Audit. Front Pediatr 2016;4:38.
32. O'donnell CP, Kamlin CO, Davis PG, Morley CJ. Ethical and legal aspects of video recording neonatal resuscitation. Arch Dis Child Fetal Neonatal Ed 2008;93:F82-F4.
33. Jansen-van der Weide MC, Caldwell PH, Young B, et al. Clinical Trial Decisions in Difficult Circumstances: Parental Consent Under Time Pressure. Pediatrics 2015;136:e983-92.
34. Woolfall K, Frith L, Gamble C, et al. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. BMJ Open 2015;5:e008522.
35. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. Pediatrics 2012;129:480-4.
36. Wet medisch-wetenschappelijk onderzoek met mensen. https://wettenoverheidnl/BWBR0009408/2018-08-01 artikel 6.4.
37. Council of Europe. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Article 352014.
38. Federal Register. Waiver of Informed Consent Requirements in Certain Emergency Research. Rules and Regulations 1996;61.
39. National Health and Medical Research Council. National Statement on Ethical Conduct in Human Research. 2007.
40. Songstad NT, Roberts CT, Manley BJ, Owen LS, Davis PG, investigators Ht. Retrospective Consent in a Neonatal Randomized Controlled Trial. Pediatrics 2018;141.
41. Schilleman K, Witlox RS, Lopriore E, Morley CJ, Walther FJ, te Pas AB. Leak and obstruction with mask ventilation during simulated neonatal resuscitation. Arch Dis Child Fetal Neonatal Ed 2010;95:F398-F402.

42. van Vonderen JJ, Witlox RS, Kraaij S, te Pas AB. Two-minute training for improving neonatal bag and mask ventilation. PLoS One 2014;9:e109049.
43. Schilleman K, Siew ML, Lopriore E, Morley CJ, Walther FJ, te Pas AB. Auditing resuscitation of preterm infants at birth by recording video and physiological parameters. Resuscitation 2012;83(9):1135-9.
44. L. Root, H.A. van Zanten,, M.C. den Boer, E.E. Foglia, R.S.G.M. Witlox, A.B. te Pas. Improving guideline compliance and documentation through auditing neonatal resuscitation. submitted.
45. Poets CF, Roberts RS, Schmidt B, et al. Association Between Intermittent Hypoxemia or Bradycardia and Late Death or Disability in Extremely Preterm Infants. JAMA 2015;314:595-603.
46. van Zanten HA, Tan RN, van den Hoogen A, Lopriore E, te Pas AB. Compliance in oxygen saturation targeting in preterm infants: a systematic review. Eur J Pediatr 2015;174:1561-72.
47. Di Fiore JM, Poets CF, Gauda E, Martin RJ, MacFarlane P. Cardiorespiratory events in preterm infants: interventions and consequences. J Perinatol 2016;36:251-8.
48. van Zanten HA, Kuypers KL, Stenson BJ, Bachman TE, Pauws SC, te Pas AB. The effect of implementing an automated oxygen control on oxygen saturation in preterm infants. Arch Dis Child Fetal Neonatal Ed 2017;102(5):F395-F399
49. Martin RJ, Abu-Shaweesh JM, Baird TM. Apnoea of prematurity. Paediatr Respir Rev 2004;5 Suppl A:S377-82.
50. Cramer SJE, Dekker J, Dankelman J, Pauws SC, Hooper SB, Te Pas AB. Effect of Tactile Stimulation on Termination and Prevention of Apnea of Prematurity: A Systematic Review. Front Pediatr 2018;6:45.
51. Narayen IC, Blom NA, van Geloven N, et al. Accuracy of Pulse Oximetry Screening for Critical Congenital Heart Defects after Home Birth and Early Postnatal Discharge. J Pediatr 2018;197:29-35.

Prof.dr. A.B. te Pas

1987-1995	Medical school, University of Leiden
1996-2001	Paediatric Residency Training, Leiden University Medical Centre
2001-2004	Fellowship Neonatology, Leiden University Medical Centre
2004-2006	Consultant neonatologist, Leiden University Medical Centre
2007-2008	Research Fellow, Royal Women's Hospital in Melbourne, Australia
2008-present	Consultant neonatologist, Leiden University Medical Centre
2009	PhD, Leiden University, thesis: "Spontaneous breathing and respiratory support of preterm infants at birth."
2018-present	Professor in Paediatrics, in particular "the perinatal transition and neonatal resuscitation"

Arjan te Pas was born at home at a gestational age of 43 weeks in Spijkenisse in 1968. His birth was supervised by the general practitioner and his perinatal transition was uneventful. After becoming a paediatrician and neonatologist he performed research in spontaneous breathing and respiratory support of preterm infants at birth, for which he received a PhD degree. Next to his clinical work, te Pas has set up a research program "Perinatal transition and neonatal resuscitation". His aim is to expand the knowledge in (patho)physiological processes during perinatal transition and to develop the best strategies for neonatal resuscitation. He performs experimental studies, for which he closely collaborates with professor Stuart Hooper, physiologist at Monash University, Melbourne, Australia. The experimental findings are then translated to the clinic by performing clinical studies with physiological measurements in newborns at birth, which will then be used to inform protocols for large clinical trials.

Universiteit Leiden
The Netherlands