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Question report 22 maggio 2020 – Professor Te Pas

1 The small volume breaths during intra uterine life starts from which gestational age?

Fetal breathing movements can already be observed early in pregnancy (around 12th weeks of gestation) and is essential stimulus for lung growth and development. FBM occur episodically, with small volumes and low-pressure changes.

2 What is the exact nature (and use) of the (physiologic) interstitial positive pressure? What influences it and (how) does it vary?

To establish pulmonary gas-exchange the lungs need to be cleared from lung liquid and aerated. At birth the transpulmonary pressure difference, generated by breathing effort, is responsible for clearance of lung liquid and lung aeration. By generating a pressure that is high enough and duration long enough to overcome the high resistance of liquid in the airways, liquid will be moved distally towards the end-distal airways (sacculi/alveoli, depending which gestational age), through the epithelium into the interstitial tissue. As it will take time for lymphatics and blood vessels to clear the liquid in the interstitial space (4-6 hours), the presence of the liquid will lead to a positive pressure. The level of pressure depends on how much liquid needs to be cleared (e.g. more lung liquid after elective caesarean). Due to the presence of positive pressure liquid has the tendency to return into the airways during expiration, which will compromise FRC and gas-exchange. The positive pressure in the interstitial tissue can also prevent dilation of the pulmonary capillaries situated in the interstitial space and cause PPHN.

A good example is TTN after elective caesarean section could evolve into RDS and PPHN: the return of lung liquid due to a high interstitial pressure is causing the symptoms of TTN. The back and forward movement of liquid through the epithelium could induce injury and RDS can develop. The pressure on the capillaries then could lead to PPHN.

It is not all bad news about the positive interstitial pressure, it triggers the j-receptor (juxta-capillary receptors), which are pressure sensitive, causing a direct neural reflex, leading to an increase in the heart rate and decrease in pulmonary vascular resistance.

3 What happens to the transitioning pulmonary blood flow when high level of mean airway pressure is applied at birth as during sustained lung inflation?

That depends when a sustained inflation is given and whether the lung was already aerated. In the phase that the airways are still liquid-filled, a higher pressure or longer duration is needed to overcome the resistance.

Experimental studies demonstrated that, in contrast to what is assumed, a sustained inflation gives a larger and faster increase in pulmonary blood flow as compared to tidal ventilation. This is due to the fact that the sustained inflation led to a better clearance of

liquid and aeration. In other words, aeration of the lung is the master switch for increase in pulmonary blood flow.

However, once the lung has been fully aerated, lung characteristics obviously have changed and a high mean airway pressure could then compromise pulmonary blood flow.

4 During resuscitation of nasphyxiated Newborn with an intact umbilical cord, when would be the best time to clamp and cut

Waiting with cord clamping prevent the rebound hypertension, that gives extravasation into the brain and more injury. Experimental studies have demonstrated that rebound hypertension, that occurs after return of cardiac output, can be prevented when the cord is still attached. The placenta has a low vascular resistance and works as a “release valve”.

Clinical studies have to be performed to confirm that physiological based cord clamping lead to less injury. However, it is important to understand that this clamping should not be based on time and can vary between infants.

5 Should we begin resuscitation before clamping the umbilical cord? For how long, before taking to the resuscitation place?

Resuscitation should never be delayed and when you wish to practice time-based delayed cord clamping or physiological based cord clamping, resuscitation should take place close to the mother. This has shown to be feasible.

Waiting with cord clamping in an apneic/insufficiently breathing preterm infant, where the lungs have not been aerated, means you are only postponing the sudden loss of venous return from the placenta, with all consequences. Lung aeration, and thus increase in pulmonary circulation, is important for the cardiac output to be less dependent from the venous return from the placenta.

Resuscitation In asphyxiated term infant should never be delayed.

6 could the umbelical cord clamp in preterm infants with no respiratory activity cause not only transitional bradycardia but more severe events, and how to overcome them if resuscitation is necessary

The transitional bradycardia is a symptom of a bigger problem, the sudden loss in cardiac output.

Below the results of clamping **before** ventilation versus clamping **after** ventilation in a preterm lamb model. Due to sudden loss in venous return, cardiac output decreases, leading to a decrease in heart rate. The effect of cord clamping and decrease in cardiac output can be noted in the carotid arterial pressure and flow. There is first an increase in

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peripheral resistance due to clamping, leading to an increase in pressure and flow in carotid, then a decrease due to the loss in venous return. These effects can be mitigated by first ventilating and aerate the lungs, the cardiac output is more dependent on the pulmonary venous return than placental venous return (figure 2). In figure 3 the effect on oxygenation and cerebral blood flow.

The preterm brain is highly susceptible for the swings in blood flow and pressure.

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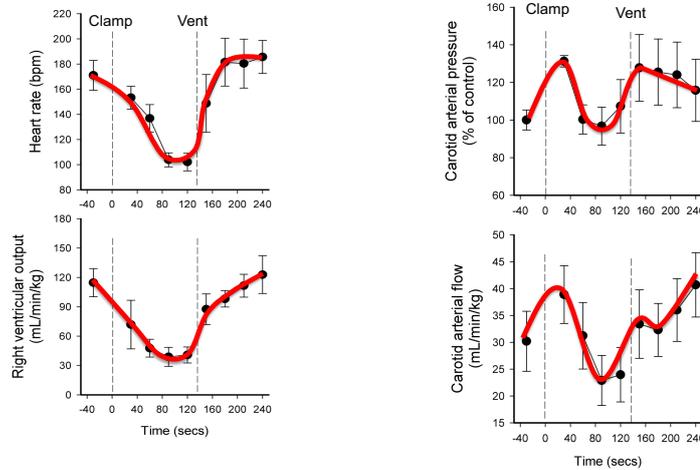
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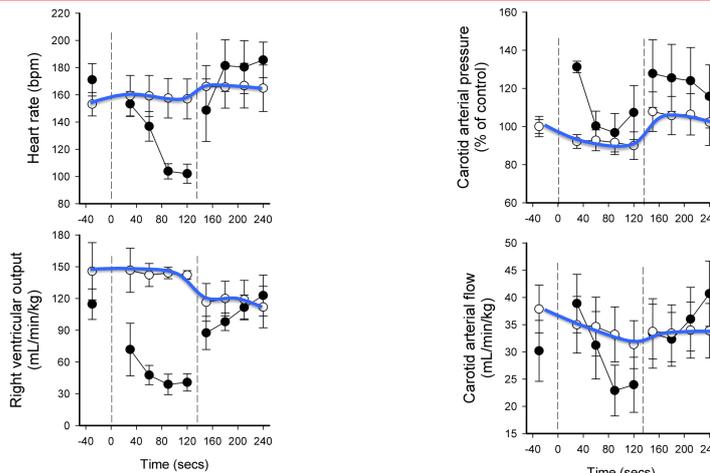
Cord clamping followed by ventilation



Bhatt et al. J Physiol feb 2013



Ventilation before cord clamping



Bhatt et al J Physiol feb 2013

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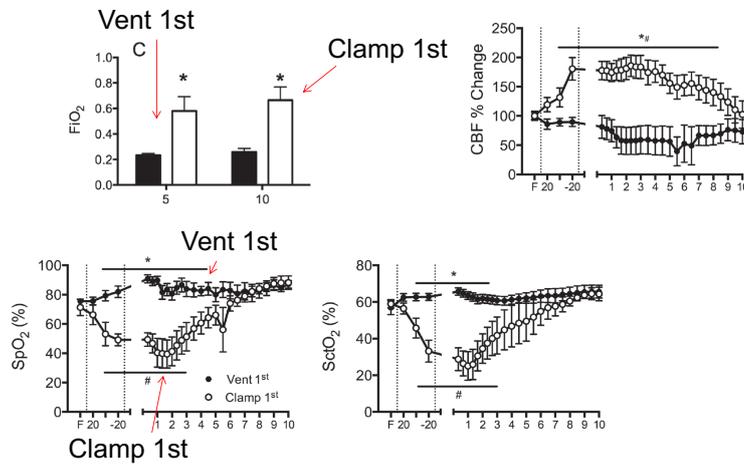
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Plos One 2015

7 According to what it has been showed about cardio-vascular transition and LVO, in your centre have you started using neonatal rianimation with intact placental circulation?

I think you are asking 2 questions, for the first part I refer you to my reply above. The physiological based cord clamping is based on scientific evidence provided in animal models. In our centre we started PBCC in research setting. We have demonstrated that it is feasible, safe and that resuscitation is at least as good as the standard approach. We currently perform a large multicentre RCT to investigate the efficacy of PBCC in preterm infant, with intact survival as outcome.

8 With that in mind what would be your suggestion for the fio2 in DR

It seems that we have been so much focusing on the starting level of FiO2, while the main focus should be good oxygenation and avoid hypoxia/hyperoxia. I think the answer lies in careful titration of FiO2, not in the starting level of FiO2 per se.

Nevertheless: studies have shown that hypoxia in the first 5 minutes is associated with IVH and death. Hypoxia occurred more often in the low oxygen group then in the high oxygen group. We demonstrated (in animals and human preterms) that starting with a high level of oxygen (and careful titration!) led to more breathing effort, without inducing more hyperoxia.

I cannot tell you which level you should use, but my recommendation would be to avoid hypoxia as much as we try to avoid hyperoxia

9 Does high flow help at transition

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If it generates a pressure that is high enough for lung liquid clearance and maintain FRC, then yes this would help. Unfortunately, the pressure generated by current high flow (max 8 L/min) is likely to be too low, especially for phase 1: lung liquid clearance.

12 How can oxygen come into the baby if the larynx is closed?

Yes, it almost sounds like a catch 22. Luckily, most preterm infants are helping us and breathe at birth, but this can be subtle and insufficient. When they take a breath, oxygen will enter, improving oxygenation and breathing effort increases.

When they do not breathe and the larynx is closed, it will be very difficult to aerate the lungs. The hypoxia will worsen at a level that the larynx will relax and open, then it is possible to aerate the lungs. This is obviously not a healthy start, so we must find better ways to stimulate and support breathing effort. Another option is of course bypassing the larynx and intubate, but we try to avoid this.

13 Methods to facilitate glottic opening other than stimulation

At this moment I do not know methods to open the larynx than stimulate breathing, but I am open for suggestions. We investigated 3 different ways to stimulate breathing at birth: tactile stimulation, caffeine and oxygen. All three seem to have an effect and increase breathing effort, but the response to tactile stimulation and caffeine is dependent on the oxygenation level. Oxygenation seems to be the most important factor.

Caffeine is an adenosine antagonist, the more hypoxia there is, the higher the adenosine level. It is possible that different dosages are needed than we currently investigated (caffeine base 10 mg/kg).

14 Un porcentaje de distres por pulmón húmedo ocurre en RN a termino nacidos por parto vaginal, por que cree usted que ocurre esto?

I used google translate, so forgive me if I misunderstood.

I can only speculate why some babies born vaginally have “wet lung”. I suspect that this has a different etiology and that transient respiratory distress after vaginal delivery is due to decreased respiratory effort as a consequence of hypoxic ischemic events during labour. This could lead to generating inadequate pressures to clear lung liquid and also to maintain lung aeration. We diagnose this as “wet lung”, but perhaps is misnomer.

15 In the last decades we progressed a lot in understanding the physiology of transition, however the optimal way to aerate the lung still need to be determined. What is in your opinion the optimal approach to individualise lung aeration at birth?

Focus on stimulation and support of spontaneous breathing. Find the optimal way to stimulate (oxygenation plays a major part in this) and optimal CPAP level strategy (taking the different phase of lung adaptation in mind) higher pressure initially for lung liquid clearance and aeration and titrating down to a lower pressure to maintain lung volume)

More research is needed, e.g surfactant can also play a role in lung aeration at birth.

16 Thank you very much. Please, what is your opinion about "milking" of cord blood for preterm newborns?

I would advise against it. Large swings in blood pressure has been demonstrated in a preterm lamb model and can be detrimental for the brain. This is now confirmed in a trial in human preterm infants and the trial was stopped due to a high number of IVH in the milking group. (near)term infants are less susceptible for these swing in blood pressure and cord milking could be performed without detrimental effects.

17 Do you have any data about how many seconds could we wait before clamp the cord? Is it different in the different gestational age?

There is no fixed time and clamping should be based when the infant is stabilized (breathing or ventilated, with good heart rate and oxygen sat while FiO₂ can be decreased, which indicates that probably lungs are aerated and pulmonary blood flow has increased). So not the clock is defining it, the baby does.

18 What about Fi O₂ in ventilating prematures < 26 w. They say using 21-30%. Should we use 21 according to have more luck relaxing vocal cords?

See question 8

It seems that we have been so much focusing on the starting level of FiO₂, while the main focus should be good oxygenation and avoid hypoxia/hyperoxia. I think the answer lies in careful titration of FiO₂, not in the starting level of FiO₂ per se.

Nevertheless: studies have shown that hypoxia in the first 5 minutes is associated with IVH and death. Hypoxia occurred more often in the low oxygen group than in the high oxygen group. We demonstrated (in animals and human preterms) that starting with a high level of oxygen (and careful titration!) led to more breathing effort, without inducing more hyperoxia.

I cannot tell you which level you should use, but my recommendation would be to avoid hypoxia as much as we try to avoid hyperoxia

19 Delayed cord clamping should be a routine paramount. What about the physiological meaning of milking? Thanx

That is simple: milking is not physiological

20 Closed larynx when does it open.. What is the ideal time to start CPAP if required

I explained the transition of the larynx above. The larynx is open when the infant takes a breath, when infants are stable and regular breathing the larynx will be open most of the time.

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21 Could the administration of furosemide in TTN promote the absorption of Na from pneumocytes?

Furosemide has no effect on the duration and severity of TTN symptoms (Cochrane review 2015)

I guess furosemide has a role when there is excess of extravascular water in the interstitial space due to a volume overload in the circulation. The mechanism in TTN is not caused by volume overload.

22 How often does TTN lead to RDS?

That can vary between studies, but approximately 1 in 10 infants with TTN develop RDS. This is probably underestimated/underreported as they are still considered as separate entities. 1) prolonged TTN is diagnosed, but this could be RDS, 2) near term infants develop respiratory problems and is diagnosed RDS due to immaturity, but this could be due to TTN.

23 Based on all of this do you recommend mask ventilation or mask CPAP before the clamping of the umbilicus?

Depends if the baby is breathing or apneic. Breathing effort is frequently missed as it can be very subtle and/or difficult to observe as babies are immediately wrapped. A respiratory function monitor can help in recognizing breathing effort.

When a baby is breathing, but insufficient, supporting this by CPAP would be the best approach. We still need to find the optimal level of CPAP.

When a baby is apneic, mask ventilation is still the best approach, as long as you are aware that the larynx might be closed and you are not ventilating the lungs. It is not a new thing that mask ventilation is failing and you need to intubate and the infant restores quickly. This could be that you bypassed the larynx.

24 What is your opinion about the administration of corticosteroids before program caesarean to prevent respiratory distress?

This has been shown to decrease the respiratory problems in infants, but still around 7% develop TTN

25 Should we use a differentiated normal range of blood pressure in for example the first 24 hours of life for preterm infants or how does the normal blood pressure develop?

When infants go through transition without problems, the right and left ventricular output increases in the first ten minutes of life. This will influence the blood pressure measured, as will the increase in vascular resistance after cord clamping.

Using gestational age as a lower threshold for blood pressure is commonly used, but unfortunately nature is more complicated than a fixed number that is similar to the

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gestational age. Blood pressure does not appear the best parameter to evaluate the perfusion of organs. Several experts in the field have and are investigating this, but no one knows what range blood pressure we should consider to be normal. It is better to combine blood pressure with other parameters to evaluate the infant hemodynamically and then decide whether a blood pressure is acceptable or not.

26 delayed cord clamping in the premature: for how long?

Please see my previous replies

27 What about Delayed Cord Clamp for COVID-19 Mother?

Covid + pregnant mother is not a contra-indication for PBCC or DCC

28 Do diuretics have a role for reducing interstitial pressure? Thank you!

Furosemide has no effect on the duration and severity of TTN symptoms (Cochrane review 2015)

I guess furosemide has a role when there is excess of extravascular water in the interstitial space due to a volume overload in the circulation. The mechanism in TTN is not caused by volume overload.

29 Dr Omesh Khurana : Any special precautions to be taken during LSCS to prevent transient tachypnoea of NB

We are currently looking into this. There is a trial ongoing to investigate whether inducing uterine contractions by giving oxytocin before CS would reduce the incidence of TTN.

30 how can you realize if you are ventilating against a close or open larynx?

Closely observing whether you see chest excursion. This can be difficult to observe and a respiratory function monitor would help you. Alternatively using a colorimetric CO2 detector could differentiate whether you are ventilating the pharynx or the lungs.

31 Please clarify better what happens ventilating a newborn with closed glottis

See my replies above, hope that will clarify things better

32 Are there pharmacological interventions to sustain larynx overture time? (of course we also want it to close to help with auto-peep)

Not sure what overture means, but caffeine stimulates breathing effort, which will lead to an increase in percentage of an open larynx.

33 SHOULD WE DELAY CORD CLAMPING IN TERM BABIES

Yes, we should and it is also recommended in international guidelines.

Healthy term infants have aerated their lungs very fast after birth and there is less concern in creating a temporary loss in cardiac output, but in case uterine contractions have

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occurred before birth, they will benefit from a restoration of placental blood returning to the infant ("placental transfusion") when we wait with clamping until 3 minutes after birth.

34 How could we understand that the lung is well ventilated to close the clamp?

I agree, that it is difficult to say when exactly the lungs are aerated, we can only use indirect parameters for this. Based on experimental data and observational studies we came to the following definition: when the infant is regular breathing or well ventilated, heart rate is above 100 and can reduce the oxygen < 40% while SpO2 is in the normal range, then probably lung aeration has occurred well enough and the cord can be clamped.

35 Should perhaps LMA be used at all times rather than a mask to cover the oesophagus and have more success ventilating "closer" to the vocal chords?

I am not completely sure if I understand this correctly, why would an LMA overcome the vocal cords issue because an LMA is closer to the cords?

36 what about milking of the cord?

Please see my replies above.

37 We know that the cord milking is contraindicated in anemic asphyxiated babies, in which cases is the cord milking safety?

Please see my replies above

In very preterm infants cord milking is not safe, it increased the chance for developing IVH.

38 How do you oxytate the newborn that is with closed larinx?

Please, see my replies above.

39 Do you know any method to facilitate the opening of the glottis? any drug? Thank you

Please, see my replies above.

40 Baby last night 34/40 dips in HR and o2 88 to 91 % coordination with baby moaning ?cause cxr rds steroids x 1 pre delivery cpap 6cm 23 to 26 % O2 sats

I am not sure if there is a question you would like to ask me?

41 which is the best management for preterm neonate? Sometimes some preterm need intubation only for a closed glottis and once the tube has been inserted

Yes, we would like to avoid intubation if possible, please see my replies above on this matter.

42 in a resuscitated baby how soon you would evaluate hemodynamic using ecography.

That depends whether there is an indication, only if there are problems with PPHN, perfusion, blood pressure?

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43 What else can we do to prevent neonatal hypotension in elbw?

I am not sure if this question is within the scope of the subject of my presentation. If you referring to intervention in the delivery room is PBCC a good option to prevent sudden loss in cardiac output. Of course, when perinatal blood loss is expected, we should transfuse.

44 what do you think about incremental PEEP in delivery room to aereate the lung slowly and homogeneously?

This could be an option, but you have to be aware that there are different phases in pulmonary transition. Taking these phases into account it would be logical to start with a higher CPAP/PEEP level and then titrate downwards, instead making incremental steps

45 What about the umbilical cord milking in preterm infants?

Please, see my replies above

46 In the picture of lokal Ventilation and afterwards Perfusion of the hole Lung, I ask myself if the Euler-Liljestrand-Mechanism is not yet activated? or which mechanism is more present?

Interesting point you raise, but I am not sure how I can fit this in. This mechanism would protect us from ventilation/perfusion mismatch.

The increase in pulmonary blood flow is directly linked to ventilation of the lung, independent which gas you use. The increase in pulmonary blood flow increases also when we ventilate with N₂ instead of O₂. If an inactivated E-L mechanism would play a part, then we would not get increase in pulmonary blood flow anywhere.

When a vagotomy is performed, no significant increase in pulmonary blood flow occurs. This means that it must be a neural reflex, probably by triggering the juxta-capillary receptor due to increase in interstitial pressure created with lung liquid clearance.

47 Can you comment on how much lung fluid "reabsorption" happens before term birth ?

This varies between infant and also depends from timing and mode of delivery. It is important to realize that the lung volume of a liquid filled lung before birth is much greater than the volume of an aerated lung after birth. At birth, still a large part of lung liquid is present and needs to be cleared, this is much higher after elective CS when compared to delivery after labour.

48 how long one should continue to do tactile stimulation?, in home delivery by midwife, it is normal to do prolonged tactile stimulation without much harm

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As soon as the infant is well oxygenated and regular breathing, tactile stimulation has no extra benefit. I don't think that tactile stimulation is harmful, as long as it is performed in a gentle way.

49 t-piece e diving reflex anche nei piccolissimi?

I used google translate, so forgive me if I misunderstood the question. The diving reflex is part of the trigeminocardiac reflex (TCR). There are several ways to induce a TCR, pressure on the area around nose and mouth (by placing a mask), but also a sudden increase in air flow in the face or nasopharynx. There is probably a hierarchy and more research is needed which is causing TCR the most and how this can be prevented.

There is an inverse relationship between the occurrence of TCR after placing a mask and gestational age.

50 Preterm infants requiring resuscitation manouvers were recruited to the SAIL trial. Is there a possible relation between the outcome of the trial and the possible closed position of the larnyx due to hypoxia?

We do not know what caused the early mortality in the SAIL study, exploration of the data did not reveal any signal. There was no difference in the occurrence in hypoxia between groups.

While we translated the experimental findings of the beneficial effect of SI to the clinical situation, we overlooked the problem with the larynx. The animals in the studies were intubated and the infants in the SAIL study were mask ventilated.

51 Are there any evidence on umbelical cord milking when clamping can't be retarded?

That depends for which benefit you are looking for. When it comes to placental "transfusion", milking can have similar effect as DCC. You then have to make sure you perform a milking procedure where blood does not return to the umbilical vein after the milking, or else there will be netto effect.

Milking is not physiological, we do not know what we infuse in the infant next to blood volume, e.g cellular debris. In addition, animal experiments demonstrated that there is great hemodynamic disturbance, which is likely the cause for the large number of IVH observed in trial where milking was compared with clamping in very preterm infants.