Improving ventilation performance at birth

Breathing is not a problem for most newborns, but the others deserve the best possible assistance.

More than 130 million babies are born each year. Just as fantastic as it is to see a baby draw its first breath and start life, just as dramatic it can be when that does not happen as expected. One in ten newborns needs some sort of support to start breathing, ranging from gentle clearing of airways to more extensive resuscitation procedures and about 3 to 6 % require manual ventilation of the lungs. Preterm babies – babies born prior to 37 completed weeks of gestation – are even more susceptible to breathing problems due to fragile and underdeveloped lungs.

The initiation of breathing at birth is a dynamic process that involves clearing the airways and lungs of fluid and filling the lungs with air. When the newborn does not initiate breathing or does not breathe adequately, care providers assist ventilation to stabilize the newborn's cardiorespiratory status. Advances in management of newborn infants requiring delivery room resuscitation have been made over the past decades, however, approximately 700 000 yearly deaths result from this global problem (Pearlman et al, 2012). There is thus room for improvement and procedures for adequate manual ventilation and efficient resuscitation have been identified as major opportunities for continued development in the clinical care of newborns.

Walking a fine line blind-folded

Even with a less fatal outcome, it is non debatable that underventilation leading to hypoxia, is harmful. It may lead to prolonged trauma, the need for intubation, chest compressions and increased morbidity. On the other hand, there is also clear evidence that excessive air volumes can be just as harmful. Large tidal volumes delivered to the newborn baby can cause extensive and sometimes irreversible damage to both lungs and brain. There is thus a fine line between underventilation and overventilation leading to volutrauma.

Despite being one of the most important interventions taking place in the delivery room, ventilation support is one of the least controlled. The tidal volumes given during resuscitation are rarely monitored and it is up to the care giver to estimate the volumes given trusting his or her clinical experience. Often the resuscitator is instead guided by the air pressure used. Subsequently, if the baby is admitted to the neonatal intensive care unit, the tidal volumes given are, however, very carefully measured, monitored and adjusted.

> *10 % of newborns need support to establish regular breathing – preterm babies being more vulnerable than term babies. Overventilation can be just as harmful as underventilation and efficient resuscitation procedures have been identified as a major opportunity for improvement in the clinical care of newborns.*

How resuscitation of newborns is performed

The situation where a newborn baby, and even more so a particularly fragile preterm baby, needs to be resuscitated is a very stressful event. Skilful clinical assessment is imperative and decisions have to be made quickly. The cornerstone of respiratory support at birth is positive pressure ventilation (PPV) which is commonly used in the delivery room. PPV is given via a face mask with a self-inflating bag, a flow-inflating bag or a T-piece device. The self-inflating and the a flow-inflating bags, squeezed to generate an air flow, are made of silicone rubber and are equipped with a pressure limiting valve. Using a T-piece device connected to an external air flow, the Peak Inflation Pressure (PIP) and Positive End Expiratory Pressure (PEEP) can be set at a fixed value. With all three devices the rate of ventilation and the volume of air given is entirely controlled by the care giver, and when using the two bag types so is the PIP.

The purpose of ventilation with all three devices is delivering an appropriate tidal volume (V_T) as well as establishing a functional residual capacity to prevent the alveoli from collapsing both of which will enable an effective gas exchange as well as improving pulmonary circulation in the transition to extrauterine life. The success of the assisted ventilation is judged by assessing chest movement, heart rate and skin colour.

In contrast to resuscitation of adults, where cardiac compressions and an automated external defibrillator (AED) has a primary role, the primary focus for newborn resuscitation is establishing regular breathing. Once accomplished, an increase in heart rate usually follows. According to both the Neonatal Resuscitation Algorithm (American Heart Association, 2015) (Bancalari, 2019) and European Resuscitation Council Guidelines for Resuscitation (CoSTR, 2015) (Wyllie et al. 2015). PPV should be initiated within 60 seconds after birth if the baby is not breathing spontanoeusly.

> *The top priority in resuscitation of newborns is to establish regular breathing. According to both American and European guidelines PPV should be initiated within 60 seconds after birth if the baby is not breathing spontaneously. The goal in PPV is delivering an appropriate V_T and establishing a functional residual capacity.*

Why peak inflation pressure is not a good proxy for tidal volume

The standard technique for assisting ventilation with positive pressure is regulating breath size through the amount of pressure applied to the device used. One approach is applying a low pressure to start with, and then increasing it until an increase in heart rate is achieved or there is a visible rise of the chest. It has, however, been found very difficult to estimate V_T judging from the pressure applied and this has several reasons.

First of all the neonatal lung requires different air pressures at different stages during the pulmonary transition occurring at birth. The neonatal lung goes through three distinct phases. At birth the lungs are filled with fluid. Breathing support during this phase should focus on clearing the lungs from fluid to enable gas exchange. Several mechanisms are thought to be involved in clearing the lung from fluid, one and possibly the most forceful one, being the inflation-driven increase in pressure across the airway wall. This creates a hydrostatic pressure gradient that drives the lung fluid from the airways into the surrounding tissue (Hopper et al, 2015).

Once the lung fluid is cleared and replaced with air, gas exchange can take place. As the fluid moves from the airways faster than it is cleared form the surrounding tissue, the pressure from the tissue increases at that stage and the alveoli therefore have tendency to collapse. This also depends on how much surfactant, ie a lipoprotein film lowering the alveolar surface tension, is present which in turn depends on the structural maturity of the infant's lungs. To avoid collapsing of alveoli and re-entry of fluid to the lungs, it is important that a positive end expiratory pressure (PEEP) is maintained to establish a functional residual capacity. Once the lungs are cleared of liquid and are aerated the focus for ventilation should be gas exchange and metabolic homeostasis including carbon dioxide control (Foglia et al, 2018).

To be able to adjust PPV according to stage of pulmonary transition, the resuscitator needs to pay close attention to the compliance changes of the lung. This is however, easier said than done because these changes are not easily detected.

Clinical professionals with different levels of experience of neonatal resuscitation participated in a study using a computerized lung model programmed to display compliance changes similar to those presented by a neonate undergoing pulmonary transition. They were asked to maintain constant tidal volumes rather than inflation pressures when ventilating the model using either of three different devices: self-inflating bag, flow-inflating bag and T-piece resuscitator. Gas flow rates were set at 10 L/min for the flow-inflating bag or T-piece resuscitator.

When only pressure was displayed, it was found that only relatively large changes in compliance could be detected by the average clinician, but not very well and only when using the self-inflating bag. The mean volume delivered was lower than the minimum of the acceptable range during low compliance and by far exceeded the maximal limit during high compliance when the clinicians were presented only with pressure. Individual volumes varied between 1 mL/kg and 16 mL/kg.

On the other hand, when the subjects could instead see the volumes they were giving they were able to change the pressures in the right direction with all three devices tested. The authors conclude that resuscitators can be far more responsive to compliance changes if they are able to view volume rather than only pressure when delivering PPV to changing neonatal lungs (Kattwinkel et al, 2009).

Another factor that has been shown very difficult to control is face mask leak that can be substantial and highly variable. In a study on resuscitation of preterm infants born prior to 32 weeks, mask leak varied from almost 0 to 100 %, both between inflations and between resuscitators. Moreover, the resuscitators were unable to accurately estimate face mask leak with underestimation being the far most common mistake (Schmölzer et al, 2010).

As a consequence of not knowing the proportion of air leaking out of the mask, it is very difficult to correctly estimate the V_T delivered. In the mentioned study, the resuscitators were unable to assess their delivered V_T. Moreover, the peak inflation pressure (PIP) had little relationship with the resulting V_T. When PIP was set at 30 cm H_2O using a t-piece resuscitator, V_T varied between 0 to 31 mL/kg (Schmölzer et al, 2010). In a study on manikin it was shown that even if the resuscitator was presented with information on PIP the V_T delivered were highly variable. In addition, a target PIP was possible to achieve despite large mask leaks. The authors of the study therefore conclude that airway pressure is a poor proxy for volume delivered during PPV via a mask (O'Donell et al, 2005).

> *PIP is not a good proxy for V_T. Firstly, the resistance of the lungs vary during pulmonary transition at birth and different pressures need to be applied at different times to achieve an appropriate V_T. The compliance changes of the lungs are very difficult to detect and V_T is easily under- or overestimated. Secondly, face mask leak is very difficult to estimate and greatly affects the V_T delivered irrespective of PIP. Thirdly, even if PIP is presented to the resuscitator the V_T delivered are highly variable.*

Targets of key respiratory parameters are not well defined

The critical target values of key respiratory parameters in PPV of neonates, such as pressure and volume, are not well defined. They obviously also largely depend on the phase of pulmonary transition and the changing resistance of the lung. The pressure needed to clear the lungs of liquid, is likely far too high if applied at a later stage to achieve an appropriate V_T (Foglia et al, 2018).

In term newborns tidal volumes during spontaneous breathing have been measured as ranging from 6 to 8 mL/kg and in preterm neonates with respiratory distress syndrome from 4 to 6 mL/kg (Kattwinkel et al, 2009). For neonates receiving mechanical ventilation in the NICU it is recommended to maintain a V_T from 4 to 8 mL/kg, at a rate of 40 to 60 breaths per minute (WHO, 2016).

However, the optimal tidal volumes, inflation times, and rates required to establish a functional residual capacity and to achieve normal extrauterine oxygen saturation and carbon dioxide control after birth are not known. What is known though, is that during spontaneous breathing by an infant on Continuous Positive Airway Pressure (CPAP) the resulting tidal volumes are lower with less breath-to-breath variation than tidal volumes delivered during PPV inflations (Kaufman et al, 2013).

> *During spontaneous breathing V_T are lower and less variable than during PPV. The optimal V_T during manual ventilation at birth is unknown, but is usually targeted at 4–8 mL/kg. This is in the range of tidal volumes of breathing infants and is below levels exceeding total lung capacity. (Schmölzer et al, 2008)*

High tidal volumes can cause persisting lung and brain damage

The link between ventilator-induced lung injury (VILI) and high V_T is well established and it is clear that overdistension of the lung wall starts a cascade of inflammatory events. Animal studies have shown that manual ventilation apart from causing a local inflammatory response in the lung also can cause a systemic inflammatory reaction leading to multiple organ damage including cerebral white matter inflammation and injury. Such an acute systemic inflammatory reaction as evidenced by circulating pro-inflammatory cytokines has been shown in several studies to occur also in term and late preterm babies 2 hours after ventilation (Barton et al, 2015).

In preterm lambs it has been shown that it doesn’t take more than a few breaths with large tidal volumes during manual ventilation to cause an inflammatory response and bronchopulmonary dysplasia (Björklund et al. 1997). These injuries may persist and lead to reduced lung capacity throughout life. On the other hand an inflammatory response can be initiated also by inadequate ventilation if a PEEP is not maintained. This happens when the alveoli in the absence of a functional residual capacity will repeatedly collapse and reopen which subjects them to high shear forces releasing cytokines and activating accumulating leucocytes (Schmölzer et al, 2008).

Children born preterm have higher rates of learning difficulties, sensory deficits and cerebral palsy than other children. Such difficulties may be caused by the above mentioned localized cerebral inflammation originating from the inflammatory response in the lung. Microglia are activated and free radicals are produced as a result of the inflammatory cascade causing brain damage. Moreover, the integrity of the blood-brain barrier is reduced. However, there is yet another link between manual ventilation and brain damage. Over-distension of the lung compresses the alveolar capillaries leading to a fluctuating lung blood flow. This instability in lung blood flow alters pulmonary venous return and cardiac output which in turn leads to large fluctuations in cerebral blood flow risking to damage the fragile immature brain. Term babies have mechanisms to compensate for changes in cardiac output and can thereby protect cerebral bloodflow. This is less developed in preterm babies making their brains more vulnerable to intraventricular haemorrhage (IVH) which is a major neurological complication of prematurity (Barton et al, 2015). Moderate to severe IVH is associated with neurological negative consequences. 50 to 75 % or preterm survivors develop cerebral palsy, mental retardation and/or hydrocephalus, and 25 % develop psychiatric disorders and problems with executive functions (Ballabh 2014).

Brain damage caused by high V_T has been shown not only in animal studies. In an observational study on preterm babies receiving manual ventilation the impact of high V_T were examined. The babies were ventilated with either V_T < 5.8 mL/kg or V_T > 5.8 mL/kg. In the high V_T group 51 % of the babies were diagnosed with IVH as compared to 13 % in the low V_T group. Considering the high risk of persistent problems associated with IVH, the authors stress the need for techniques to reduce the incidence of brain injury in preterm babies. More specifically, they state that strategies to limit delivery of high V_T during mask ventilation are needed (Mian et al, 2018).

> *Both over- and underventilation can lead to persistent lung and brain damage. Overextension of the lung wall elicits an inflammatory response, as do the high shear forces on repeatedly collapsing and reopening alveoli in the absence of a functional residual capacity. The local inflammatory reaction may progress into a systemic inflammatory cascade with multiple organdamage as a result, including cerebral white matter inflammation and injury. Overventilation may also lead to pulmonary haemodynamic instability which in turn leads to large fluctuations in cerebral blood flow increasing the risk for IVH.*

Knowing what is important but lacking necessary data

It is clear that both under- and overventilation is harmful to neonates, born both term and preterm. Even though all professionals experienced in resuscitation of newborns, probably are well aware of barotrauma, the full width of volutrauma and the problems it can cause may not be quite as well-known. However, no matter how well-understood the risks of volutrauma is, it still is not easy to fully avoid harmful V_T since PPV in most delivery rooms is performed with very little objective data available. PPV is usually performed with PIP at a set value chosen with the assumption that it will deliver an appropriate V_T. Trying to hit the appropriate V_T guided only by pressure is however, very difficult due to reasons mentioned earlier. Another parameter easily leading to accidental overventilation is the small difference in volume between functional residual capacity and total lung capacity in preterm infants.

With feedback from a respiratory function monitor displaying pressure, expired V_T and face mask leak data during PPV several studies have shown substantial improvement in quality of resuscitation with minimized face mask leak and more correct V_T given (Kattwinkel et al, 2009, 2012).

In a manikin study healthcare professionals attending a newborn resuscitation course were randomized to have a respiratory function monitor visible or masked. Before training, face mask leak in the two groups were 63 % and 51 % respectively. After training face mask leak in the group receiving feedback from the respiratory function monitor decreased to 23 % compared to 35 % in the group that did not have any feedback. The former group also had less variation in V_T given (O'Currain et al, 2018).

In another manikin study the objective was to see if feedback from a respiratory function monitor during training could help health care providers avoid excessive PIP and V_T, and how long after training a possible effect persisted (Kelm et al, 2012). Before training the median V_T was

6.7 mL and directly after significantly lower: 3.5 mL. One month after training the median V_T was 4.1 mL. The majority of participants reduced the V_T given after training. Also PIP was significantly reduced directly after training and remained so after one month. The authors conclude that the effect of training seems to wear off with time and that trainees seem to fall back into their previous behavior. They state that their results strongly support the use of monitoring equipment displaying both pressure and volume during neonatal resuscitation in the real-life scenario to ensure sustained ventilation performance.

The authors of yet another manikin study with the objective to compare two different devices, a flow-inflating bag and a T-piece resuscitator, emphasize the need for information on volume rather than pressure since there was large variation in volume despite generating very similar airway pressures regardless of device used (O'Donell et al, 2005).

> *In most delivery rooms PPV is performed with very little objective data available. There is growing evidence that ventilation performance could be substantially improved if resuscitators had easy access to more ventilation related parameters such as actual V_T delivered and face mask leak, and not only PIP.*

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