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ABSTRACT

Some neural circuits within infants are not fully developed at birth, especially in preterm infants. Therefore, it is unclear whether reflexes that affect breathing may or may not be activated during the neonatal stabilisation at birth. Both sensory reflexes (eg, tactile stimulation) and non-invasive ventilation (NIV) can promote spontaneous breathing at birth, but the application of NIV can also compromise breathing by inducing facial reflexes that inhibit spontaneous breathing. Applying an interface could provoke the trigeminocardiac reflex (TCR) by stimulating the trigeminal nerve resulting in apnoea and a reduction in heart rate. Similarly, airflow within the nasopharynx can elicit the TCR and/or laryngeal chemoreflex (LCR), resulting in glottal closure and ineffective ventilation, whereas providing pressure via inflations could stimulate multiple receptors that affect breathing. Stimulating the fast adapting pulmonary receptors may activate Head's paradoxical reflex to stimulate spontaneous breathing. In contrast, stimulating the slow adapting pulmonary receptors or laryngeal receptors could induce the Hering-Breuer inflation reflex or LCR, respectively, and thereby inhibit spontaneous breathing. As clinicians are most often unaware that starting primary care might affect the breathing they intend to support, this narrative review summarises the currently available evidence on (vagally mediated) reflexes that might promote or inhibit spontaneous breathing at birth.

INTRODUCTION

Most very preterm infants breathe at birth, but this is often insufficient for adequate respiratory gas exchange, requiring infants to initially receive non-invasive ventilation (NIV) (eg, continuous positive airway pressure (CPAP), intermittent positive pressure ventilation (iPPV)) via a face mask or bi-nasal prongs.[1 2] By applying a positive pressure to the airway, NIV increases the surface area for gas exchange by promoting alveolar liquid absorption and by preventing alveolar collapse at end-expiration.[3] NIV strategies are universally adopted as the first choice for respiratory support at birth, but their effect on breathing is unclear. It is well established that cutaneous sensory reflexes (eg, tactile stimulation), can stimulate the respiratory centre and thereby increase spontaneous breathing.[4 5] However, the application of NIV may have a variable response. By improving oxygenation, it could stimulate breathing, but it could also induce vagally mediated reflexes that inhibit spontaneous breathing at birth. As neural circuits are more immature in preterm infants, the breathing responses to different types of stimuli are unclear.[6 7]

In this review, we discuss the current available evidence on (vagally mediated) reflexes that might promote or counteract spontaneous breathing of the preterm infant at birth. We performed a literature search on PubMed for reviews and (pre) clinical studies investigating the trigeminocardiac reflex (TCR), Hering-Breuer inflation and deflation reflex, Head's paradoxical reflex and laryngeal chemoreflex (LCR) in newborns. The reference list of included articles was checked to identify articles excluded in the primary search.

APPLYING AN INTERFACE

Most very preterm infants receive respiratory support at birth. While it is assumed that the application of an interface (eg, face mask) to the infant's face should support breathing, it may trigger a vagally mediated reflex via the trigeminal nerve that innervates the skin of the face. Applying a face mask with adequate pressure to acquire seal and prevent mask leak could activate the cutaneous stretch receptors of the trigeminal nerve, leading to apnoea and a decrease in heart rate.[2] This trigeminal response is often referred to as the diving reflex which is one of the three peripheral subtypes of the TCR. The diving reflex covers the first branch of the trigeminal nerve and can be stimulated by cold air or water to the infant's face. Two other TCR subtypes are the oculocardiac reflex, which can be stimulated by pressure on the eye globe, and the maxilla-mandibular/nasopharyngeal reflex covered by the second and third branch.[8 9] As the face mask is placed over the mouth and nose covering all three branches of the trigeminal nerve, we will refer to the effect of the facemask as the peripheral TCR in general. The peripheral TCR is an oxygen preserving brainstem reflex, which can be activated by stimulating at least one of the three branches of the trigeminal nerve. The intensity of the TCR depends on the type (pressure, thermic or nociceptive,[10] duration, intensity and localisation of the trigeminal stimuli.[6 10–13] During activation of the peripheral TCR there is a strong synergistic co-activation of the parasympathetic and sympathetic system resulting in closure of the larynx which will tend to avoid aspiration, a reduction of heart rate thereby lessening oxygen consumption, and peripheral vasoconstriction which should preserve cerebral blood flow and delay progression of asphyxia.[14] Thus, activating the peripheral TCR could lead to apnoea, bradycardia and closure of

the larynx, which can severely hamper NIV during stabilisation of preterm infants at birth.

The effects of applying a face mask in infants have been reported in several studies. Studies in term infants reported a change in breathing pattern with an increased tidal volume and decreased breathing rate after application of just the face mask rim, which persisted for at least 5 min and returned to control values after removing the rim.[15–17] There might be a threshold to exceed for provoking the peripheral TCR as applying a light-weight cardboard ring did not have similar effects as compared with a face mask (rim). We recently investigated the effect of applying a face mask on breathing in preterm infants and observed that in 54% of infants who were initially breathing, stopped breathing after applying the face mask and these infants had a lower heart rate as well.[2]

To avoid the use of face mask, different interfaces could be considered. Bi-nasal prongs, a single nasal tube or a nasal mask could diminish stimulation of the sensitive area around the mouth and nose and decrease the chance of inducing a TCR. Previous studies[18–20] comparing a single nasal tube with a face mask reported no differences in breathing, oxygen saturation and heart rate between the interfaces during respiratory support at birth. It is possible that any or all of the various hand-held interfaces may result in stimulation of the trigeminal area. A randomised study[21] comparing bi-nasal prongs and face mask during neonatal resuscitation reported less intubations and chest compressions when bi-nasal prongs were used. However, the effect of applying bi-nasal prongs or nasal mask on breathing in preterm infants at birth has so far not been investigated.

The use of a laryngeal mask for NIV may be an alternative approach for avoiding the TCR, although placing the laryngeal mask could stimulate the mechanoreceptors of the larynx and provoke the LCR leading to apnoea and bradycardia. Currently, a large randomised trial (n=1240), the NeoSupra (NCT03133572), is comparing a supraglottic airway (i-gel) and face mask as interface for preterm infants at birth. While this trial is ongoing, the direct effect of the interface on breathing has not been defined as an outcome measure.

AIRFLOW

In addition to applying a face mask, airflow could also stimulate the nasal mucosa and/or skin and thereby trigger the peripheral TCR. Breathing rates and heart rates were reduced in preterm infants when a sudden airstream was delivered via the nostrils to infants at 1 cm distance from their face.[7] Humidification and temperature of the air given could play an important role in inducing this response. While heated and humidified gases are used to reduce hypothermia, this may then also have an additional positive effect on breathing at birth.[22] Whether only the temperature of the airstream or also the airstream itself is responsible for triggering the peripheral TCR is unclear.

Airflow can elicit the LCR as well. The LCR can be induced by chemical and mechanical stimuli as it protects the airway from aspiration of materials into the lungs. The LCR can differentiate between liquids based on the chemical composition, particularly their chloride ion concentration. As foetal lung liquid has a high chloride ion concentration, the glottis tends to close in response to liquids with lower chloride ion concentration (eg, upper airway secretion or gastric fluid),[23] which is thought to prevent the entry of liquids that might be hazardous to the lower airways. Next to this chemical stimuli, different mechanoreceptors are sensitive to mechanical stimuli, such as pressure, air flow and laryngeal movements.[24] These receptors are innervated by the superior laryngeal nerve, which may activate a reflex similar to the TCR.[25 26] In a study using newborn kittens and puppies the investigators observed that the LCR inhibited breathing when the flow receptors in the upper airway were stimulated with cold or warm air, while this did not occur when a local anaesthetic was applied to the laryngeal area or when the larynx was bypassed.[27]

PRESSURE (CPAP, SUSTAINED INFLATIONS AND IPPV)

While NIV is often used and intended to support breathing, the pressure given can stimulate laryngeal and pulmonary receptors, for example, stretch-receptors, irritant-receptors and J-receptors.[25 28] When the pressure-sensitive laryngeal receptors are activated, laryngeal closure and thus apnoea could occur. Pulmonary receptors can be activated in different ways. Stretch and irritant receptors are stimulated by lung inflation and/or chemical irritants. J-receptors are stimulated by interstitial oedema, likely activated during lung aeration at birth due to the clearance of airway liquid into lung tissue by inflations and/or spontaneous breaths.[25] When the glottis is open and the lungs are being aerated, lung inflations may stimulate the pulmonary stretch and/or irritant receptors, triggering the Hering-Breuer reflex and/or Head's paradoxical reflex.[25 29]

Hering-Breuer reflex

The Hering-Breuer reflex consists of an inflation and deflation reflex. When lung inflation increases afferent output from slowly adapting lung stretch receptors, the refractory time between signals from the inspiratory motor neurons increase to prevent overdistention of the lungs. This delays the start of the next inspiration and prolongs expiration, resulting in both a reduction in breathing rate and tidal volume.[25] The incidence and duration of the inflation-induced apnoea is correlated to the functional residual capacity (FRC) in preterm infants.[30] However, this effect might not only be dependent on lung afferents signalling via the vagus (eg, Hering-Breuer reflex), since lung inflation should have reduced inspiratory times. In contrast, they increased both inspiratory and expiratory times in preterm infants, suggesting that a separate mechanical reflex may have been activated, that is responsive to factors such as lung volume, chest wall reflexes or chest wall stability.[30]

The deflation reflex can be observed during expiration when the lung deflates and could play a role in protecting the newborn's FRC, particularly during accentuated breathing when expirations are forced. During forced expirations, pulmonary proprioceptors can be activated, which truncate expiration by contracting the diaphragm or closing the larynx. Also, irritant receptors can be stimulated, making it possible to inspire again. The magnitude of inspiratory response is dependent on the breathing rate before the deflation, the amount of reduction in lung volume below FRC, deflation pressures and deflation rate.[31 32] Rapid lung deflation may cause high rates of inward rib cage retraction thereby activating the intercostal-phrenic inhibitory reflex. This could lead to the same response as seen in the Hering-Breuer inflation reflex (eg, inhibition of inspiration).[31 33 34] Further studies are needed to define the exact mechanism(s) of these reflexes more clearly, however, CPAP can reduce the frequency and severity of apnoeic event, perhaps by increasing stability of the rib cage.[34]

Head's paradoxical reflex

Head's paradoxical reflex is provoked when lung inflation increases the afferent output from the rapidly adapting irritant

receptors (into the respiratory centre), stimulating inspiration.[32 35] It triggers an infant to abruptly breathe in and might be responsible for the first effective inspiratory volume during resuscitation and the first appearance of FRC after birth.[36–38] Indeed, Harris *et al*[39] reported that an infant's first breath tended to occur during a sequence of five sustained (2–3 s) inflations after birth, with a median time of 7 s from the first inflation, possibly due to Head's paradoxical reflex. Thus, Head's paradoxical reflex may help to stimulate breathing and is most commonly seen in the first 24 hours of life.[40]

Spontaneous breaths during sustained inflations in initial apnoeic infants are often reported.[2 29 41] It is possible, that the sustained inflations provoke a Head's paradoxical reflex, which triggers spontaneous breathing. However, it is unclear why lung inflation could stimulate the stretch receptors in some infants (Hering-Breuer inflation reflex) and the irritant receptors in others (Head's paradoxical reflex). It is quite possible that the degree and uniformity of lung aeration could play a role in this distinction.

Cardiovascular response to stimulating pulmonary receptors

In addition to an effect on breathing, pulmonary slow adapting receptors that also signal via vagal afferent nerve fibres can influence the cardiovascular response that is observed during the diving reflex.[42] Stimulating these pulmonary receptors (eg, lung inflations, spontaneous breathing movements) may reduce or even abolish the bradycardia associated with the diving reflex.[42] Besides this, it has been suggested that high intrathoracic pressures (>15 cmH_2O)[43] reduce venous return, thereby increasing efferent sympathetic activity and heart rate and thus preventing the bradycardia associated with the diving reflex from manifesting.[42–45]

TACTILE STIMULATION

During stabilisation of preterm infants, tactile stimulation is recommended by international guidelines to prevent apnoea and stimulate spontaneous breathing.[46 47] Rubbing the sole of the foot or the infant's back supposedly activates proprioceptors or somatic/visceral mechanoreceptors in the thorax, respectively, which are known to stimulate spontaneous breathing.[48] These afferent somatosensory pathways are functional even before 25 weeks of gestation.[49]

If the newborn is apnoeic or has an irregular or unstable breathing pattern at birth, the larynx is predominantly closed and opens only during a spontaneous breath.[50] Therefore, NIV could be ineffective in apnoeic infants. Glottis function is regulated by the recurrent laryngeal nerves, which form part of the vagal trunk, exiting the vagus nerve within the thorax and then passing cranially alongside the trachea to innervate the glottis.[51] As they initially form part of the vagal complex and have a variety of both respiratory and non-respiratory functions (including postural), it is possible that tactile stimulation (or other interventions that stimulate spontaneous breathing) might be able to counteract the reflexive closure of the glottis as result of the TCR or LCR as well.

Although the use of tactile stimulation has been recommended internationally, there is no consensus about how tactile stimulation should be provided; the duration and method of stimulation is widely variable between caregivers and centres.[52 53]

However, a randomised controlled trial[48] comparing repetitive stimulation to standard stimulation reported a clinically relevant improvement in respiratory function in the repetitive stimulation group.[48] In the repetitive stimulation group, the incidence of a tactile stimulation episode was higher and the duration of the stimulation episode was shorter. These findings are consistent with those of Dumont *et al*,[49] who reported that preterm infants habituate to tactile stimulation, with the ability to distinguish between stimulus location and inter-stimulus time.[49] Recently, the effects of different tactile stimulation sites have been reviewed and truncal stimulation appeared to be more effective in eliciting a response, for example, crying and movements, than foot flicks.[54] The physiological benefits of increased tactile stimulation that have been observed in preterm infants include an increase in oxygen saturation along with significantly fewer intubations.[52 55]

SUCTIONING

Oronasopharyngeal suction is used in newborns to expedite lung aeration at birth by removing amniotic fluid, meconium, mucus and/or blood from the pharynx to prevent aspiration into the lower airways.[56 57] However, suctioning could also stimulate receptors within the laryngeal epithelium and provoke the LCR, leading to changes in heart rate and oxygen saturation. Studies investigating the effect of suctioning in newborns immediately after birth reported heart rate disturbances, a significantly lower breathing rate and an increase in time to reach an arterial oxygen saturation ≥92%.[56 58–60] Therefore, suctioning during or after delivery is not recommended when there is clear or no meconium-stained amniotic fluid and no obvious obstruction.[57]

TEMPERATURE

When infants are born, there is a sudden environmental temperature change from the warm uterus (~38°C) to a relatively cool ambient room temperature (20°C–22°C). Infants are placed under a radiant heater and heated and humidified gases are used to prevent hypothermia. Despite the current heath management, infants are still at risk for both hypothermia and hyperthermia and this could directly affect vagally mediated reflexes.[22]

Animal data suggest that body temperature directly affects vagal activity and thereby may affect breathing activity. Studies in newborn rats have demonstrated that hyperthermia ≥38°C and ambient air temperature ≥36°C enhanced apnoea induced by vagally mediated reflexes, for example, LCR and Hering-Breuer reflex.[61 62] In contrast, hypothermia reduced the strength of the Hering-Breuer reflex.[63]

The effect of temperature on breathing has been confirmed in infants, as both hypothermia and hyperthermia are associated with an increased incidence of apnoea.[64–66] Neonatal hypothermia could affect breathing by reducing lung compliance, causing pulmonary vasoconstriction and influencing the recovery from birth asphyxia. In infants this led to less effective surfactant therapy, a decrease in left atrial pressure and a more severe metabolic acidosis at birth.[67] In addition, prolonged exposure to cold air is associated with respiratory distress, delayed circulatory transition and an increased morbidity and mortality.[68] All of these findings stress the importance of maintaining normothermia at birth.

Humidification and temperature of the inhaled air are equally important. Besides preventing hypothermia, exposure to warm air/water (35°C–39°C) inhibits and cold air/water (<26°C) stimulates the trigeminal receptors, provoking the TCR. The primary excitation factor of nasal receptors seems to be temperature changes.[43 69–71] Yet, very low temperatures (≤4°C) may be perceived as painful, thereby activating the sympathetic nervous system and increasing the heart rate. This suggests that the heart rate response to temperatures applied to the face might be J-shaped.[72] In line with this finding, face immersion in colder water (≤10°C) reduces the maximal apnoeic time and stimulates ventilation as result of a cold shock-like response, which drives

Table 1 Risk factors and its' effect on vagally mediated reflexes

Risk factor	TCR	Hering-Breuer reflex	LCR	References
Gestational age (increasing)	–	C	?	2 7 78 79
Postnatal maturation (increasing)	–	–	?	78 80 81
Gender (male)	C	?	+	2 9 82
Anaesthesia	–	–	?	83 84
Maternal medication	- (Beta-adrenergic agonist) + (selective serotonin reuptake inhibitor)	?	- (Beta-adrenergic agonist)	13 85
Prenatal nicotine exposure	+	?	?	9 86
Hypoxia	+	+	+	9 62 86–88

Heightens the response (+), weakens the response (-), contradictive literature (C), unknown (?).
LCR, laryngeal chemoreflex; TCR, trigeminocardiac reflex.

inspiration and appears to override the diving response.[73] The effect of water temperature causes the least response when it is considered to be thermoneutral (35.5°C).[42 72]

OTHER RISK FACTORS

Next to all the factors mentioned above, vagally mediated reflexes can be influenced by risk factors aside from the interventions involved during the stabilisation. These risk factors are presented in table 1. Studies have shown that Hering-Breuer reflex activity was independent of race[74] and caffeine administration.[75–77]

CONCLUSION

While we now recognise that the optimal use of NIV requires the infant to breathe spontaneously, the optimal way to stimulate and support spontaneous breathing in preterm infants at birth is currently unclear. Nevertheless, it is important to recognise that simply by applying NIV, we might compromise breathing by inducing reflexes. Different vagally mediated reflexes are heightened in preterm infants due to neural immaturity and can be provoked during the stabilisation. Applying an interface could provoke the TCR by stimulating the trigeminal nerve resulting in apnoea and a reduction in heart rate. Airflow can elicit the TCR and/or LCR, resulting in glottal closure and ineffective ventilation. Pressure via inflations may induce the Head's paradoxical reflex promoting breathing, while the Hering-Breuer inflation reflex and LCR inhibits breathing. Tactile stimulation promotes spontaneous breathing, which opens the glottis and might counteract the reflexive closure of the glottis as result of the TCR or LCR. Suctioning may provoke the LCR as well. In addition to this, temperature management is very important as it can influence vagally mediated reflexes as well.

Clinicians should be aware that starting primary care could compromise the breathing they intend to support. Some reflexes are inevitable to provoke. Nevertheless, understanding the underlying mechanisms, the hierarchy and the thresholds for activating these reflexes will be important for improving the primary care of neonatal stabilisation. Further studies are warranted to investigate the mechanism of these reflexes before recommendations can be made for an interface or effective ventilation (eg, airflow, pressure) during the stabilisation at birth.

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