Touched by technology: automated tactile stimulation in the treatment of apnoea of prematurity

Cramer, S.J.E.

TOUCHED BY TECHNOLOGY

Automated tactile stimulation in the treatment of apnoea of prematurity

Sophie Josephine Elisabeth Cramer

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COLOFON

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Automated tactile stimulation in the treatment of apnoea of prematurity

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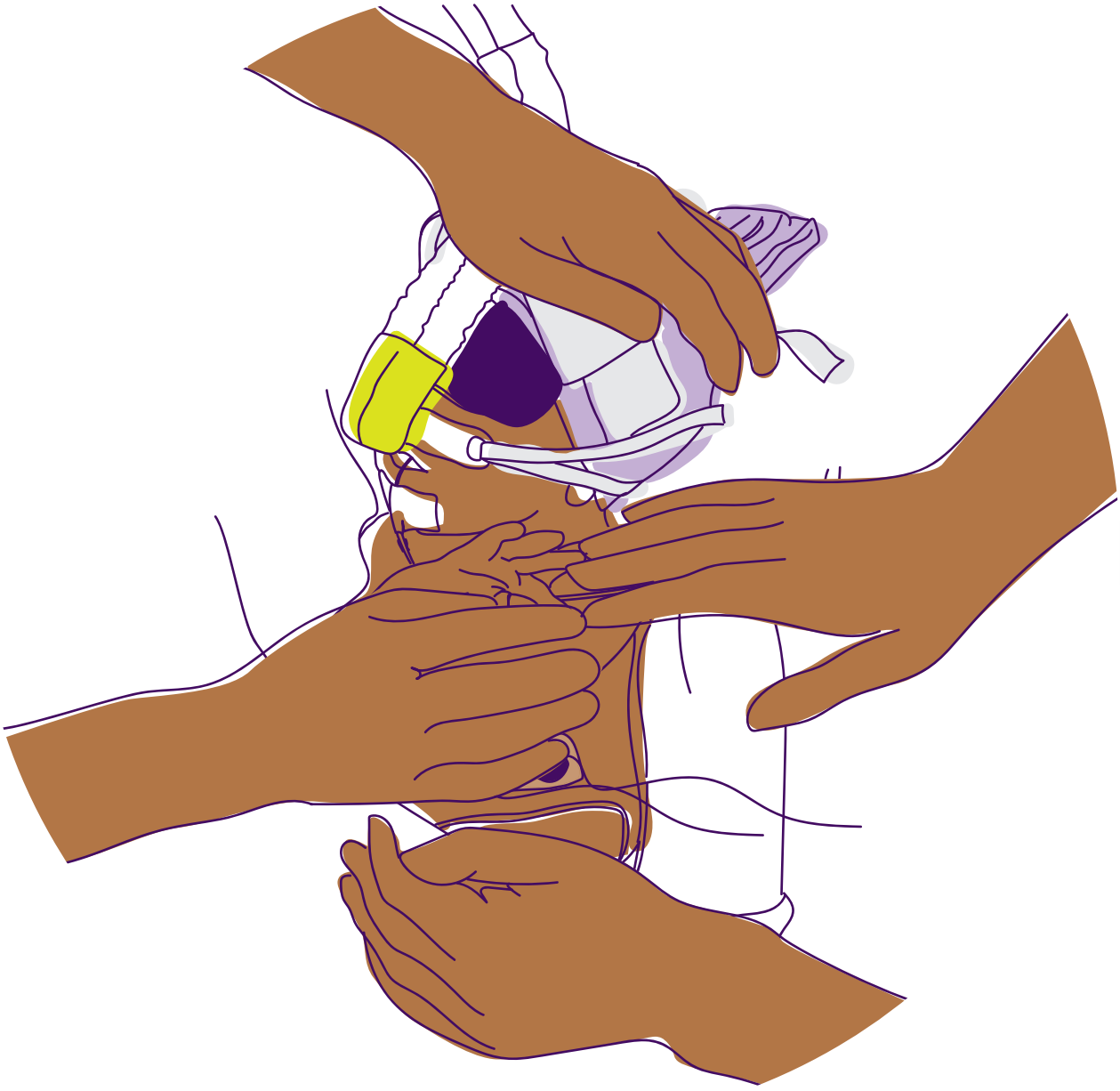

PART 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

In humans, full-term pregnancy lasts 37 to 40 weeks from the last menstruation. The infant is then fully matured and has the best chance of being born healthy. Preterm birth refers to the delivery of an infant before 37 completed weeks of pregnancy, and is further categorized into late or moderate preterm (32-37 weeks of gestation), very preterm (28-32 weeks of gestation) and extreme preterm birth (<28 weeks)(Figure 1). The degree of prematurity is directly linked to the immaturity of the organs and organ systems, hence to the inability to adapt to extrauterine life independently. Most infants born at less than 30 weeks' gestation require respiratory support, medication, and continuous monitoring to survive and are admitted to a Neonatal Intensive Care Unit (NICU) for several weeks to months.

The WHO estimated 15 million infants being born prematurely each year in 2010 [1], and that number is still rising [2, 3]. Approximately one million infants die due to direct complications of preterm birth and when they survive there is an increased risk for a range of severe complications in the neonatal period which can consecutively result in lifelong complications including respiratory, cardiovascular, gastrointestinal and renal disease, as well as neurodevelopmental and cognitive disorders [4, 5]. Although the survival and overall outcome of premature infants has improved dramatically over the last decades, it remains the single major cause of neonatal mortality and morbidity around the world. In addition to the personal and emotional burden, the economic costs of preterm birth are large in terms of the required intensive neonatal care, complex long-term health needs as well as lost economic productivity. Therefore, there is strong endorsement for re-evaluating current treatments and developing new approaches to prevent clinical conditions resulting in mortality or morbidities that extend to later life.

APNOEA OF PREMATURITY

One of the challenges preterm infants encounter is the establishment of a rhythmic and stable spontaneous breathing pattern, necessary for effective ventilation and gas exchange. As the lungs and brains of preterm infants are not sufficiently developed, preterm infants exhibit altered immature control of breathing including aberrant activity of central and peripheral chemoreceptors as well as poor neuromuscular control [6].

The onset of periodic breathing is one of the most common symptomatic indicators of immature respiratory control and is manifested by rapid breathing interspersed with respiratory pauses. Pauses lasting longer than 10 seconds are defined as apnoea and are typically accompanied by bradycardia and/or hypoxia [7]. The incidence of apnoea is inversely related to gestational age, affecting almost all preterm infants born at <28 weeks'

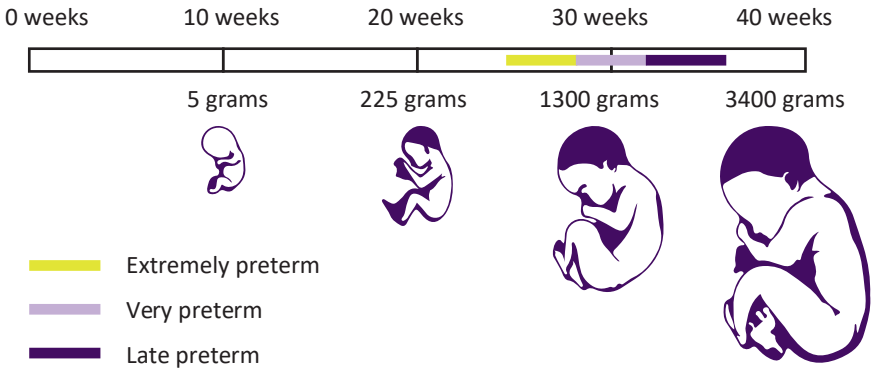

Figure 1. Categories of preterm birth

gestation or with a birthweight of <1000g, which makes it one of the most prevalent and recurrent problems in the NICU [8, 9].

Based on the underlying physiology, apnoeic episodes in preterm infants are traditionally classified in three categories: central, obstructive or mixed. Central apnoea originates from the absence of respiratory drive from the responsible brain parts, manifested by cessation of chest wall motions. Obstructive apnoea results from an occlusion of the upper airways and is in turn recognized by impeded airflow despite chest wall movements. However, the majority of apnoeic episodes in preterm infants have a mixed origin, where central apnoea leads to obstructive apnoea or vice versa [10].

AETIOLOGY OF APNOEA

Research in the development of respiratory control in foetal animals and preterm infants has improved our understanding of the pathophysiology of apnoea, but the responsible mechanisms appear to be complex and are still not fully understood [11-13]. Apnoea of prematurity (AOP) is the net result of impaired ventilatory responses to hypoxia and hypercapnia [14-18], enhanced inhibitory reflexes to airway afferents [19-21], immature respiratory anatomy [22, 23] and long active sleep durations leading to increased inhibitory signals and decreased muscle tone [24-26]. The control of breathing improves over time due to maturation and the occurrence of apnoea usually resolves on average at 34 to 36 weeks gestation, although it may persist to a postmenstrual age of 40 to 44 weeks [27, 28].

In addition to immature respiratory control, recurrent apnoea can be caused by other diseases associated with prematurity, such as inflammation, infection, metabolic disbalances, intracranial haemorrhage or seizures [9, 29-31]. AOP is therefore a diagnosis of exclusion and requires thorough examination and appropriate investigation to rule out or identify and treat potential secondary causes.

CONSEQUENCES OF APNOEA

Although AOP is by definition an age-specific and self-limiting disorder that resolves with maturation, it can lead to direct adverse events as well as have a negative impact on long-term outcome. The major pathophysiological consequences of apnoea are presumably caused by the accompanying hypoxia and bradycardia, which have been associated with increased mortality, oxidative stress, serious cerebral injury and long-term neurodevelopmental impairment [27, 32-34].

While it is well understood that longer apnoeic episodes will increase the risk, duration and severity of subsequent hypoxia and bradycardia [35-38], also brief respiratory pauses contribute substantially to physiological instability given their numerical preponderance [39-41]. Therefore, not only apnoea's but also frequent shorter pauses should be considered clinically significant and warrant treatment [41].

CURRENT TREATMENT OF AOP

The easiest way to prevent hypoventilation and apnoea in preterm infants is to take over respiratory control by intubation and mechanical ventilation. However, given the recognition that invasive ventilation can lead pulmonary and cerebral injury in preterm infants [42-45], pharmacologic and non-invasive respiratory therapies are preferred as safer and more effective options to prevent and/or treat apnoea.

The first-line pharmacological therapy to treat apnoea is the use of methylxanthines, primarily aminophylline, caffeine and theophylline. Methylxanthines act both centrally and peripherally and result in increased CO2 sensitivity, enhanced diaphragmatic activity, increased minute ventilation, decreased hypoxic depression and less periodic breathing. Caffeine has become the most preferred option because it is better tolerated, has a wider therapeutic range and long half-life that allows for dosing once a day [46-48].

Nasal continuous positive airway pressure (CPAP) is a commonly applied non-invasive respiratory treatment option, resulting in increased functional residual capacity (FRC) of the lung hence improved oxygenation. The distending pressure furthermore prevents from upper airway obstruction and reduces inhibitory feedback from the mechanoreceptors in the upper airways [49, 50]. Providing heated humidified high flow via a nasal cannula (HFNC) also provides distending pressure and thus allows for similar stabilizing effects as CPAP [51, 52]. Also, non-invasive positive pressure ventilation (NIPPV) has become increasingly popular as it seems to be more effective than CPAP in reducing AOP, particularly when synchronized with spontaneous breaths [53, 54].

In case of persistent AOP, despite caffeine treatment and respiratory support, continuous infusion of doxapram is often considered as an additional prophylactic therapy. Although doxapram was already introduced in the 1980s to treat infants with persistent idiopathic AOP [55, 56], it is still used off-label in preterm infants and evidence about efficacy and safety is lacking [57, 58].

CHALLENGES IN TREATMENT OF AOP

Although the existing preventative therapies have shown effect, most preterm infants are still subjective to apnoea. In order to avoid harmful consequences, an adequate response consisting of a sequence of interventions of the nurse is required. This sequence usually commences with tactile stimulation such as rubbing the foot of back of the infant, but can escalate to providing increased supplemental oxygen, positive pressure ventilation and, eventually, intubation [59].

Manually applied tactile stimulation is the first, most frequently and arguable the most important used intervention in response to apnoea. However, although tactile stimulation has been recommended and applied for years, treatment of apnoea entirely depends on caregivers' actions. Its execution is therefore subject to human factors such as the perceived workload, perceived importance, walking distances and cultural norms [60, 61]. These factors delay, or can even avert, effective action to counteract apnoea, causing potential injury to the infant [38].

The magnitude of these challenges has increased with the increased survival of extremely low birth weight infants. In addition, many NICU's have transitioned from traditional open-bay units (OBU's) to single room unit (SRU's). This new architectural layout provides (preterm) infants with a more suitable developmental environment and promotes family centred care, although it comes at the cost of increased physical distances between patients and increased dependence on technology such as alarm distribution systems and remote monitoring [62, 63].

AUTOMATION OF TACTILE STIMULATION

Providing a direct and reliable response by utilizing automated tactile stimulation seems a logical solution to address the aforementioned challenges and improve the treatment of AOP. Assuming mechanical stimulation is equally effective to manual stimulation, an automated and direct response could shorten brief respiratory pauses and apnoea hence prevent the onset or exacerbation of hypoxia and bradycardia. Combining mechanical stimulation with a predictive algorithm could potentially even lead to a preventative treatment, avoiding cardiorespiratory instability. In addition to the benefits for the infant, implementing such a system could aid the nursing staff as it will reduce the need for manual intervention.

This thesis serves as a scientific basis for the development and evaluation of an automated tactile stimulation device, in which we primarily focussed on the design of an effective and safe mechanical stimulus.

AIM AND OUTLINE OF THIS THESIS

The general aim of this thesis is to explore the potential added value of automating tactile stimulation in the treatment of apnoea in preterm infants. The preface and this general introduction together form *Part 1* of this thesis, containing background information about the topic.

In *Part 2*, the aim was to evaluate and investigate current practice regarding the reactive response to apnoea in preterm infants. Although nurses are trained to apply manual tactile stimulation in response to apnoea world-wide, there are no protocols or guidelines available that define or recommend certain methods and the optimal way to end apnoeic episodes is currently unknown. **Chapter 1** describes an observational study evaluating the methods of tactile stimulation currently used by nurses of the NICU of the Leiden University Medical Centre. This study was performed using a simulated scenario with a manikin and included 47 nurses. All nurses demonstrated their methods three times in succession, with the manikin positioned either prone, supine or lateral. The demonstrations were recorded and afterwards logged in chronological order by describing both the technique and the location used, which resulted in unique overview of stimulation methods used. To get a better quantitative overview of the reactive treatment of apnoea in general, a prospective observational study was set up in our NICU (**Chapter 2**) investigating nurses' response rates, response times and response methods to cardiorespiratory events. This data was gathered by placing a camera on the foot-end of the incubator which was activated following every clinical alarms from the patient monitor.

The aim of *Part 3* was to evaluate the potential benefits of mechanical and automated tactile stimulation. In **Chapter 3**, an overview of existing literature is given on the effects of tactile stimulation on the prevention and termination of apnoea in preterm infants. Although most mechanical systems show positive results when applied either in a continuous or reactive manner, the benefits of a quick anticipated and/or automated response over a relatively late reactive response have not yet been assessed. For that reason, we performed a preclinical study (**Chapter 4**) comparing anticipated and reactive mechanical stimulation in spontaneously breathing preterm rabbits at the SPring-8 synchrotron in Japan. Intrathoracic oesophageal pressures, ECG signals and phase contrast X-ray images were used to obtain and analyse breathing rates, heart rates and FRC values.

The insights and results of *Part 2* and *3* served as main input for the design and development of a purpose built automated stimulation device, which we called BOBBY (Breathing Operator for BaBY). *Part 4* starts with **Chapter 5**, in which the development process and final design of BOBBY is described. **Chapter 6** describes a randomized cross over study in 16 preterm infants

on the NICU of the Leiden University Medical Centre aiming to assess the feasibility and safety of the device in a clinical setting. The participating infants underwent two consecutive study periods of 24 hours each; one period of standard care in which the nurses decided if and how to respond to clinical alarms and one period in which the BreatheBuddy was used as an addition to standard care, providing direct vibratory stimulation in response to clinical alarms.

Part 5 places the application of automation in a broader context. It consists solely of **Chapter 7**, which reviews how automated tactile stimulation and other technological innovations could improve care for preterm infants in the delivery room immediately after birth.

In *Part 6* the main findings of this thesis are discussed and future perspectives are given as well as suggestions for further research (**Chapter 8**). In **Chapter 9** and **Chapter 10** the studies are summarized in Dutch and English, respectively.

Finally, *Part 7* contains the appendices, including a word of thanks to everyone involved in the realization of this thesis.

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PART 2

CHAPTER 1

High variability in nurses' tactile stimulation methods in response to apnoea of prematurity - a neonatal mannikin study

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ABSTRACT

AIM

Neonatal intensive care unit (NICU) nurses provide tactile stimulation to terminate apnoea in preterm infants, but guidelines recommending specific methods are lacking. In this study we evaluated current methods of tactile stimulation performed by NICU nurses.

METHODS

Nurses were asked to demonstrate and explain their methods of tactile stimulation on a manikin, using an apnoea scenario. All nurses demonstrated their methods three times in succession, with the manikin positioned either prone, supine, or lateral. Finally, the nurses were asked how they decided on the methods of tactile stimulation used. The stimulation methods were logged in chronological order by describing both the technique and the location. The nurses' explanations were transcribed and categorized.

RESULTS

In total, 47 nurses demonstrated their methods of stimulation on the manikin. Overall, 57 different combinations of technique and location were identified. While most nurses (40/47, 85%) indicated they learned how to stimulate during their training, 15/40 (38%) of them had adjusted their methods over time. The remaining 7/47 (15%) stated that their stimulation methods were self-developed.

CONCLUSION

Tactile stimulation performed by NICU nurses to terminate apnoea was highly variable in both technique and location, and these methods were either based on prior training or intuition.

INTRODUCTION

Apnoea of prematurity (AOP), defined as a cessation of breathing for 10 to 20 seconds and sometimes accompanied by bradycardia and hypoxia, is one of the most common problems diagnosed in the Neonatal Intensive Care Unit (NICU) [1]. To reduce the occurrence of AOP, breathing is stimulated with methylxanthines and non-invasive respiratory support. Although these methods are effective [2-4], apnoea can persist in a proportion of infants. In order to restore breathing and avoid subsequent intermittent hypoxia and bradycardia, tactile stimulation is applied by the nurse, often combined with supplemental oxygen and, if required, mask ventilation.

NICU nurses are trained to apply manual tactile stimulation in response to AOP, an intervention that has been used worldwide for decades. There are, however, no protocols or guidelines available that define or recommend methods of tactile stimulation, and the optimal stimulation method to end AOP is currently unknown. In this study we aimed to determine the methods of tactile stimulation nurses currently use in response to AOP in our NICU.

METHODS

This prospective observational study was carried out at the NICU of the Leiden University Medical Centre (LUMC) from April to July 2018. Nurses were asked to demonstrate and explain their current procedures for stimulating preterm infants during a simulated scenario of AOP using a manikin. At the end of the demonstrations, all nurses were asked how they had developed their methods of tactile stimulation.

SIMULATION SET-UP

We created a scenario involving an apnoeic preterm infant in an unoccupied patient room at the NICU. The study set-up was equivalent to the clinical set-up; the manikin was placed in a closed and covered incubator, wrapped in a snuggle, and covered with a blanket. Nurses were invited into the room one by one and were asked to demonstrate the tactile stimulation they would usually perform when their patient is apnoeic. During the demonstration the nurses were informed that breathing had not been regained, encouraging them to show all the methods of tactile stimulation they would usually perform before considering mask ventilation. The scenario was repeated three times, with the manikin placed randomly in either prone, lateral or supine position.

DATA COLLECTION

All demonstrations were recorded using a webcam with an integrated microphone at the foot end of the incubator. The webcam was placed so that only the manikin and the hands of the nurse were visible.

ANALYSIS

The recordings were independently reviewed and analysed by two NICU nurses involved in the study (MB and NH). Tactile stimulation methods were logged in chronological order by describing both the technique and the location of stimulation. In situations that were unclear, consensus was achieved with the help of two researchers (SC and HZ). The techniques were subsequently numbered in chronological order; the first technique was assigned the number one, the last 10, and the remaining techniques a proportional value in between one and 10. The nurses' explanations about the development of their tactile stimulation methods were transcribed and categorized.

ETHICS

In concordance with the laws and guidelines, the Ethics Review Committee of Leiden University deemed that formal ethical approval was not required and issued a statement of no objection. The nurses who participated in the study gave consent for us to record the demonstrations and use the data.

RESULTS

In total, 47/59 nurses (80% of the team) participated in the study. The working experience of the 47 nurses varied; 24 (51%) nurses had worked at a NICU for over 10 years, 12 (26%) for 5-10 years, and 11 (23%) for less than five years.

Nurses used 10 different stimulation techniques; press, massage, rub, scratch, shake, squeeze, stroke, tap, tickle and vibrate (Figure 1), in 10 different locations; arms, back, abdomen, buttocks, cheek, feet, hands, head, legs and side. We also observed three tactile interventions that involved an additional component and were related to specific locations: supporting the neck or chin to obtain an open airway, lifting the thorax and turning the infant into either a lateral or prone position. In total, when combining the techniques and locations, we observed 57 different methods of tactile stimulation.

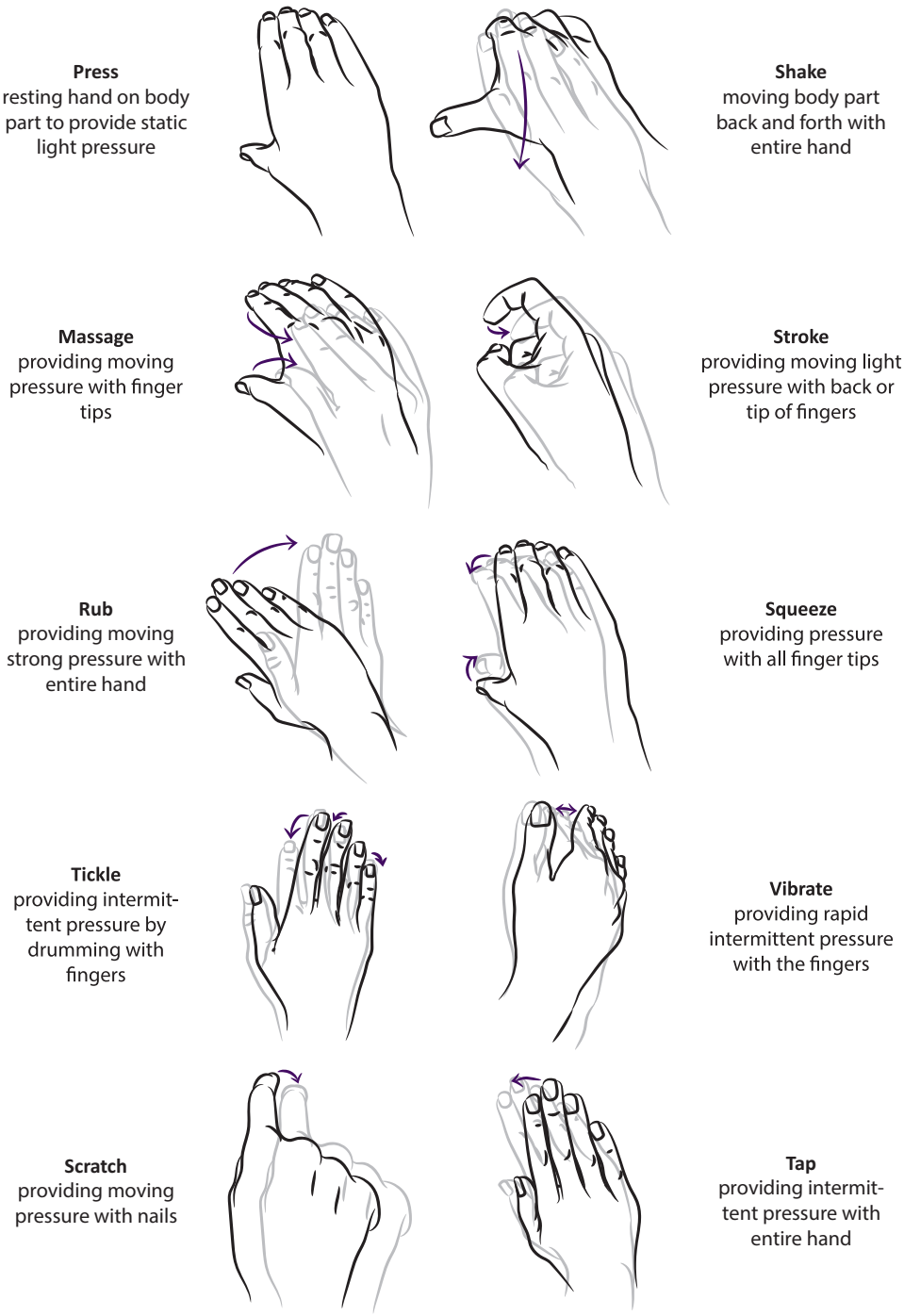

Figure 1. Identified stimulation techniques

STIMULATION TECHNIQUES

The most favoured techniques, demonstrated by more than 70% of the nurses, were pressing, rubbing, and turning the mannikin over when it was in a lateral or prone position (Fig 2). The ranking of the techniques indicates that most nurses performed their stimulation routine in that order.

The least commonly used stimulation techniques, demonstrated by fewer than 10% of the nurses, were scratching, tapping, tickling and vibrating (Fig 2). The median rank of these techniques shows that in most cases a different technique had preceded them.

Little difference was observed in the percentage of use between the different initial positions of the manikin for the stimulation techniques that consisted solely of a tactile component; press, shake, massage, stroke, rub squeeze, tickle, vibrate, scratch and tap (0-13%). The tactile interventions; open airway, turn over and lift, show larger variations in use between the different positions (9-72%).

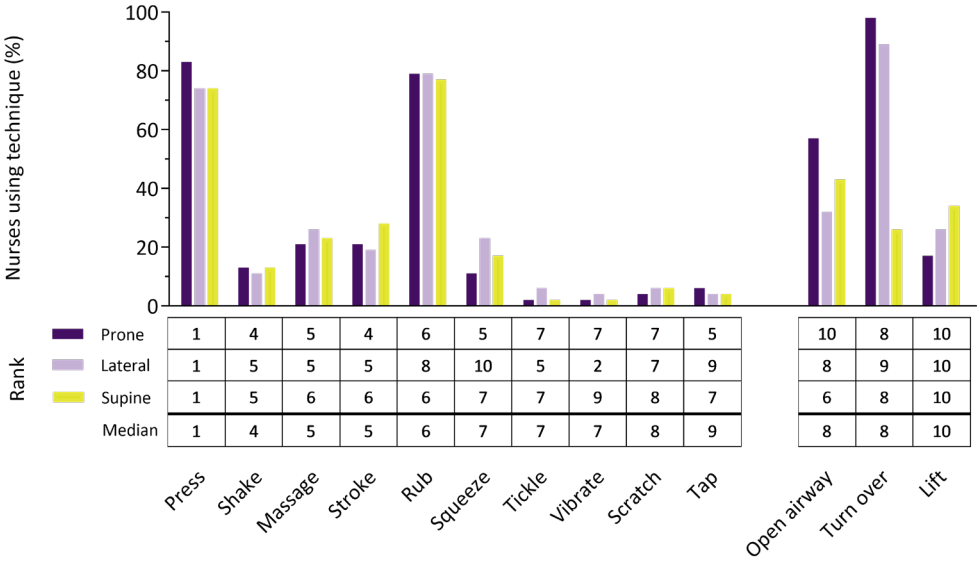

Figure 2. Percentage of nurses using the different identified stimulation techniques (press-tap) and interventions (open airway-lift) for prone, supine and lateral positioning of the manikin and succession rank of different identified tactile stimulation techniques and tactile interventions per position of the manikin.

STIMULATION LOCATIONS

Tactile stimulation was mainly applied on the feet, back, abdomen and head while the arms, cheeks, buttocks and hands were the locations least commonly stimulated areas (Fig 3a).

The feet were a favoured stimulation location in all positions, while the nurses chose to stimulate the torso predominantly on the side facing upwards – the back in prone position, and the abdomen in supine position (Fig 3b). The head was stimulated in all positions but almost solely in order to provide light pressure. The legs were stimulated more frequently, and using a wider range of techniques, when in lateral and supine positions compared to prone position.

Rubbing and massaging, the stimulation techniques that were demonstrated most often, showed the biggest variation in locations (8-9 different locations). The techniques that were least used - tapping, scratching, vibrating and tickling - showed the least diversity in stimulation location (2-4 different locations).

Tactile intervention to obtain an open airway consisted of supporting the chin or neck of the manikin, predominantly the latter. In 75% of the cases when the manikin was turned over it was turned to supine position, and in 25% of cases to lateral position. Finally, the thorax was the only body part that was lifted during the demonstrations.

STIMULATION METHODS

Overall, the most demonstrated stimulation methods to terminate apnoea in preterm infants were rubbing the feet, turning the infant over into a supine position, providing light pressure on the head, opening the airway by supporting the neck, and rubbing the back.

CHOICE OF STIMULATION METHOD

Of all nurses taking part in the study, 40/47 (85%) indicated that their choice of methods of tactile stimulation were based on instructions of supervisors or observations of fellow nurses during their training period. Of these nurses, 15/40 (38%) had adjusted their methods of stimulation over time, based on intuition or experience. The seven remaining nurses (15%) stated that their methods were entirely self-developed.

DISCUSSION

This was the first study to examine the tactile stimulation methods used by NICU nurses to stimulate breathing in response to AOP. The results show that the stimulation techniques and locations used were highly variable.

In general, the most frequently used methods were proving light pressure on the head, rubbing the feet or the torso, supporting the neck, and turning the infant over. However, our study also shows that both the stimulation techniques and locations that nurses use vary depending on the initial position of the mannikin. Furthermore, we observed that nurses used multiple stimulation methods with an increasing intensity if the apnoea persisted. Stimulation usually started with gently resting a hand on the infant to provide light pressure and ended with more vigorous forms of stimulation such as moving the infant into another position.

Our nurses developed their set of different methods of tactile stimulation by observing colleagues and supervisors, their own experience of performing stimulation, or a combination of both.

Unlike tactile stimulation methods to counteract apnoea, tactile stimulation methods to initiate breathing directly after birth have previously been described [5, 6]. These methods include warming, drying, rubbing the back, or flicking the soles of the infant's feet. Although the locations of these methods are similar to the most stimulated locations in this study, the selection of methods described is not scientifically underpinned. Recently, it has been shown that the methods and timing of tactile stimulation to initiate breathing at birth also vary considerably between caregivers and centres [7-12]. It has been suggested that rubbing the thorax region is most effective in providing timely initiation of breathing, but this was based on observations in small cohort studies [9, 11].

Although different forms of manual and mechanical tactile stimulation can prevent or terminate apnoea [13], their effectiveness could well be technique and/or location dependent. Several studies have hypothesized that tactile stimulation exerts its effect on the respiratory centre via activation of cutaneous nerves [14, 15]. Animal studies have shown that electrical stimulation of these nerves facilitates breathing [16] and attenuates inhibitory reflexes by increasing afferent input to the respiratory centre [17]. Alternatively, other studies suggest that tactile stimulation affects the respiratory oscillator by activating proprioceptors in the hands and feet [18] or receptors in the chest wall muscles [19]. Apart from the different neuronal pathways, the effectiveness of tactile stimulation is presumed to be primarily location dependent, as density and sensitivity of receptors varies per skin region [20]. Both the high variability in stimulation methods and the way nurses develop

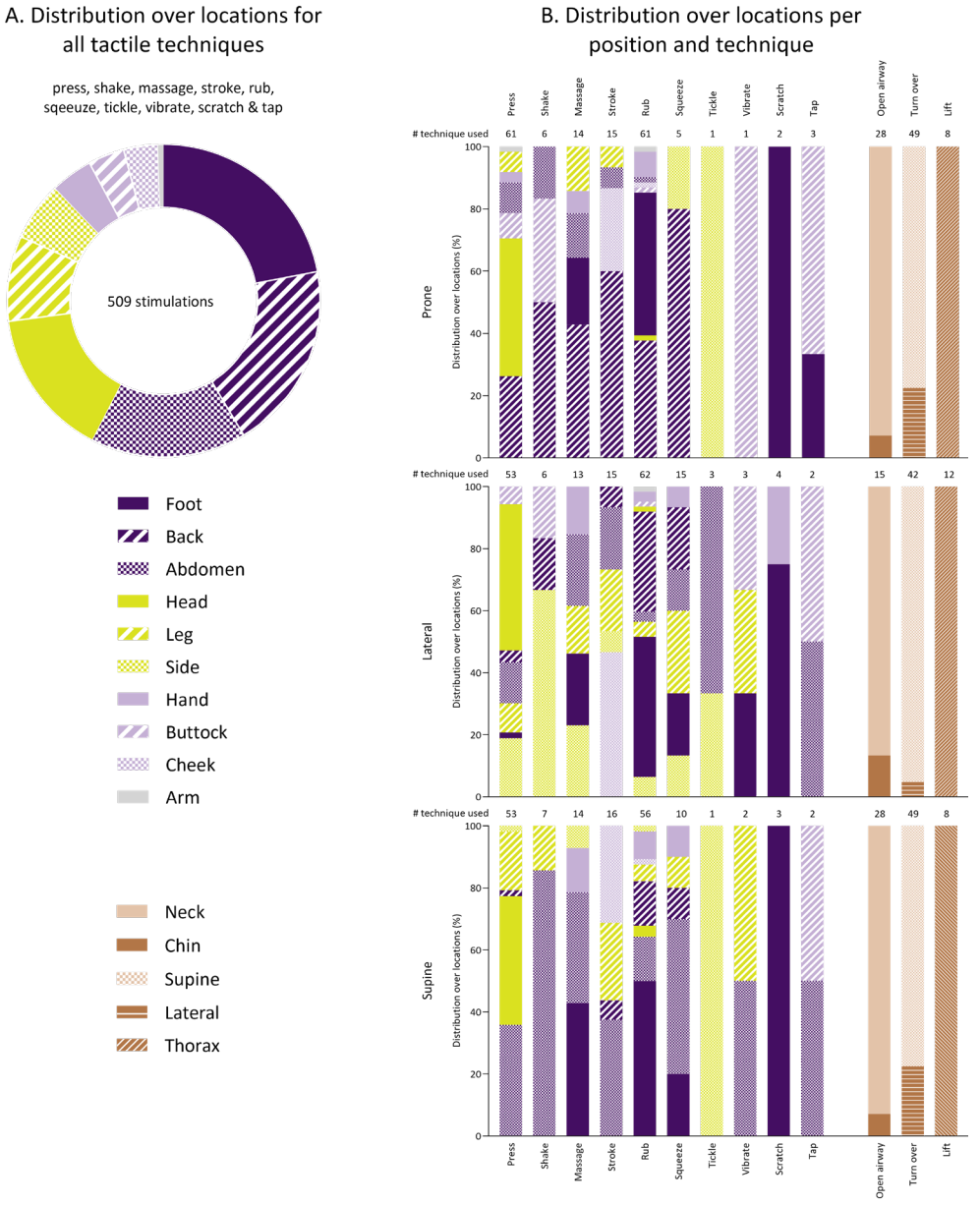

Figure 3. (a) Stimulation locations where tactile stimulation was applied with tactile techniques (press-tap) (b) Stimulation locations that were stimulated per technique and position of the infant.

their methods reflect the lack of detailed protocols, and, in turn, the lack of knowledge about neural activation and pathways to the brain's respiratory centre.

The optimal timing and most effective technique and location of tactile stimulation are currently unknown. In this study, we have provided an inventory of the tactile stimulation methods used by nurses. Although limited by the fact that apnoeic episodes were simulated with the aid of a mannikin, this study has used an objective and pragmatic approach to identify different tactile stimulation methods used by nurses following apnoea in preterm infants. As this study is performed on a small cohort of nurses from a single centre, the results are not commonly generalizable. However, albeit it is conceivable that tactile stimulation methods are more consistent between nurses in other centres, this does not alter the need for evidence instead of intuition or eminence based methods.

CONCLUSION

In conclusion, our study showed that nurses use many different tactile stimulation methods to counteract apnoea in preterm infants. The large variation can be partly explained by the fact that most nurses used multiple methods of stimulation with increasing intensity. However, we hypothesize that the large variations in practice is mainly due to the lack of clear and detailed protocols or guidelines. A prompt, adequate, and effective response is pivotal to minimizing the potentially life-long consequences of frequent or long-lasting apnoeic episodes, but the timing, location and method of stimulation are currently dependent on the discretion of the nurse. In order to improve the management of apnoea in preterm infants, large prospective studies comparing different methods of tactile stimulation should be performed in order to develop evidence-based recommendations.

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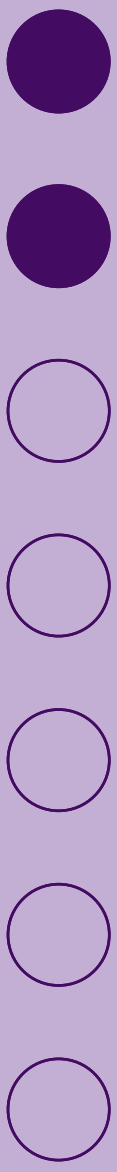

CHAPTER 2

Caregivers' response to cardiorespiratory events in preterm infants in the NICU – a quantitative overview

SJE Cramer, HA van Zanten, HH Salverda, SB Hooper, J Dekker & AB te Pas

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ABSTRACT

AIM

Cardiorespiratory events in preterm infants pose a major challenge in the Neonatal Intensive Care Unit as they require a prompt response. We aimed to describe caregivers' responses to these events.

METHODS

We performed a prospective observational study in 19 preterm infants (28 ± 2 weeks) on non-invasive respiratory support using video recordings of the inside of the incubator for 72 (55-72) hours. Caregivers' responses to these events were then identified from the videos.

RESULTS

We recorded and assessed 1851 cardiorespiratory events with a median duration of 11.0 (5.0-23.0) seconds. No response was observed in the majority of the events (91.5%). In the remaining 8.5% events, caregivers responded by pausing the alarm, adjusting devices and/or providing tactile stimulation with an average response time of 25.4 (13.8-35.9) seconds. Stimulation was the most observed response and was applied in 38 different ways. On average, stimulation lasted 18.7 (11.6-44.6) seconds and the cardiorespiratory events were resolved 30.6 (19.5-47.6) seconds after stimulation started.

CONCLUSIONS

Our study showed that cardiorespiratory events are common in preterm infants in the NICU, but often not followed by intervention of the caregiver. The indication, timing and execution of responses to cardiorespiratory events is highly variable.

INTRODUCTION

Preterm infants have difficulties establishing and maintaining regular and effective breathing due to, amongst others, the immaturity of their lungs and musculature, poor respiratory drive and increased metabolic oxygen consumption. In order to avoid potentially harmful invasive ventilation, spontaneous breathing is commonly supported by providing continuous positive airway pressure (CPAP) and/or administration of caffeine. Although these interventions are proven effective, cardiorespiratory events such as apnoea, bradycardia and desaturation remain very common [1, 2].

As frequent or long lasting events can lead to serious cerebral injury and adverse neurodevelopmental outcome [3-5], caregivers are expected to promptly intervene by providing an escalating sequence of interventions. This includes tactile stimulation, supplemental oxygen, positive pressure ventilation and eventually intubation and artificial ventilation. Manually applied tactile stimulation is the first, most frequently used and arguably the most important intervention in response to cardiorespiratory events in preterm infants. However, albeit recommended and commonly used for many years, there are no guidelines available defining when, where, how and how long to stimulate and data on when and how it is actually applied in clinical practice is lacking.

In order to design guidelines, protocols or future studies on the use of tactile stimulation, more quantitative data on the response to cardiorespiratory events in preterm infants is vital. Therefore, the aim of this study was to observe caregivers in the NICU and to provide a quantitative overview of their way of responding to cardiorespiratory events.

PATIENTS AND METHODS

STUDY SETTING

We performed a prospective observational study at the NICU of the Leiden University Medical Center (LUMC), a tertiary care centre with a total of 25 NICU beds, divided over 17 private rooms and 4 twin rooms.

All infants who are admitted to the unit are continuously monitored via a patient monitor at the bedside (Philips Intellivue MP70, Philips Medical Systems, the Netherlands). The parameters and associated alarms from the patient monitors, connected ventilators (SLE6000, SLE Limited, UK) and infusion pumps (Infusomat Space, BBraun, Germany) are aggregated at the central post (PIC iX, Philips Medical Systems, the Netherlands) and automatically logged in a data warehouse (PIIC iX, Data Warehouse Connect, Philips Medical

Systems, the Netherlands). All modes of ventilatory support are provided using the SLE6000 ventilator and can be supplemented with automated titration of the fraction of inspired oxygen (FiO2) using the embedded "OxyGenie" option. This means that the ventilator controls the FiO2 delivery in order to keep the patient within a SpO2 target range set by the caregiver. In addition to the desaturation alarms indicating a low SpO2 value, caregivers will receive oxygenation alarms indicating high FiO2 requirement or a steep increase in FiO2, hence possible deterioration of the infant.

All activated cardiorespiratory alarms are visible on the devices it originates from as well as the Philips monitor. The caregivers wear handheld devices (Xcover 3, Samsung, South-Korea), via which they receive a selection of the alarms within a few seconds after the onset. These alarms includes: apnoea, desaturation and oxygenation alarm from the ventilator, and bradycardia directly via the patient monitor. Alarms indicating a low heart frequency are only visible on the Philips monitor and not transferred to the handhelds. Apnoea alarms based on impedance via the electrocardiogram (ECG) leads are disabled. More information about the alarm settings in our unit is provided in the supplemental material (Appendix S1 and Table S1).

STUDY POPULATION AND PROCEDURES

Preterm infants born between 24 and 32 weeks of gestation, receiving non-invasive ventilation support (high flow nasal cannula (HFNC), CPAP, or non-invasive positive pressure ventilation (NIPPV)), were considered eligible for this study. As there was no data available on which to base a sample size, the observations were conducted within a predetermined period of 4 months.

The incubators of included infants were equipped with a custom-built infrared camera affixed underneath the cover at the foot end side. Video recording started at the onset of a clinical alarm and stopped 5 minutes after the most recent alarm ended. Onset and end of the alarms were detected using a light sensor placed on top of the alarm light of the patient monitor which was connected to a small computer (Raspberry Pi 3, Raspberry Pi Foundation, UK), on which the videos were temporarily stored (Figure 1). Audio was not recorded.

Infants received standard treatment and all alarm parameters, including alarm limits, delays and averaging times, were set at the discretion of the caregiver during the study. The observations were terminated when invasive ventilation was required, respiratory support was no longer needed or the infant was discharged from our NICU.

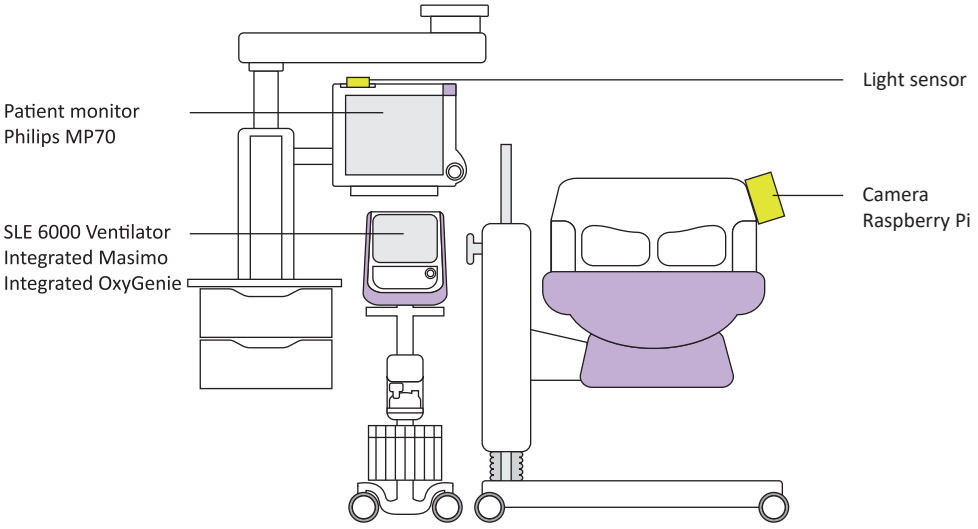

Figure 1. Study set-up

The Leiden-Den Haag-Delft Ethics Review Committee (METC LDD) issued a statement of no objection for this study (P18.182). For each infant, written informed parental consent for collecting and using patient data was acquired prior to participation.

DATA COLLECTION AND ANALYSIS

Clinical details and patient demographics were retrieved from the patient record. Oxygen saturation (SpO2), heart rate (HR), respiratory rate (RR) and FiO2, as well as the timestamps and labels of all clinical alarms were collected from the data warehouse. The recorded videos were subsequently matched to the vital signs and alarm labels based on its time stamps.

For each patient, a maximum of three consecutive days of data were used for analysis. The caregivers' bedside notes were used to select days where the patients showed cardiorespiratory instability. In case a patient was included for less than three days, all available data was used for analysis.

The detected alarms were first assessed on relevance, meaning that only cardiorespiratory alarms were selected for further analysis. Subsequently, the alarms were labelled as isolated or clustered alarms, where the latter was defined as multiple alarms starting within 15 seconds after each other. Based on the alarm labels, the alarm(s) were then classified as a type of event. We distinguished 5 different cardiorespiratory events: (1) apnoea events (consisting only of apnoea alarm(s) from the pressure breath detection of our ventilator or chest impedance), (2) bradycardia events (consisting only of low heart frequency and/or bradycardia alarm(s) from the ECG leads), (3) desaturation events (consisting only of

desaturation alarm(s) from pulse oximetry), (4) oxygenation events (consisting only of oxygenation alarms from the OxyGenie) and (5) a combination of these (i.e. a bradycardia alarm followed by an oxygenation alarm). Finally, the responses to the events were analysed using the videos. Events for which the reactive response could not be assessed were excluded from analysis. This included videos where: (1) the infant was not visible due to kangaroo care or a displaced or misfunctioning camera, (2) the caregivers were already providing care or performing a planned intervention and (3) parents were already touching the infant when the alarm went off. All assessments were performed by the same researcher (SC) and in case of uncertainty reviewed by a second researcher (JD).

For the included events, the following items were assessed: duration of the entire event (time between alarm onset and end), whether there was a response and, if applicable, the type of response, response time (time from alarm onset until a visible response), completion time (time from start response until alarm end), stimulation location, stimulation technique and stimulation duration. Stimulation location and technique were assessed using the same categories as an earlier performed study on tactile stimulation [6].

STATISTICAL ANALYSIS

All data analysis was performed using IBM SPSS Statistics V.25 (IBM, Chicago, Illinois, USA, 2021). Continuous data were given as mean ± SD or median (IQR), as appropriate. Dichotomous data were given in percentages. A binary regression was performed to predict the likelihood that a caregiver responds to an event by using the event duration. Two-tailed p-values of < 0.05 were considered statistically significant.

RESULTS

Between January and April 2019, a total of 19 infants were included in the study (baseline characteristics in Table 1). These infants generated 7286 alarms during the study period, of which 4007 (55%) alarms were considered relevant. Of these relevant alarms, 1708 represented isolated events and 2299 occurred in clusters around 750 events. In 607 of these 2458 events the response could not be assessed (235 events where the camera was blocked or turned away, 192 events where the infant was not visible in the incubator because of kangaroo care, 166 events where the caregiver was already providing regular care time and 14 events where parents were already touching the infant), resulting in 1851 events included for analysis. A visual overview of all results is presented in Figure 2.

Table 1. Patient characteristics

	n=19
Gestational age (weeks.days)[a]	28.1 (± 2.1)
Birth weight (grams)[a]	1117 (± 335)
Gender (female/male)	6/13
Postnatal age at study entry (days)[a]	14.2 (± 11.8)
Ventilation mode at study entry (NIPPV/CPAP/HFNC)	1/14/4
OxyGenie (on/off)	17/2
Hours of video monitoring per patient[b]	72 (55 – 72)

Data is presented as mean ± SD for normally distributed data (a) or median (IQR) for data that were not normally distributed (b)

EVENT TYPES AND DURATION

The total number of events consisted of 40 apnoea's, 344 bradycardia's, 855 desaturations, 311 oxygenation events and 301 combined events with an overall median duration of 11 (5-23) seconds (Table 2).

RESPONSE TYPES, RATES AND TIME

In 91.5% of the events no response was seen. In the remaining events, four types of response could be distinguished: (1) alarms were paused on the monitor without further intervention, meaning that the alarm sound was suppressed and alarm transfer to the handheld was stopped while the alarm condition was still existed (Pause; 1.8% of events), (2) medical device placement (i.e. CPAP mask and saturation probe) was checked or adjusted (Devices; 1.5% of events), (3) medical device placement was checked and tactile stimulation was provided (Devices + stimulation ; 1.1% of events) and (4) only tactile stimulation was provided (Stimulation; 4.1% of events)(Table 2). When dividing the events per type, the percentage of alarms that were responded to was 3% for apnoea, 16% for bradycardia, 2% for desaturation, 2% for oxygenation and 25% for combined events.

In general, short-lasting events (<20 seconds) were more common than longer lasting events (21-40 seconds, 41-60 seconds and >60 seconds), but were less frequently responded to (Table 3). For the events lasting >60 seconds, caregivers responded primarily to bradycardia events (11/12, 92%), followed by combination events (36/53, 68%), oxygenation events (3/6, 50%) and finally desaturation events (5/24, 21%). There were no apnoea events lasting > 60 seconds. For all 158 events that were responded to, the median response time was 25.4 (13.8-35.9) seconds.

Table 2. Event incidence, duration, response rate and response rate subdivided by event type

Event type	Number, n	Duration, median (IQR)	No response, n(%)	Response, n(%)	Response			
					Pause, n(%)	Devices, n(%)	Devices + stimulation, n(%)	Stimulation, n(%)
Apnoea	40	4 (3-7)	39 (97.5)	1 (2.5)	0 (0)	1 (2.5)	0 (0)	0 (0)
Bradycardia	344	12 (5-24)	288 (83.7)	56 (16.3)	13 (3.8)	8 (2.3)	5 (1.5)	30 (8.7)
Desaturation	855	9 (5-15)	836 (97.8)	19 (2.2)	8 (0.9)	3 (0.4)	1 (0.1)	7 (0.8)
Oxygenation	311	11 (5-20)	304 (97.7)	7 (2.3)	2 (0.6)	3 (1.0)	2 (0.6)	0 (0.0)
Combination	301	34 (20-54)	226 (75.1)	75 (24.9)	11 (3.7)	13 (4.3)	13 (4.3	38 (12.6)
Total	1851	11 (5-23)	1693 (91.5)	158 (8.5)	34 (1.8)	28 (1.5)	21 (1.1)	75 (4.1)

Table 2. Event incidence and response rate subdivided by event duration

Event duration	Number, n	No response, n(%)	Response, n(%)	Response			
				Pause, n(%)	Devices, n(%)	Devices + stimulation, n(%)	Stimulation, n(%)
0-20 seconds	1320	1305 (98.9)	15 (1.1)	8 (0.6)	3 (0.2)	0 (0)	4 (0.3)
21-40 seconds	320	273 (85.3)	47 (14.7)	14 (4.4)	8 (2.5)	4 (1.3)	21 (6.6)
41-60 seconds	116	75 (64.7)	41 (35.3)	7 (6.0)	10 (8.6)	5 (4.3)	19 (16.4)
>60 seconds	95	40 (42.1)	55 (57.9)	5 (5.3)	7 (7.4)	12 (12.6)	31 (32.6)

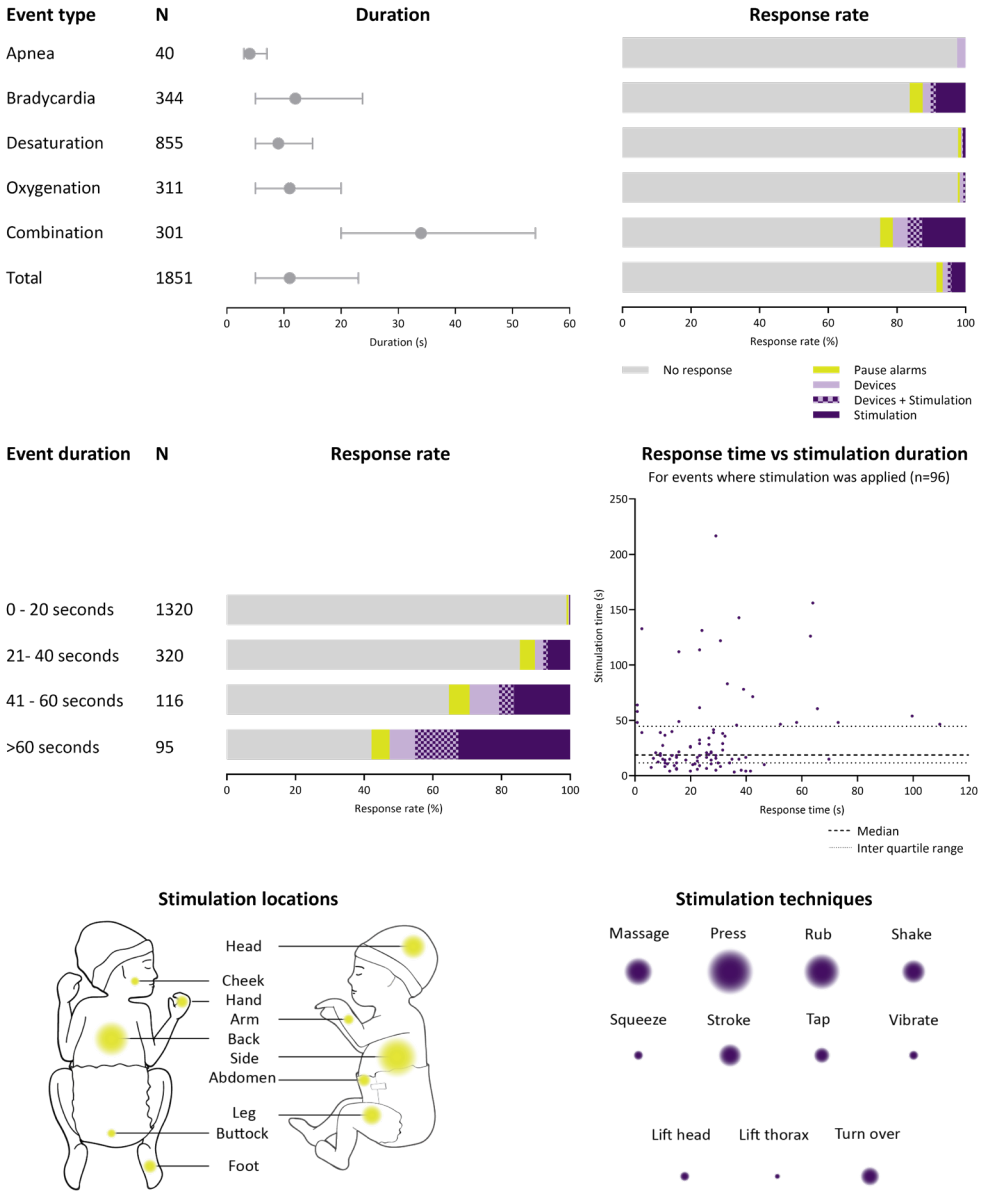

Figure 2. Overview of results showing (at the top) the number, the median (IQR) duration and response rate to the total amount of events and per event type, (in the middle) the number of events of different ranges in duration, the response rate to these events and a visual representation of the relation between event duration and response time and (at the bottom) a visual representation of the different stimulation locations and methods that where observed, with the size of the circle indicating the extent to which each occurred.

A binary logistic regression was performed to evaluate the association of the event duration on the likelihood that a caregiver responded to the alarms. The model was statistically significant, $\chi2(7)=52.4$, $p<0.001$, explained 31.8% (Nagelkerke R2) of the variance in response and correctly classified 91.5% of cases. A longer event duration was associated with an increased likelihood of response.

STIMULATION METHODS AND TIME

When tactile stimulation was applied following an event, this consisted on average of 2 (1-3) sequentially applied stimulation methods. There were 38 different methods observed, of which 35 consisted of a combination of 1 out of 10 identified stimulation locations and 1 out of 8 identified stimulation techniques (Figure 2). The other three methods involved interventions with a location specific tactile component: supporting the head, lifting the thorax and turning over to side or back.

The most selected locations for stimulation were the side (50%), back (40%) and head (20%) of the infants (Figure 2). Providing pressure on the skin, rubbing the skin and massaging the skin were the most used stimulation techniques (64%, 39%, 24%). Overall, the most common stimulation methods seen were providing pressure on the side (32%), rubbing the back (23%), providing pressure on the head (19%), massaging the side (15%) and shaking the side of the patient (11%).

Tactile stimulation lasted on average 18.7 (11.6-44.6) seconds per event and the completion time following stimulation was on average 30.6 (19.5-47.6) seconds.

DISCUSSION

This is the first study to provide a detailed description of current practice on how caregivers respond to cardiorespiratory events within a NICU. Using video recordings, we observed four ways of responding to cardiorespiratory events, of which providing tactile stimulation was most frequent provided, although with a large degree of variability in the way it was executed. However, our most important finding is that for the vast majority of events (>90%), no active response was provided, although longer event durations were associated with an increased likelihood of response.

Previous studies that looked at the response rate of NICU caregivers to alarms in general [7], and to hypoxia [8] and bradycardia [9] alarms specifically, reported similar results. From our data we hypothesize several different causes that could be responsible for the low response rate that is generally reported. Firstly, the majority of events in this population are short-lived and therefore likely to be resolved before a caregiver is able to respond.

This is reflected by the fact that the median duration of events in our study was 11 seconds while the average response time was 25 seconds. Another explanation is that caregivers deliberately wait to intervene to see whether the patient recovers on its own in order to minimize unnecessary interruptions in their work [7] and/or with the intention of minimal handling. This could clarify why in our study caregivers responded by pausing the alarms but refrained from intervening thereafter. However, the fact that in 40% of long-lasting events (>60 seconds) any form of response was omitted makes it plausible that unintentional non-response due to for example alarm fatigue or high workload also frequently occurs [7, 10].

In addition to pausing the alarms, caregivers responded by checking and adjusting medical devices on the infant, providing stimulation or a combination of both. While the idea of adjusting the medical devices is probably to remove (possible) external causes of the event, such as a displaced and leaking CPAP mask, tactile stimulation is provided in order to assist the recovery of the patient. Manually providing NIPPV or increasing the FiO2 level would serve the same goal, but these responses were not observed in our study. We assume that this is the result of utilizing the OxyGenie algorithm in 17/19 of the included patients, acting directly on a fall in SpO2. Although caregivers can manually override the FiO2 settings of the algorithm, a previous study in our centre showed that this is rarely done [11]. In addition, applying Oxygenie is probably the reason why tactile stimulation was mainly observed in response to bradycardia and combined events, particularly as it is believed to positively affect respiratory effort and oxygenation [12-15]. The relatively high response rate to bradycardia events, including both HR<80 and HR<100 alarms, stands out because HR<100 alarms were not transferred to the caregivers' handhelds and thus may have resulted in less and/or delayed awareness compared to apnoea, desaturation and oxygenation events. It is possible that the caregivers consider a high chance of spontaneous recovery without (tactile) intervention and rely on the automated response of the Oxygenie, even in the case of long lasting desaturation.

In accordance with previously reported manikin studies [6, 16], our data shows that when caregivers do choose to apply tactile stimulation, they use a wide range of different methods. Contrary to what caregivers showed on a manikin, stimulation was most commonly applied to the torso and in the majority of cases consisted of at least providing static pressure. Very vigorous interventions, such as turning over the infant or lifting the thorax were far less common. On average, the stimulation duration was shorter than the completion time of the event, which again seems to imply that caregivers are reticent in intervening.

Recognizing it is impossible for caregivers to respond to all events, it is unclear whether the apparent current reticence and prudence regarding active intervention is justified and desirable. While evidence exists that excessive exposure to stimuli is associated with adverse

consequences in the short and long term [17-19], others report beneficial effects of tactile intervention [20-23]. Despite the fact that caregivers focus mainly on longer events, short-lasting and self-limiting events might also benefit from active intervention as they contribute substantially to physiological instability – and thus clinical outcome – given their numerical preponderance [24]. Automated response systems could aid the caregiver in maintaining or restoring cardiorespiratory stability of the patient. However, the trade-off between the possible burden and benefit of timely intervention needs further research.

This study is limited by the fact that it is a single-centre design, in which the results are affected by a wide range of factors that are unique for our unit, particularly the use of automated oxygen supply, type of monitoring devices used, alarm settings, architectural ward layout, patient population and alarm culture [7, 8, 25-30]. The distribution of the number of alarms in our study is however exemplary for a preterm population, with the vast majority of events being due to desaturation, followed by bradycardia and apnoea . The proportion of apnoea events is indeed low, which is likely attributable to the fact that apnoea alarms based on respiratory impedance are silenced in our unit and the ventilator's apnoea alarm is only activated by default during NIPPV. Finally, the caregivers might have adjusted their behaviour due to awareness of the recordings. However, we expect this effect to be small, given the long study duration and the placement of the camera underneath the covers of the incubator. Although our results require verification by other NICU's, it gives a unique first impression of the reactive responses to cardiorespiratory events in preterm infants.

CONCLUSION

We observed caregivers in the NICU using a video-observation study in order to quantify their responsiveness to cardiorespiratory events. In >90% of the recorded events no response was observed, although an increased event duration was associated with a higher response rate. Tactile stimulation was the most performed intervention, but with a large variability in execution. Our results emphasize that the indication, timing and execution of responses to cardiorespiratory events in preterm infants is very subjective and optimal response to these events is currently unknown.

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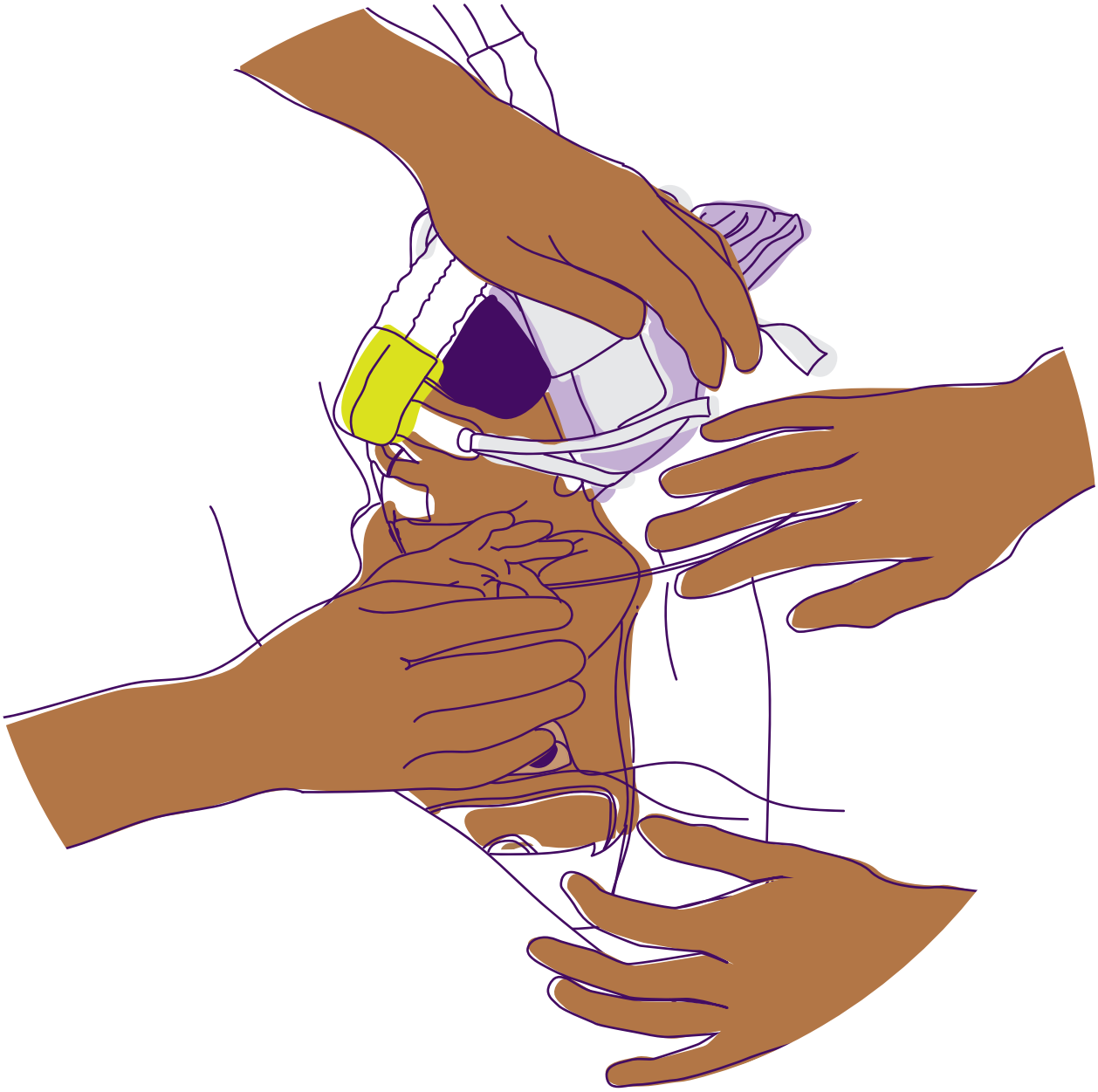
SUPPLEMENTAL MATERIAL

CARDIORESPIRATORY ALARM SETTINGS

Alarms that are activated for cardiorespiratory monitoring by default are (1) low heart frequency (HF<100 bpm) and bradycardia (HF<80 bpm) alarms originating from the electrocardiogram (ECG) signal via the Philips monitor, (2) desaturation alarms (SpO2<90%) originating from the ventilator's built-in pulse oximeter (Masimo SET, Masimo, USA), (3) alarms indicating an (automated) increase in FiO2 above a set limit (FiO2>0.6) originating from the ventilator and (4) alarms indicating a steep automated increase in FiO2 (0.05 over 30 sec) originating from the ventilator. Apnoea alarms based on impedance from the ECG leads are disabled but apnoea alarms originating from the ventilator's pressure breath detection module (no breaths detected for 15 sec) are occasionally activated on discretion of the caregiver. Only a selection of these alarms is transferred to the handhelds of the caregivers, including apnoea, bradycardia, desaturation and alarms related to the automated FiO2 titration. During the study, caregivers were allowed to deviate from the default settings as we were primarily interested in the response to the alarm, irrespective of its limit.

Table S1. Overview of cardiorespiratory alarm settings

Event type used for data analysis	Alarm type	Detection method	Device	Default alarm limit	Status	Transferred to handheld caregivers	Delay/
Apnoea	Apnoea	Impedance via ECG leads	Philips patient monitor	-	Disabled	No	N/A
	Apnoea	Breath detection via a pressure line	SLE 6000	No breath detected for 15 seconds	Activated on discretion of the caregiver	Yes	None/None
Bradycardia	Low heart rate	ECG	Philips patient monitor	<100 bpm	Activated by default	No	None/12 most recent R-R intervals
	Bradycardia	ECG	Philips patient monitor	<80 bpm	Activated by default	Yes	None/12 most recent R-R intervals
Desaturation	Desaturation	SpO2 via pulse oximeter	Masimo SET module build in SLE6000 ventilator	<90%	Activated by default	Yes	None/2-4 seconds
Oxygenation	High FiO2 requirement	Oxygen sensor	SLE6000, Oxygenie	FiO2 > 0.6	Activated when OxyGenie is used	Yes	None/None
	Steep automated FiO2 increase	Oxygen sensor	SLE6000, Oxygenie	0.05 increase over 30 seconds	Activated when OxyGenie is used	Yes	None/None



PART 3

CHAPTER 3

Effect of tactile stimulation on termination and prevention of Apnoea of Prematurity: a systematic review

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ABSTRACT

Apnoea of prematurity is one of the most common diagnoses in preterm infants. Severe and recurrent apnoea's are associated with cerebral injury and adverse neurodevelopmental outcome. Despite pharmacotherapy and respiratory support to prevent apnoea's, a proportion of infants continue to have apnoea's and often need tactile stimulation, mask and bag ventilation and/or extra oxygen. The duration of the apnoea and the concomitant hypoxia and bradycardia depends on the response time of the nurse. We systematically reviewed the literature with the aim of providing an overview of what is known about the effect of manual and mechanical tactile stimulation on apnoea of prematurity. Tactile stimulation, manual or mechanical, has been shown to shorten the duration of apnoea, hypoxia and or bradycardia or even prevent an apnoea. Automated stimulation, using closed-loop pulsating or vibrating systems, has been shown to be effective in terminating apnoea's, but data are scarce. Several studies used continuous mechanical stimulation, with pulsating, vibrating or oscillating stimuli, to prevent apnoea's, but the reported effect varied. More studies are needed to confirm whether automated stimulation using a closed loop is more effective than manual stimulation, how and where the automated stimulation should be performed and the potential side effects.

INTRODUCTION

Almost all infants born at <28 weeks gestational age or with a birth weight of <1000g are diagnosed with Apnoea of Prematurity (AOP) [1]. The American Academy of Pediatrics defines apnoea as a cessation of breathing for 20 seconds or a shorter pause accompanied by bradycardia, cyanosis or pallor [2]. Based on their origin, apnoeic spells are classified as central, obstructive or mixed. Central apnoea is distinguished by a cessation of airflow due to absence of respiratory drive, obstructive apnoea is characterized by impeded airflow caused by closure of the upper airways and mixed apnoea implies that central respiratory pauses are followed by obstruction in the upper airways or vice versa [3-5]. Studies have shown that most of the apnoea' s in a preterm infant have a mixed character, starting with a central or an obstructive episode [6].

The aetiology is related to the immaturity of respiratory control and poor myelination of the brainstem [5, 7] but the exact responsible mechanisms are still not fully understood [5, 8]. Although apnoea generally resolves with maturation, it is one of the most common diagnoses and therefore a major concern in the Neonatal Intensive Care Unit (NICU) [4, 8, 9]. Frequent apnoeic spells can lead to serious cerebral injury and affects neurodevelopmental outcome [10-12]. It has been postulated that the adverse outcome is not caused by the apnoea itself but the associated recurrent hypoxia [4, 9, 13].

In most NICU's both pharmacotherapy and breathing support are used to prevent recurrent AOP. Despite these preventative interventions, a proportion of infants continue to have apnoea [14], which requires further intervention of the caregiver. The termination of apnoea is accomplished by tactile intervention of the nurse, often combined with extra oxygen and, if needed, mask ventilation [6, 15-17]. The duration of the apnoea and the concomitant hypoxia and/or bradycardia is then dependent on the response time of the nurse. Heavy workload and alarm fatigue might have a negative influence on prompt and adequate treatment of apnoea's [18]. The longer the delay in response time, the longer the total duration of apnoea and the lower the peripheral oxygen saturation (SpO2) values [19]. Also, administration of tactile stimulation increases the risks of infection due to cross-contamination and will interrupt sleep, which can be disadvantageous for the growth and development of the infant [20].

Mechanical stimulation might improve the common used and effective tactile stimulation technique by enabling a direct response, as this will shorten the apnoea hence reducing hypoxia and bradycardia. In addition, combining mechanical stimulation with the detection of imminent apnoea could lead to preventive stimulation methods. The effect of mechanical tactile stimulation on apnoea has been studied but has not led to implementation in the

NICU or a commercially available device yet.

We systematically reviewed the literature with the aim of providing an overview of what is known about the effects of manual and mechanical tactile stimulation on the termination and prevention of apnoea in preterm infants.

METHODS

In order to identify convenient studies the online databases MEDLINE, PubMed and Scopus were searched for English articles from 1970 to 2017, using the search strategy as described in Table 1. The time span was based on the results of a Cochrane review of kinaesthetic stimulation to treat AOP [21]. A manual search of the references and citations of the selected articles was performed to collect other possible relevant literature. Unpublished data were not considered for this review.

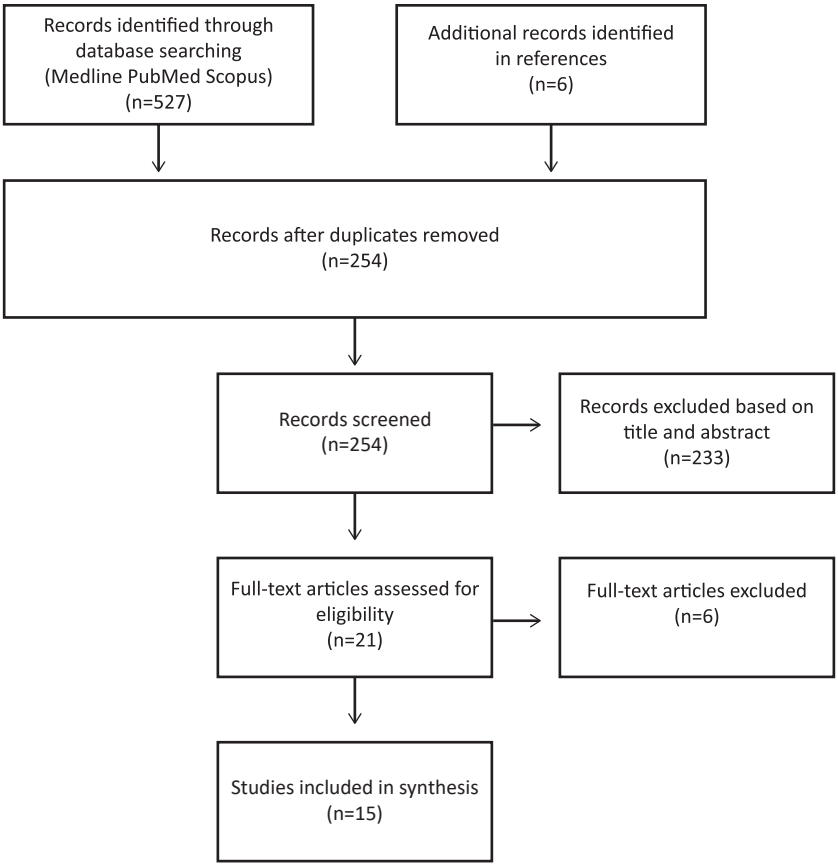

Figure 1. Flowchart of article selection

Table 1. Search strategy

Database	Keywords	Hits
Medline	(touch OR touching OR touches OR touched OR rub OR rubbing OR rubbed OR scratch OR scratched OR scratching OR cutaneous OR skin OR mechanosensory OR vibration OR vibrating OR vibratory OR vibrotactile OR foot OR feet OR sole OR back OR thorax OR arousal OR stochastic resonance).ti,ab. AND (vibration OR vibrations OR vibratory OR vibrate OR vibrates OR vibrated OR physical stimulation OR stimulation OR stimulations OR stimulate OR stimulates OR stimulated OR stimulus OR stimuli OR system).ti,ab. AND (apnoea OR apnoea OR breathing OR breath OR breathe OR breathes OR breathed).ti,ab. AND (premature OR prematures OR prematurity OR preterm OR preterms OR neonate OR neonates OR neonatal OR infant OR infants).ti,ab. AND (treat OR treatment OR treating OR treated OR interrupt OR interruption OR interrupting OR interrupted OR stabilize OR stabilizing OR stabilized OR analyze OR analysis OR analyzing OR analyzed OR transform OR transformation OR transforming OR transformed OR generate OR generation OR generating OR generated OR effect OR effects OR effecting OR effected).ti.ab.	105
PubMed	("touch"[mesh] OR "touch"[tw] OR "touching"[tw] OR "touches"[tw] OR "touched"[tw] OR "rub" [tw] OR "rubbing" [tw] OR "rubbed" [tw]OR "scratch" [tw] OR "scratched" [tw] OR"scratching" [tw] OR "cutaneous"[tw] OR "skin"[tw] OR "mechanosensory"[tw] OR"vibration" [tw] OR "vibrating" [tw] OR "vibratory" [tw] OR "vibrotactile" [tw] OR "foot"[mesh] OR "foot"[tw] OR "feet"[tw] OR "sole"[tw] OR "back" [tw] OR "thorax" [tw] OR "arousal"[mesh] OR "arousal"[tw] OR "stochastic resonance" [tw]) AND ("vibration"[mesh] OR "vibration"[tw] OR "vibrations"[tw] OR "vibratory"[tw] OR "vibrate"[tw] OR "vibrates"[tw] OR "vibrated"[tw] OR "physical stimulation"[mesh] OR "stimulation"[tw] OR "stimulations"[tw] OR "stimulate"[tw] OR "stimulates"[tw] OR "stimulated"[tw] OR "stimulus"[tw] OR "stimuli"[tw] OR "system"[tw]) AND ("apnoea"[mesh] OR "apnoea"[tw] OR "apnoea"[tw] OR "breathing"[tw] OR "breath"[tw] OR "breathe"[tw] OR "breathes"[tw] OR "breathed"[tw]) AND ("infant, premature"[mesh] OR "premature"[tw] OR "prematures"[tw] OR "prematurity"[tw] OR "preterm"[tw] OR "preterms"[tw] OR "neonate"[tw] OR "neonates"[tw] OR "neonatal"[tw] OR "infant"[tw] OR "infants"[tw]) AND ("treat"[tw] OR "treatment"[tw] OR "treating"[tw] OR "treated"[tw] OR "interrupt"[tw] OR "interruption"[tw] OR "interrupting"[tw] OR "interrupted"[tw] OR "stabilize"[tw] OR "stabilization"[tw] OR "stabilizing[tw]" OR "stabilized"[tw] OR "analyze"[tw] OR "analysis"[tw] OR "analyzing"[tw] OR "analyzed"[tw] OR "transform"[tw] OR "transformation"[tw] OR "transforming"[tw] OR "transformed"[tw] OR "generate"[tw] OR"generation"[tw] OR "generating"[tw] OR "generated"[tw] OR "effect"[tw] OR "effects"[tw] OR "effecting"[tw] OR "effected"[tw])	190
Scopus	TITLE-ABS("touch" OR "touching" OR "touches" OR "touched" OR "rub" OR "rubbing" OR "rubbed" OR "scratch" OR "scratched" OR"scratching" OR "cutaneous" OR "skin" OR "mechanosensory" OR "vibration" OR "vibrating" OR "vibratory" OR "vibrotactile" OR "foot" OR "feet" OR "sole" OR "back" OR "thorax" OR "arousal" OR "stochastic resonance") AND TITLE-ABS ("vibration" OR "vibrations" OR "vibratory" OR "vibrate" OR "vibrates" OR "vibrated" OR "physical stimulation" OR "stimulation" OR "stimulations" OR "stimulate" OR "stimulates" OR "stimulated" OR "stimulus" OR "stimuli" OR "system") AND TITLE-ABS ("apnoea" OR "apnoea" OR "breathing" OR "breath" OR "breathe" OR "breathes" OR "breathed") AND TITLE-ABS ("premature" OR "prematures" OR "prematurity" OR "preterm" OR "preterms" OR "neonate" OR "neonates" OR "neonatal" OR "infant" OR "infants") AND TITLE-ABS ("treat" OR "treatment" OR "treating" OR "treated" OR "interrupt" OR "interruption" OR "interrupting" OR "interrupted" OR "stabilize" OR "stabilizing" OR "stabilized" OR "analyze" OR "analysis" OR "analyzing" OR "analyzed" OR "transform" OR "transformation" OR "transforming" OR "transformed" OR "generate" OR "generation" OR "generating" OR "generated" OR "effect" OR "effects" OR "effecting" OR "effected")	153

All clinical trials reporting the effects of tactile stimuli on apnoea in premature infants or animals were included in this review. Studies using devices that are believed to affect the breathing patterns by other forms of stimulation that involved a tactile component, like oscillating waterbeds, were included. Clinical trials examining the effect of stimulation of multiple senses on apnoea were excluded. The same applied to articles comparing only the effects of tactile stimulation with stimulation of another sense. Abstracts or other forms of articles that are not primary research studies were also excluded. Two authors (SC, AtP) reviewed the records for inclusion and exclusion criteria, and disagreements were resolved by consensus.

Study characteristics from the included studies were identified using a data extraction form. The following data were extracted: author, year, study objects, study design, detection signals, stimulation mode, stimulation characteristics, duration and main results.

RESULTS

The search strategy led to 448 articles. Five additional articles were selected from the references of the studies that met the inclusion criteria. After elimination of the duplicates, a selection of twenty-one articles was made based on title and abstract. Another six articles were excluded following full-text assessment, resulting in a selection of fifteen articles for this review (Figure 1). Four of these studies investigated the effect of tactile stimulation on the termination of apnoea and eleven focussed on the effect on the prevention of apnoea.

Combining the data of the studies for a meta-analysis was not possible since there was no homogeneity in study designs, study objects, mode of stimulation and measure for effect size. For this reason the results were reviewed in a narrative format, where we report separately for the terminating and the preventing apnoea's. The extracted data of the articles are summarized in Table 2 and 3.

TERMINATION OF APNOEA

Four studies were included that provided tactile stimulation in order to terminate apnoea in 13 preterm infants. The sample size ranged from 1 to 4 infants with a median of 4 infants. The mean gestational age varied between studies from 28 to 31.25 weeks and the mean birth weight varied from 1280 to 1495.5 grams. Two studies only reported inclusion criteria instead of mean values for gestational age and birth weight [19, 22]. In one study, aminophylline was administered during the study, which started seven days after birth [23]. Frank et al. only included sleeping infants [24].

STUDY DESIGNS

The included studies described different study designs: two observational [22, 24] and two randomized crossover studies [19, 23]. In the observational studies the amount of successfully terminated apnoea's were compared with the total amount of apnoea's. In the randomized crossover studies, the infants were stimulated alternately by hand or with an automatic device for a set time. Lovell et al. (1999) used periods of 8 hours with a total time of 16 hours [23] and Pichardo et al. (2003) used periods of 12 hours with a total time of 24 hours [19].

STIMULATION SYSTEMS

There was a considerable variation between the studies in the detection of apnoea's and stimulation systems used. Camargo et al. (2014) used heart rate and oxygen saturation measurements to identify apnoea [22]. A decrease in oxygen saturation or heart rate below the set of 80% and 80 or 100 bpm automatically actuated a vibrating disk attached to the infants' thorax, which exerts a vibration of 250 Hz for 4 seconds. Frank et al. (1973) also used a closed-loop system [24]. Breathing pauses were identified by impedance plethysmography. Exceeding of the set threshold, ranging from 5 to 15 seconds, automatically actuated a balloon placed under the neck of the infant, which then inflated and deflated three times. The remaining two studies used similar systems, which were manually actuated by the nurses. Lovell et al. (1999) recorded heart rate and oxygen saturation and used a 3-sec vibrating stimulus of 250Hz at the foot sole [23]. Pichardo et al. (2003) additionally recorded airflow, ECG and thoracic impedance and used the same apparatus with the same stimulus but applied it at the thorax [19].

EFFECT

The pulsating balloon of Frank et al. (1973), placed underneath the neck, led to resumption of breathing in 99 of the 105 detected apnoeic spells [24]. Camargo et al. (2014) observed resumption of breathing following vibratory stimulation in 9 of 10 apnoea's [22]. The other two studies reported that the vibrating stimulation was as effective as manual stimulation in aborting apnoeic spells [19, 23], but that the duration of the vibratory stimulus was shorter than the manual stimulation. The response time for mechanical stimulation was shorter than for manual stimulation in the study of Pichardo et al. (2003) while in the study of Lovell et al. (2001) they were of equal duration [23].

Table 2. Termination of apnoea

Author / Study design	Study objects	Detection signals	Stimulation characteristics	Duration / Stimulation time	Results of stimulation
Camargo, V.C. et al. 2014 Observational study	4 infants GA inclusion: <36,6 weeks Weight inclusion: <2500 g	PF by oximeter SpO2 by oximeter	Instrument: VBW32 skin transducer, Audiological Engineering Location: Thorax Stimulus: 4s, 250 Hz	Stimulation: 4 s	*Apnoea (HR<100bpm, SpO2<80 % for <35 weeks, HR<80bpm, SpO2< 80 % for >35 weeks):* Resumption of breathing in 9 of 10 apnoeic episodes
Pichardo, R. et al. 2003 Randomized crossover study	4 infants GA inclusion: >28 weeks Weight inclusion: >1000g	AF HR by chest leads and saturation probe SpO2 ECG Thoracic impedance	*Mechanical* Instrument: VTS transducer VBW32, Audiologic Engineering Location: Thorax Stimulus: Not described *Manual* No specifications	Stimulation: 3s Mode switch: after 12 hrs or after 5 apnoeic attacks Duration: 24 hrs Repetitions: 2x for one infants	*Apnoea:* Similar effectiveness in ending apnoeic spells (p=0.62) Significant decrease in stimulus duration (p<0.001) Decrease in reaction time to apnoeic spell (p=0.058)
Lovell, J. et al. 1999 Randomized crossover study	1 infant GA: 28 weeks Weight: 1280g Day start study: 7 Treatment: Aminophylline, first two days on CPAP	RR HR SpO2	*Mechanical* Instrument: Model 1220 Audiological Engineering Location: Sole of the foot Stimulus: 250 Hz square wave, impedance of 22 Ohms (vts) *Manual* Location: trunk and extremities Stimulus: gentle to vigorous stroking or shaking of the trunk and/or extremities (manual)	Stimulation: approximately 3 sec Mode switch: after 8 hours Duration: 16 hours Repetitions: three times after 2, 6 and 11 days	*Apnoea (>20 sec or <20 sec + bradycardia/IH):* Similar effectiveness in ending apnoeic spells (p>0.05) Decrease in stimulation time of 3,9 sec (p=0.05) Similar reaction time (p=0.93) Similar time to termination (p=0.67) Similar apnoea duration (p=0.94)

Author / Study design	Study objects	Detection signals	Stimulation characteristics	Duration / Stimulation time	Results of stimulation
Frank, U.A. et al. 1973 Observational study	4 infants GA: 31.25 weeks Weight: 1495.5 g All infants asleep	RR by impedance plethysmography	Instrument: balloon with a towel. Location: transversely under the neck Stimulus: 4 psi pressure source, inflation in 0,5s	Stimulation: 3 pulses	*Apnoea (10 sec, sometimes 5 or 15 sec):* Resumption of breathing in 99 of the 105 apnoeic episodes

PREVENTION OF APNOEA

In total 11 studies investigated the prevention of apnoea by tactile stimulation and included 290 preterm infants. The sample size ranged from 6 to 122 infants with a median of 15 infants. The mean/median gestational age varied between studies from 28 to 32.1 weeks. Three studies reported the gestational age at the start of the study, ranging from 32 to 35 weeks [14, 25, 26] and five studies reported the (mean/median) age when the study started, ranging from 4.3 to 35 days after birth [27-31]. The mean/median birth weight also differed between studies from 1080 to 1760 grams. Three studies reported a mean weight of 1264 to 2013 grams at the start of the study [14, 26, 29]. In a number of studies (some of) the infants were supported by means of: administered caffeine [14, 25, 26], theophylline [28, 30, 32, 33] or antibiotics [29], supplemental oxygen [14, 25, 26] and CPAP or assisted ventilation [27, 32, 33].

STUDY DESIGNS

The following study designs were used in the included preventative research: two randomized controlled trials [33, 34], three counterbalanced quasi-experimental studies [27-29] and six crossover studies of which four were randomized [14, 25, 26, 30] and two were quasi-experimental [31, 32]. In most of these studies, the data of equal lasting periods with and without stimulation were compared. The shortest on/off period took 10 minutes with a total duration of one hour [26] and the longest four days with a total duration of eight days [28]. Kattwinkel et al. (1975) stimulated 5 out of 15 minutes instead of continuous stimulation during the stimulation period. In the controlled randomized trials half of the included infants only received continuous stimulation, which lasted for 7 days [33, 34].

STIMULATION SYSTEMS

Only one study used manual stimulation, which was accomplished by rubbing the extremities of the infant [31]. Cardiorespiratory monitoring and heart rate and respiratory pneumograms were used to detect apnoea. All other studies used mechanical ways of continuous stimulation composed of the following: a cuff placed

Table 2. Prevention of apnoea

Author / Study design	Study objects	Detection signals	Stimulation characteristics	Duration / Stimulation time	Results of stimulation
Kasevan, K, et al. 2016 Randomized crossover study	15 infants GA: 29.0±2.5 weeks Weight: 1257±535 g Study age: 32±2.3 weeks Treatment: 12 caffeine, 12 supplemental oxygen	RM by thoracic wall movement measurement HR via 3 leads SpO2 by pulse oximetry ECG signals	Instrument: Vibrating disk (10x10x3mm) connected to vibration motor Location: Palm or wrist of one hand and the ankle or sole of the foot at the same side Stimulus: 0.3 gm/128 Hz vibration	Stimulation: 6 hrs alternatively on or off Duration: 24 hrs	*Breathing pauses – significant reduction of:* Amount >5sec by39%(p<0.001); Amount 3-5 sec by 21%(p=0.024) Duration >5sec by 36%(p<0.001); Duration 3-5 sec by 20% (p=0.034) *IH – significant reduction of:* Amount <90% by 28% (p=0.001); <88% (p=0.001); <85% (p<0.001) Duration <90% by 30% (p=0.002); <88% (<=0.001); <85% (p=0.023) *Bradycardia – significant reduction of:* Amount <110 bpm (p=0.001); <100 bpm (p=0.002) Duration <110 bpm (p=0.003); <100 bpm (p=0.006)
Smith, V. et al. 2015 Randomized crossover study	36 infants GA: 30.5±2.9 weeks Weight: 1409±450 g Study age: 35.0±1.5 Study weight: 2013±453 Treatment: 13 caffeine, 5 supplemental oxygen	RR by VueLogger system HR SpO2 ECG Pulse plethysmography	Instrument: 13 TheraSound mattress, 23 custom build mattresses Location: Not described Stimulus: Displacements with frequency bandwidth of 30-60Hz and displacements of 10-20 microns	Stimulation: 30 min alternately on or off Duration: 3-4 hrs	*Breathing pauses* Reduction amount of pauses >10 sec by 50% *IH (<87% for >35 weeks GA, <90% for <35 weeks GA) – significant reduction of:* Amount by 18% (p=0.01), duration by 35% (p<0.0001), intensity by 21% (p<0.0001) *Bradycardia (<80 bpm for >34 weeks GA, <100 bpm for <34 weeks):* No change in amount and duration of bradycardia Significant reduction intensity of bradycardia of 20% (<0.0001) *Other:* No significant effect of supplemental oxygen, caffeine, pma and weight. Significant effect of light on duration and intensity IH Significant effect of sound on duration of IH

Author / Study design	Study objects	Detection signals	Stimulation characteristics	Duration / Stimulation time	Results of stimulation
Bloch-Salisbury, E. et al. 2009 Randomized crossover study	10 infants GA:30.1±1.9 weeks Weight: 1348±497g Study age: 33.1±1.7 weeks Study weight: 1500±441g Treatment: 1 nasal cannula oxygen, 3 caffeine before test	RM by respiratory inductance plethysmography AF & CO2 by thermistor or cannula PF by pulse oximeter SpO2 by pulse oximeter Skin temperature by temperature probe	Instrument: Therasound mattresses Location: Chest, side or back, depending on position Stimulus: Filtered white noise, 30-60 Hz band, stimulus intensity of 0.021mm RMS, 0.090mm max displacement	Stimulation: 10 min alternately on or off Duration: 1 hr Repetitions: 8 of 10 infants completed the experiment twice	*Interbreath intervals – a significant reduction of:* Variance IBI's (p=0.024) Amount IBI's; >5sec (p=0.013); >10sec (p=0.042) *IH – a significant reduction of:* Amount of time O2<85% (p=0.04) *Bradycardia:* Reduction in pulse rate variance (p=0.086) Mean pulse rate was unaffected by stimulation (p=0.14) *Other:* No significant changes in behavioural state or EEG power spectra during stimulation transitions No significant changes in skin temperature
Svenningsen, N.W. et al. 1995 Quasi-experimental cross-over study	12 infants GA: 31.1 weeks Weight: 1.760g Treatment: 6 theophylline, 4 CPAP	Cardio-respirography and concomitant oxygen	Instrument: OSCILLO-unit (electronic membrane pump with 2 pneumatic valves for in- and outflow of an airfilled mattress) Location: Not described Stimulus: oscillation amplitude 10-100%, frequency 5-20 times/ min, high frequency vibrations 8-10Hz	Stimulation: 12 hours (24 hours for 9 infants) Control: 24 hours before stimulation	*Apnoea (pause of >20 sec + <85% O2 + decrease in HR of >20 bpm):* Mean apnoeic attacks control period: 8,4 per 12 hours Mean apnoeic attacks first 12 h stimulation period: 3,0 per 12 hours Mean apnoeic attacks second 12 h stimulation period: 3,8 per 12 hours *Other:* 3 infants showed restlessness after stimulation 4 infants increased intra-arterial blood pressure around 5mm Hg

Author / Study design	Study objects	Detection signals	Stimulation characteristics	Duration / Stimulation time	Results of stimulation
Jirapaet, K. 1993 Quasi-experimental counter-balanced cross-over study	29 infants GA: 32.1±1.8 weeks Weight: 1474±331 g Day start study: 4.3±3.0 days Treatment: 2 assisted ventilation	AF by thermistor HR and breathing effort by apnoea monitor (model 500, corometrics) SpO2 by oximeter	Instrument: blood pressure cuff connected to bird's mark 8 respirator which in and deflates the cuff Location: under upper thorax Stimulus: in and deflates 16+4 times per min, regular vertical wave motion of 1cm at the cuff surface	Stimulation: 6 hours alternatively on or off Duration: 24 hours	*Apnoea (HR<100 bpm or pause >15 sec):* Significant reduction of apnoeic episodes during stimulation (p<0.000) Significant reduction of central apnoea's (p<0.000) and mixed apnoea's (p<0.000) No effect on obstructive apnoea's (p=0.316)
Saigal, S. et al. 1986 Controlled randomized clinical trial	122 infants Exp. group (n=59) GA: 30.5±3.2 weeks Weight: 1294±266 Medicines: 28 theophylline, 20 CPAP/IPPV Control group (n=63) GA: 31.0±2.7 weeks Weight: 1299±41 Treatment: 22 theophylline, 12 CPAP/IPPV	Cardiorespiratory impedance Cardio-respirography for 6-hous between study days 1-3, 4-7, 8-12 and after 13 days to check nurses administration	*Experimental group* Instrument: oscillating air mattresses Location: not described Stimulus:14-16 pulses/min, longitudinal wave motions *Control group:* Conventional mattress, no stimulation	Stimulation: 7 days or more (until discharge)	*Apnoea:* No significant reduction in amount apnoea 10 -19sec No significant reduction in amount apnoea > 20 sec No significant reduction in amount apnoea >10 + bradycardia *Other:* No significant differences in weight gain No significant differences in proportions time in sleep states and state changes

Author / Study design	Study objects	Detection signals	Stimulation characteristics	Duration / Stimulation time	Results of stimulation
Korner, A.F, et al. 1982 Quasi-experimental counter-balanced cross-over study	17 infants GA: 29 weeks Weight: 1159 g Day start study: 35 days Treatment: all theophylline for 6-71 days	RR HR Visual observations for 100 min on 3rd and 4th day after feeding	Instrument: Water bed, consist of high impact styrene shell and vinyl bag with small inflatable bladder at the foot connected to an electronic oscillator. Location: Not described Stimulus: continuous gentle irregular head-to-foot oscillations, 8/10 oscillations per min with amplitude of 2.4mm	Stimulation: 4 days alternatively on or off Duration: 8 days	*Apnoea:* No significant reduction in amount of apnoea (p>0.05) No significant reduction in amount of apnoea with cyanosis (p>0.05) *Bradycardia:* No significant reduction in amount of HR 80-100 bpm (p>0.05) No significant reduction in amount of HR <80 bpm (p>0.05) *Other:* Significant more quiet sleep, les state changes, less restlessness
Jones, R. 1981 Randomized crossover study	14 infants GA (median): 29.4 weeks Weight (median): 1080g Day start study (median): 8 days Treatment: 3 theophylline	ECG Impedance pneumogram	*Oscillating* Instrument: same mattress as described by Korner, inflatable bladder under the head end. Location: Not described Stimulus: 12-14 oscillations per minute, amplitude 1-2mm. *Non-oscillating* Instrument: same mattress Location: Not described Stimulus: None	Stimulation: 4 hrs alternatively on or off Duration (mean): 23 hrs Extra: 10 infants another 11 hours with the mattress emptied of water, divided between the beginning, middle and end of the time of the waterbed.	*Apnoea:* No significant reduction in amount of apnoea 3-9 sec (p>0.1) No significant reduction in amount of apnoea >10 sec (p>0.1) Apnoea's of >10sec happened in 5 out of 6 infants more frequent on the oscillating bed. *Bradycardia:* Significant increase in amount of bradycardia <60 bpm (p<0.02) No significant reduction in amount of bradycardia <80 bpm (p>0.1) No significant reduction in time of HR <80 bpm (p>0.1) *Other:* 0,1 ºC decrease in mean body temperature Hypothermia in 1 infant No significant differences in parameters measured on the waterbed and on the emptied waterbed

Author / Study design	Study objects	Detection signals	Stimulation characteristics	Duration / Stimulation time	Results of stimulation
Korner, A.F, et al. 1978 Quasi-experimental counter-balanced cross-over study	8 infants GA: 30 weeks Weight: 1270g Day start study: 15 days Study weight: 1264g Treatment: no other than antibiotics	Respiration by mercury-filled strain gauges and a thermistor in front of each nostril EEG, electro-oculogram, EMG and ECG by electrodes	Instrument: Waterbed, Baumanometer blood pressure bladder connected to an Emerson respirator Location: Not described Stimulus: gentle irregular head-to-foot oscillations, 12-14 pulses/min, 2.4mm amplitude	Stimulation: 6 hours alternatively on or off Duration: 24 hours	*Apnoea during sleep on the waterbed:* Decrease in amount of apnoea's >10s ($p<0.06$) Decrease central apnoea's $p<0.10$ Decrease obstructive mixed apnoea's $p<0.08$ Significant decrease in amount of apnoea + HR 80-120 ($p<0.02$) Significant decrease in amount of apnoea + HR <80 ($p<0.05$) Apnoea during REM increased, during quiet sleep decreased and during intermediate sleep significantly decreased
Korner, A.F. et al. 1975 Controlled randomized clinical trial	21 infants Experimental group (n=10) GA: 32 weeks Weight: 1521 g Control group (n=11) GA: 31.3 weeks Weight: 1382 g	HR, RR, temperature, concentrations administered oxygen Apnoea by alarm and notes nurse	*Experimental group* Instrument: waterbed, styrene shell with small inflatable rubber bladder connected to Emerson respirator Location: not described Stimulus: irregular head-to-foot oscillation, inflates and deflates the bag 16±4 times per minute. *Control group* Instrument: conventional foam-rubber mattress	Stimulation: 7 days	*Apnoea (RR<20 breaths/min and/or HR<100bpm):* Significant decrease in amount of apnoea ($p<0.01$) *Other:* No significant changes in apical pulse, respiratory rate, temperature, weight and emesis
Kattwinkel, J. et al. 1975 Quasi-experimental cross-over study	6 infants GA: 28 weeks Weight: 1103g Day start study: 8	Cardiorespiratory by impedance measurements HR and respiratory pneumograms by dynograph recorder	Instrument: hand Location: extremities Stimulus: rubbing	Stimulation: 5 out of 15 minutes Duration: 3 hours Control: 3 hour before stimulation	*Apnoea:* Significant decrease in amount of apnoea ($p<0.01$). This difference was present for the entire 3-hour test period and also for the 2 hours of the test period during which time cutaneous stimulation was not being administered.

under the upper thorax pulsating 16 ± %4 times per minute [27], a 128 Hz vibrating disk attached to the foot [25], two vibrating mattress using exerting a filtered white noise signal of 30-60 Hz with a displacement of 0.01-0.02 [14] respectively 0.09mm [26], four water mattresses with varying mean frequencies ranging from 8 to 16 oscillations per minute and amplitudes of 1 to 2.4mm [28-30, 34], one oscillating air mattress with a frequency of 14-16 oscillations per minute [33] and one oscillating and vibrating mattress with a frequency of 5-20 oscillations per minute and 8-10 Hz [32]. The composition of signals that were recorded varied a lot between the studies. In almost all studies the heart rate and oxygen saturation level were monitored with the aid of a pulse oximeter or cardiorespirography. In some cases thoracic impedance derived by plethysmography [14, 26] or pneumography [30, 31] enabled the detection of ceased breathing effort. Impeded airflow was detected by nasal airflow or temperature sensors [26, 27, 29]. There was also a large variation between the studies in thresholds for identifying breathing pauses, bradycardia and hypoxia. Kesavan et al. (2016) counted breathing pauses of 3-5 sec and >5 sec while Svenningsen at el. (1995) counted apnoea's lasting for more than 20 seconds accompanied by bradycardia and hypoxia. The threshold for bradycardia ranged between <80 bpm and <110bpm and for oxygen desaturation between <85 and <90%.

EFFECT

Preventative manual stimulation showed a significant decrease in frequency of apnoea during the stimulation period ($p<0.01$). This difference was present during the whole experiment although stimulation was only administered 5 out of every 15 minutes. All four studies using a vibratory stimulus reported a significant decrease in apnoeic spells or breathing pauses [14, 25, 26, 32]. Three of these studies also showed a significant decrease in amount and/or duration of hypoxic episodes [14, 25, 26]. Kesavan et al. (2016) reported a significant reduction in amount and duration of bradycardia and Smith et al. (2015) reported only a significant reduction in intensity of bradycardia. The pulsating cuff used in the study of Jirapaet et al. (1993) significantly decreased the total amount of apnoeic episodes during stimulation [27]. However, analysis by type of apnoea showed that the decrease was only statistically significant for central and mixed apnoea. The 6 studies using oscillating stimulation via water and air mattresses showed a more variable effect. Two studies reported a significant decrease in apnoea during stimulation [32, 34]. Korner et al. (1978) showed a decrease in all types of apnoea and a significant decrease in apnoea combined with bradycardia during stimulation. Despite the positive effect on apnoea, one of these studies reported an increase in mean arterial blood pressure of 5mm Hg during oscillation in four infants and restlessness in three of the twelve infants after stimulation [27]. The remaining three studies reported no difference in the effects of oscillating mattresses

compared to non-oscillating mattresses [14, 28, 33]. One of these studies even reported that the frequency of apnoea's of >10s increased in 5 out of 6 infants and also the frequency of severe bradycardia increased and the mean body temperature decreased with 0.1ºC. One infant developed hypothermia and six infants required an increase in incubator temperature [30].

DISCUSSION

The variation in study designs and the clear division between the studies focussing on termination of apnoea and the prevention of apnoea led to a separate discussion of the results using a narrative format.

TERMINATION OF APNOEA

Animal studies have shown that sensory stimulation is important for the onset of breathing after birth [35-37]. Although manual stimulation is recommended in the local and international resuscitation guidelines, its effects on the initiation of breathing have been studied only recently in preterm infants [38, 39]. To our knowledge, the effect on termination of apnoea has not studied but is the most common method used. However, mechanical tactile stimulation has been evaluated in several studies because it might improve the stimulation technique, lead to a faster response and thus shortens the duration of apnoea and reduces the chance of cross-contamination.

Two crossover studies showed that automatic vibratory stimulation of 250Hz, at either the foot or the thorax, is at least equally effective in terminating apnoea compared to manual stimulation [19, 23]. Furthermore, both studies showed a decrease in stimulus duration upon termination when using vibrotactile stimulation. However, the response time was not significantly reduced as the nurse had to actuate the mechanical stimulation. In contrast to this, Frank et al (1973) and Camargo et al. (2014) used a closed-loop system to study the effect of stimulation on the termination of apnoea. The devices were able to terminate 94 respectively 90% of all apnoea's but these results were not compared with manual stimulation. A few other articles have described the design of a closed-loop vibratory device [10, 17, 40]. However, as far as we are aware there are no published clinical trials that compare automatic mechanical stimulation with manual stimulation.

Despite the fact that manual tactile stimulation is common therapy, the exact neural pathway(s) to the respiratory centre remain unclear. It is postulated that tactile stimulation affects respiratory control by activating the brainstem reticular formation causing arousal [41]. Ioffe et al. (1980) showed that the sleep state of foetal lambs changed following

electrical stimulation of somatic nerves [42]. The magnitude of the respiratory response differed depending on sleep type and was greatest during REM sleep. However, tactile stimuli can also induce spinal and respiratory responses in infants without resulting in cortical arousal [43, 44].

Furthermore, the effect of mechanical stimulation on the respiratory centre is dependent on nerves that are targeted. The skin contains multiple sensory receptors, which are all most sensitive to a specific frequency range [45]. The sensitivity of glabrous skin of human adults is highest at 250Hz [40, 46], which was the frequency chosen in all of our included studies that used vibratory stimulation. However, animal studies have shown that the responsiveness of the immature nervous system to vibration is restricted to lower frequencies in newborns (5-300 Hz) compared to adults (5-1000 Hz) [47, 48]. Lower frequencies applied at the thorax are believed to stimulate intramuscular mechanoreceptors such as muscle spindles and Golgi tendon organs [49, 50]. These results imply that the location of stimulation also influences the effect on breathing, depending on the presence of certain receptors.

PREVENTION OF APNOEA

In 1975 Kattwinkel et al. (1975) showed that manual tactile stimulation every 5 out of 15 minutes led to significant less apnoea in preterm infants. As this intervention will increase the workload of the nurses, various studies have been conducted to investigate the effect of mechanical stimulation on the prevention of apnoea.

Oscillating air- or water mattresses were used most often to stimulate the infants and are believed to mimic the in utero environment by activation of the somatic proprioceptors or the cutaneous receptors in the skin. In the first study, Korner et al. (1975) showed a significant reduction of apnoea associated with the irregular oscillating waterbed. In a second study they showed a decrease in all types of apnoea and a significant decrease in apnoea combined with bradycardia during stimulation [29]. However, another study using the same mattress with regular oscillation [30] has failed to demonstrate significant effects, as has a randomized trial in 122 infants [33] and a follow-up study in theophylline treated infants [28]. The inability to show positive results may be due to habituation in response to the regular oscillation in the first two studies and by the low incidence of apnoea in theophylline treated infants in the latter. However, Jones et al. (1981) even reported adverse effects in some of the infants, such as increase of apnoea, severe bradycardia and hypoxia.

In response to the oscillation beds, Jirapaet et al. (1993) aimed to develop a more suitable, feasible and cheaper stimulation system to prevent apnoeic episodes in the form of a pulsating balloon placed under the upper thorax. The balloon pulsated 16+4 times per

minute, similar to the frequency of the oscillation in the first study of Korner et al. (1975) and is also believed to provide afferent input to the respiratory centre. The amount of central and mixed apnoea's during stimulation significantly reduced. Despite these positive results, no more research has been conducted on the effects of pulsating stimulation on the prevention of apnoea.

Svenningsen et al. (1995) conducted a study using an oscillating and vibrating mattress to test the effect of multimodal stimulation and found that infants had less apnoea when compared to a normal mattress. Furthermore, longer periods of quiet sleep and shorter periods of active sleep were reported when stimulating the infant. This shift in sleep pattern may be an explanation for the lower frequency of apnoeic spells. Yet other studies have reported increased periods of quiet sleep without a significant decrease in apnoea's when stimulating the infant [28].

More recent studies have investigated the effect of vibration as the sole stimulus, which resulted in a significant reduction of apnoea or inter-breath intervals (IBIs) and a significant reduction in intermitted hypoxia in all cases. Two of the three studies also reported a positive effect on the amount and duration or the intensity of bradycardia.

Kesavan et al. (2016) stated that a vibratory stimuli applied to the sole of the foot or palm of the hand activates proprioceptors in the joints, which stabilizes breathing by using the inherent reflexive coupling between limb movements and breathing frequency. This reflex is shown in sleeping adults [51] and in neonatal rabbits [52] during passive motion of the limbs. However, the reason to use a frequency of 128 Hz is not explained in the article. Other studies showed that 80Hz is the optimal frequency for evocation of movement illusions [53].

Smith et al. (2015) and Bloch-Salisbury et al. (2009) used mattresses that provided stochastic vibratory stimuli, as they hypothesized that small noisy inputs can stabilize unstable rhythms due to the nonlinear properties of the respiratory oscillator. This hypothesis is extensively explained and substantiated through computational models by Paydarfar and Buerkel [54, 55]. Based on previous studies [49, 55], it is postulated that the stimulation in the range of 30-60 Hz might affect the respiratory centre via somatic or visceral mechanoreceptors in the thorax region. The fact that these receptors can influence the respiratory rhythm is supported by studies that used electrical stimulation to activate the intercostal afferents [56, 57]. However, Binks et al. (2001) showed that vibration of the thoracic surface could also excite intrapulmonary receptors as it vibrates the lung [58]. The stretch receptors in the lung are responsible for inhibition of inspiration following increase in lung volume [59]. Furthermore these receptors are believed to act on the airway smooth muscle tone, systemic vascular resistance and heart rate [60]. The last hypothesis is that stochastic

resonance directly stimulates gas exchange within lung tissue by mechanical perturbations [14], although this hypothesis has not been substantiated. Yet, experiments in guinea pigs showed that ventilation with added noise improved gas exchange compared to conventional ventilation [61].

It is possible that continuous mechanical stimulation, as is used in all included studies, could negatively influence the sleeping cycles of the infant by causing arousal or increasing the amount of active sleep. However, Bloch-Salisbury et al. (2009) showed that on and off switching of the vibrating mattress did not result in significant changes in behavioural state or EEG power spectrum, suggesting that this form of stimulation does not cause arousal. Although no negative effect on sleep state and other characteristics such as [28, 33] respiration rate, temperature and emesis were found in studies that used oscillating stimuli for multiple days, it remains unclear whether prolonged continuous stimulation would lead to adverse effects in the infants.

LIMITATIONS

In this systematic review only English articles were considered. Relevant articles found in three databases and additional interesting references were included. By using this methodology it cannot be ruled out that relevant articles are missed. Furthermore the decision to include all modes of stimulation led to a high variety of i.e. study designs, goals, definitions, measuring methods and results. These big differences made it very difficult to compare the results.

FURTHER IMPLICATIONS

In most of the studies, tactile stimulation had a positive effect on the amount of apnoea or was able to successfully terminate the apnoea but many important questions remain unanswered. The main issue would be finding out how to stimulate the most optimal pathway to the respiratory centre. This means that more research should be performed on the effect of different frequencies, amplitudes and locations of stimulation on all types of apnoea but also to the influence of sleep state, hypoxia and other environmental effects as well as possible adverse effects such as arousal and habituation.

Closed-loop systems should be used in studies that investigate the effect of stimulation on the termination of apnoea with the aim to prove the added value of a direct response. Although continuous stimulation of infants might prevent apnoea without causing harm, it may be more beneficial to only stimulate the infant when needed [62]. This requires development of algorithms to predict apnoeic spells or risk of AOP. Two studies proposed

algorithmic frameworks that generate predictive warnings but more research is needed to develop a watertight forecasting system [62, 63].

CONCLUSION

In conclusion, it is clear that somatic afferents can influence respiratory centre activity. Although manual tactile stimulation is the most common intervention for interruption of apnoea, the effectiveness of different techniques were not studied. Mechanical stimulation is believed to improve the current treatment by reducing the risk of cross-contamination and enabling a direct response but data are scarce. Studies demonstrated that it is possible to terminate apnoea with a closed-loop mechanical pulsating or vibrating system and that mechanical vibratory stimulation of 250 Hz is equally effective as manual stimulation in terminating apnoea.

Several studies investigated the effect of tactile stimulation on the prevention of apnoea. However, there were large variations between the studies in terms of study design, stimulation characteristics and measured outcomes. Although an oscillating mattress was used in six studies, this form of stimulation did not lead to a consistent effect in reducing apnoea. Continuous pulsating significantly reduced central and mixed apnoea but was only studied once. Different forms of vibrating stimuli were shown to significantly reduce apnoea, hypoxia and bradycardia.

In order to select the most effective way of stimulation to treat or prevent apnoea, more knowledge is required about the neuronal pathways to the brains that are activated by mechanical tactile stimulation, the effect on all types of apnoea and the corresponding adverse effects. More studies are needed to confirm whether automated stimulation using a closed loop is more effective than manual stimulation, how and where the automated stimulation should be performed and the potential side effects.

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CHAPTER 4

The effect of vibrotactile stimulation on hypoxia-induced irregular breathing and apnoea in preterm rabbits

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ABSTRACT

BACKGROUND

Manual tactile stimulation is used to counteract apnoea in preterm infants, but it is unknown when this intervention should be applied. We compared an anticipatory to a reactive approach using vibrotactile stimulation to prevent hypoxia induced apnoea's.

METHODS

Preterm rabbit kittens were prematurely delivered and randomized to either group. All kittens breathed spontaneously with a positive airway pressure of 8 cmH2O while they were imaged using phase contrast X-ray. Irregular breathing (IB) was induced using gradual hypoxia. The anticipatory group received stimulation at the onset of IB and the reactive group if IB transitioned into apnoea. Breathing rate (BR), heart rate (HR) and functional residual capacity (FRC) were compared.

RESULTS

Anticipatory stimulation significantly reduced apnoea incidence and maximum inter-breath intervals and increased BR following IB, compared to reactive stimulation. Recovery in BR but not HR was more likely with anticipatory stimulation, although both BR and HR were significantly higher at 120s after stimulation onset. FRC values and variability were not different.

CONCLUSIONS

Anticipated vibrotactile stimulation is more effective in preventing apnoea and enhancing breathing when compared to reactive stimulation in preterm rabbits. Stimulation timing is likely to be a key factor in reducing the incidence and duration of apnoea.

INTRODUCTION

Spontaneous breathing in preterm infants typically follows a periodic and irregular pattern, reflecting the immaturity of their lungs, central respiratory control centres and muscles. Breathing pauses that last more than 10 to 20 seconds are referred to as apnoea and are observed in most preterm infants born at <30 weeks gestation [1]. Apnoea can develop into a significant clinical problem as these episodes are often accompanied by bradycardia and/or hypoxia, which consequently increases the risk of lung, eye and brain injury [2, 3].

Caffeine treatment and non-invasive respiratory support are commonly used to reduce the occurrence of apnoeic episodes [4], but do not fully prevent it. In order to restore breathing, caregivers must promptly intervene by providing an escalating sequence of interventions including tactile stimulation, additional supplemental oxygen, positive pressure ventilation and, in more severe cases, intubation [5]. Manually applied tactile stimulation is arguably the most frequent and important intervention used in response to apnoea and has been recommended and applied in clinical practice for many years. However, manual interventions come with response delays [6], which makes treatment of apnoea on demand an ongoing challenge.

Mechanical and automated tactile stimulation can avoid the delay in response and so has the potential to avert or shorten the duration of apnoea, prevent the onset or exacerbation of bradycardia and hypoxia, and hence mitigate the need to escalate the required intervention. These benefits could be further enhanced when stimulation is provided when apnoea is anticipated. Although mechanical, vibrotactile stimulation has been studied in several small clinical trials, showing positive results when applied in both a continuous and reactive manner [7-11], the benefits of an anticipatory response have never been assessed [12].

The aim of this study was to investigate whether an anticipatory stimulation approach is more effective at stimulating breathing and preventing apnoea than a reactive stimulation approach in preterm rabbit kittens. Therefore, we compared the effect of mechanical vibrotactile stimulation in response to hypoxia-induced irregular breathing (IB) with stimulation in response to apnoea. We hypothesized that the anticipatory approach would be more effective than the reactive approach.

METHODS

All animal procedures were approved by the SPring-8 Animal Care and Monash University's Animal Ethics Committees. The study was conducted in experimental hutch 3 of beamline 20B2 in the Biomedical Imaging Centre at the SPring-8 synchrotron in Japan.

EXPERIMENTAL PROCEDURE

Eight pregnant New Zealand White rabbits were initially sedated using propofol (8mg/kg iv bolus, Rapinovet, Merck Animal Health) at 29 days gestational age (GA; term ≈32 d) to administer a spinal block using 2% lignocaine (4mg/kg) and 0.5% bupivacaine (1mg/kg), as previously described [13]. Following the induction of spinal anaesthesia, sedation was maintained in the pregnant doe with intravenous infusion of midazolam (1mg/kg/h) and butorphanol (0.5mg/kg/h). The rabbit's heart rate (HR), SpO2, breathing rate (BR) and hind quarter reflexes were monitored during delivery of the rabbit kittens.

Rabbit kittens were randomized to either the anticipatory or reactive approach group prior to delivery by caesarean section. After exteriorization of each kitten from the uterus, an oesophageal tube was inserted to measure intrathoracic pressure and a custom-made mask was fitted over the head of each kitten to administer continuous positive airway pressure (CPAP) and oxygen. Naloxone (1mg/kg) and anexate (10 µg/kg) were administered intraperitoneally to each kitten to reverse the effects of maternally administered butorphanol and midazolam, and caffeine citrate (20mg/kg) was given to stimulate breathing. After cutting the umbilical cord, the kittens were transferred into the imaging hutch and placed lateral on a custom-made, heated, stimulation device. Electrocardiogram (ECG) leads were attached and the facemask was connected to a purpose-built ventilator [14] to administer an initial CPAP of 15cmH20 and a fraction of inspired oxygen (FiO2) of 0.6. As the lungs aerated and the breathing pattern stabilized the CPAP level was decreased to 8 cmH20 and remained at this level for the rest of the experiment. Phase contrast (PC) X-ray imaging of the kittens then commenced for measuring lung air volumes. Subsequently FiO2 was reduced in a stepwise manner, with steps off ±0.1, to reduce oxygenation levels and hence induce an unstable irregular breathing (IB) pattern. Once IB was observed, characterized by a variable breathing pattern and amplitude, the FiO2 was returned to 0.6 in both groups. At this time, the kittens in the anticipatory approach group received vibrotactile stimulation. Kittens in the reactive approach group only received stimulation if and at the moment that IB transitioned into apnoea (Figure 1).

After delivery of the final kitten or at the conclusion of the imaging period, all does and kittens were euthanized with an overdose of sodium pentobarbitone (>100 mg/kg) administered intravenously (doe) or intraperitoneally (kittens).

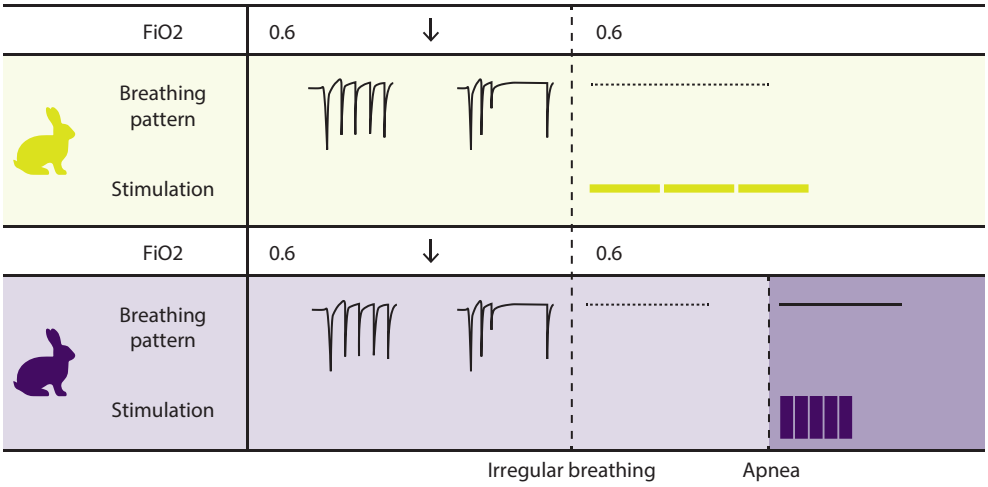

Figure 1. Protocol for the anticipatory group (green) where FiO2 is increased to 0.6 and stimulation was applied in response to irregular breathing. The reactive group (orange) where FiO2 was increased in response to irregular breathing but stimulation was only applied if irregular breathing transitioned into apnoea.

VIBROTACTILE STIMULATION

A custom-made mechanical stimulation device (Figure 2) was used to remotely administer vibrotactile stimulation while the kittens were being imaged. This device consisted of a metal box with an enclosed speaker and a small rod that connected the conus of the speaker, through a hole in the box, to a point in contact with the kitten. The kitten was placed laterally on the box, with the contact point located at the level of the thorax. The speaker was connected to a laptop via an amplifier and was actuated by playing an audio file, allowing control of the signal frequency and displacement (amplitude) of the contact point. Using an optical sensor placed inside the metal box, the frequency and amplitude of the stimulations were recorded in Labchart (Powerlab, ADInstruments; Sydney, Australia).

The stimulation in the anticipatory approach group consisted of three 30 seconds blocks of vibration, generated by a sinusoidal tone with a frequency of 100 Hz and an amplitude of 0.2mm. Although it was our initial intent to solely compare the effect of timing, we decided to adjust the length and amplitude of the reactive stimulation in order to increase the likelihood of recovery and to more closely match the characteristics of the stronger manual reactive stimulation that is usually required to restore breathing in apnoeic kittens. Vibrotactile stimulation in the reactive approach group consisted of multiple vibrations that were 5 seconds in duration with a frequency of 100 Hz and an amplitude of 1.1 mm.

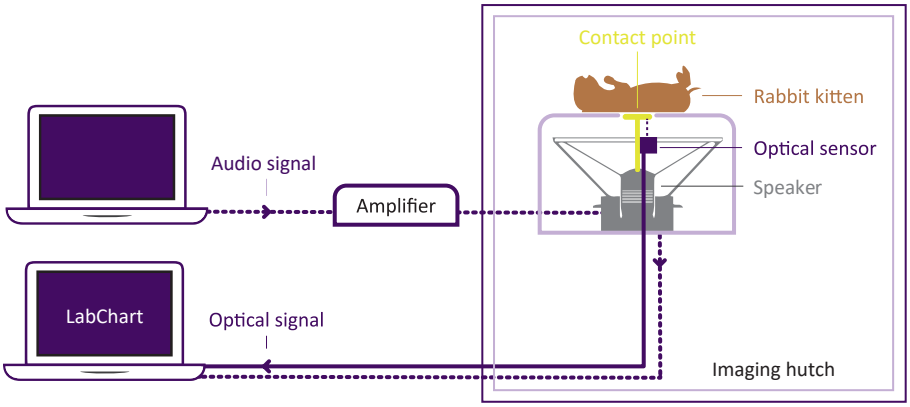

Figure 2. Set-up of the vibrotactile stimulation device.

PC X-RAY IMAGING

High resolution PC X-ray imaging was used to measure lung gas volumes using a power spectral analysis, as described previously by Leong et al [15]. The study was conducted over two beamtimes due to the number of animals used. Monochromatic synchrotron X-ray radiation was used to illuminate the lungs at an energy of 24 keV. A lens-coupled Hamamatsu ORCA Flash detector (C11440-22C; effective pixel size 15.3 micron) coupled to a 25 micron thick Gadox phosphor (P43) recorded the phase contrast images with an exposure time of 20 ms and a frame rate of 10 Hz. The source-to-kitten distance was ~210m, and the kitten-to-detector distance was 2m.

DATA ANALYSIS

Inter-breath intervals (IBI) and R-R intervals (RRI) were obtained from the recorded intrathoracic pressures and ECG signals in Labchart (Powerlab, ADInstruments; Sydney, Australia). BR were computed at 5 second intervals using a moving average over the previous 15 second period whereas HR were averaged over the previous 20 seconds also at 5 seconds intervals. Lung functional residual capacity (FRC) volumes were derived from the PC X-ray imaging and also averaged over a window of 25 seconds every 5 seconds. Motion artefacts due to the vibration of the kitten during stimulation blurred our the phase contrast required to measure lung volumes. This resulted in missing FRC averages for some time windows.

To compare the effect of an anticipatory versus a reactive stimulation approach, two comparisons between groups were performed using either the onset of IB or the onset of stimulation as a reference point (Figure 3). The average overall BR, HR and FRC, and the coefficient of variation (COV) of these parameters were used to compare cardiorespiratory

stability between groups with respect to the onset of IB. These metrics were computed using the raw values (IBI, RRI and FRC), starting 40 seconds before the onset of IB to 120 seconds thereafter. Cardiorespiratory responses to both stimulation approaches were assessed by, (i) the occurrence of apnoea – defined as one breathing pause of ⍰ 20s or multiple consecutive pauses of >15s, (ii) the maximum IBI and (iii) the area under the curve (AUC) for BR, HR and FRC, in the 120 seconds following the onset of IB. For the second comparison recovery percentages of BR and HR as well as the BR, HR, and FRC values at 120 seconds after the onset of stimulation were used. Successful recovery was defined as a BR or HR exceeding its level at IB onset within 120 seconds after stimulation onset. The two kittens (of 11) in the reactive group that did not become apnoeic were excluded from this analysis as they did not require or receive reactive stimulation.

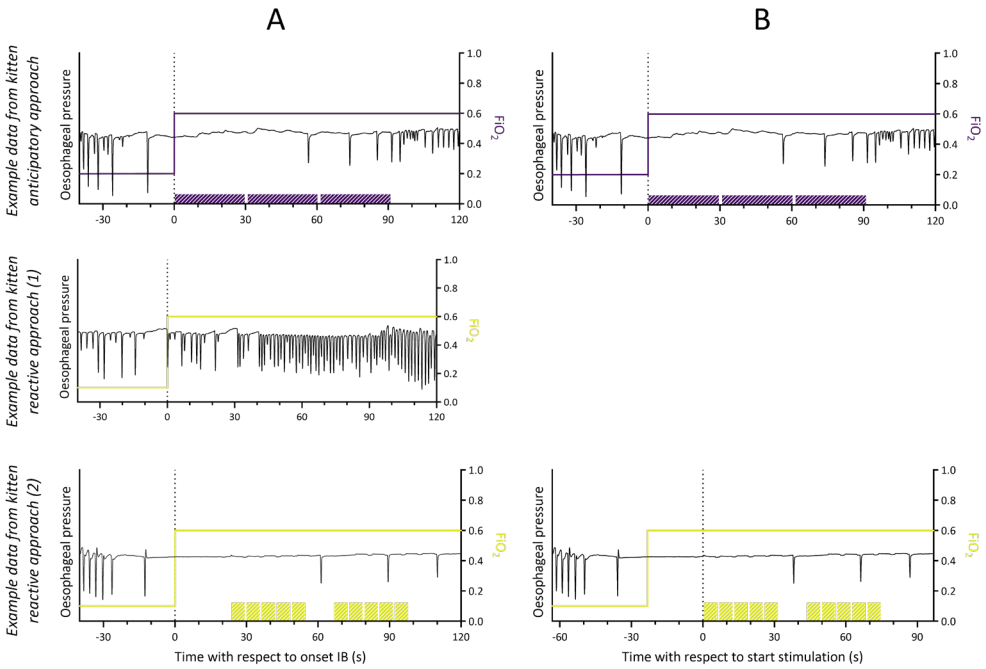

Figure 3. Visualization of both data analyses for both groups. The upper tracings are from a kitten in the anticipatory group and the middle and lower tracing are from kittens in the reactive group. Analysis A: comparing anticipatory approach versus reactive approach by using the onset of IB (t=0) as reference point. Both groups receive 0.6 FiO2 at the onset of IB, but only the kitten from the anticipatory group (upper tracing) receives stimulation simultaneously. Kittens from the reactive group (middle and lower tracing) only receive stimulation if IB transitions to apnoea (only lower tracing). Analysis B: comparing anticipatory approach versus reactive approach by using the start of stimulation (t=0) as reference point. For the kittens in the anticipatory group this timepoint is the exact same point as the onset of IB from analysis A, but for the kittens of the reactive group the reference point is shifted. This analysis only includes kittens from the reactive group that received rescue stimulation once IB transitioned in apnoea (only the lower tracing).

STATISTICAL ANALYSIS

SPSS software version 23.0 (SPSS, Chicago, Illinois) was used to perform the statistical analyses. Categorical data is presented as n (%) and compared between groups using Fishers exact test. Continuous data is presented as mean ± standard deviation (SD) if normally distributed or median and interquartile ranges (IQR) otherwise. Differences between groups were carried out on the (transformed) data accordingly, using the unpaired Student's t-test or Mann-Whitney U test. Tests were performed two-sided and p-values <0.05 were considered statistically significant.

RESULTS

Physiological data and corresponding PC X-ray images were collected from a total of 21 preterm rabbit kittens, delivered from eight does. Ten kittens were randomized in the anticipatory group and 11 in the reactive group. There were no significant differences between the two groups with regard to birth weight, administered dose of caffeine, timing of the onset of IB, and FiO2 levels at the moment IB was observed (Table 1).

Table 1. Patient characteristics

	Anticipatory approach (n=10)	**Reactive approach** (n=11)	**p-value**
Birth weight (grams)[a]	32.3 ± 5.6	32.5 ± 5.4	0.919
Caffeine dose (mL/kg)a	22.6 ± 4.1	20.6 ± 1.9	0.147
Timing of onset IB after birth (mm:ss)[a]	11:59 ± 04:06	13:22 ± 03:24	0.407
FiO2 at IB onset (%)[b]	0.20 (0.10 - 0.37)	0.10 (0.05 - 0.20)	0.107

Data is presented as mean ± SD for normally distributed data (a) or median (IQR) for data that were not normally distributed (b). IB: Irregular breathing, FiO2: fraction of inspired oxygen.

COMPARISONS WITH RESPECT TO ONSET OF IRREGULAR BREATHING

Although BR and variability in IBI's over the entire analysed period were not statistically different, kittens randomized to anticipatory stimulation tended to have higher BRs (15.3 (10.4–19.5) vs 8.5 (7.1–19.4) breaths/min, p=0.133) and lower IBI variability (60.5 (37.0–125.0) vs 108.0 (81.0–161.0)%, p=0.149) compared to the reactive stimulation group)(Table 2, Figure 4a). After the onset of IB, 3/10 kittens in the anticipatory stimulation group became apnoeic as compared to 9/11 in the control group (p=0.030). In addition, the maximum IBI was shorter (7.7 (5.1–30.8) vs 38.4 (15.5–73.9) seconds, p=0.014), and the AUC for BR higher (314.7 (123.6–424.3) vs 86.3 (46.6–142.2), p=0.025) in the anticipatory compared to the reactive stimulation group.

Overall HR and the AUC for heart rate following IB were higher in the anticipatory stimulation group, but these differences did not reach statistical significance (125.5 ±50.2 vs 93.0 ±27.4 bpm, p=0.073, 2892.0 ±1248.8 vs 2060.1 ±640.2, p=0.066)(Table 2, Figure 4a). The variability in R-R intervals was significantly lower in the group that received anticipated stimulation (18.7 ±8.8 vs 32.8 ±15.8, p=0.038).

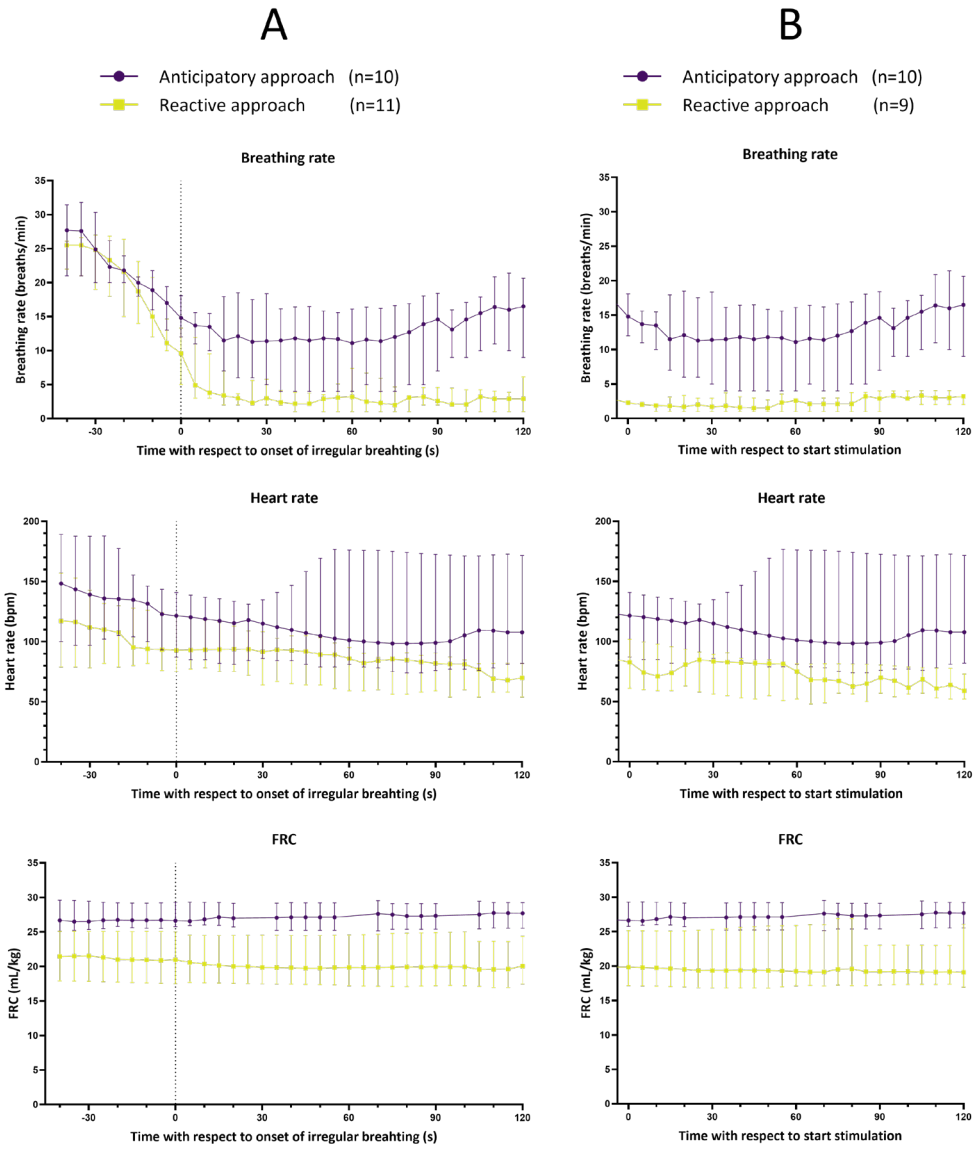

Figure 4. Breathing rate, heart rate and FRC values over time for A: anticipatory approach versus reactive approach, using the start of IB as reference point (t=0) and B: anticipatory approach versus reactive approach, using the start of stimulation as reference point (t=0).

Table 2. Comparisons with respect to onset of irregular breathing

	Anticipatory approach (n=10)	**Reactive approach** (n=11)	**p-value**
Overall BR (breaths/min)[b]	15.3 (10.4 – 19.5)	8.5 (7.1 – 19.4)	0.133
Overall IBI variability (%)[b]	60.5 (37.0 -125.0)	108.0 (81.0 – 161.0)	0.149
AUC of BR after IB onset[b]	314.7 (123.6 – 424.3)	86.3 (46.6 – 142.2)	0.025
Incidence of apnea after IB onset(n)[c]	3/10 (30)	9/11 (82)	0.030
Maximum IBI after IB onset (sec)[b]	7.7 (5.1 – 30.8)	38.4 (15.5 – 73.9)	0.014
Overall HR (bpm)[a]	125.5 ± 50.2	93.0± 27.4	0.073
Overall RRI variability (%)[c]	18.7 ± 8.8	32.8 ± 15.8	0.038
AUC of HR after IB onset[a]	2892.0 ± 1248.8	2060.1 ± 640.2	0.066
Overall FRC (ml/kg)[b]	27.1 (22.3 – 30.0)	20.0 (17.1 – 25.5)	0.226
Overall FRC variability(%)[b]	1.8 (0.7 – 3.5)	1.9 (1.4 – 4.0)	0.536
AUC of FRC after IB onset[b]	657.4 (531.3 – 726.6)	527.6 (457.5 – 686.9)	0.902

Data is presented as mean ± SE (a), median (IQR) (b) or n (%) (c). P-values are based on transformed data. BR: breathing rate, IBI: inter breath interval, AUC: area under the curve, IB: irregular breathing, HR: heart rate, RRI: R-R intervals , FRC: functional residual capacity.

There was no difference between overall FRC values (27.1 (22.3–30.0) vs 20.0 (17.1–25.5) mL/kg, p=0.226), variability in FRC values (1.8 (0.7–3.5) vs 1.9 (1.4–4.0) mL/kg, p=0.536) as well as AUC for FRC values following IB (657.4 (531.3–726.6) vs 527.6 (457.5–686.9) mL/kg, p=0.902) between groups (Table 2, Figure 4a).

COMPARISONS WITH RESPECT TO START STIMULATION

All kittens in the anticipatory group received stimulation when IB occurred, while only 9/11 kittens in the reactive stimulation group became apnoeic and so received stimulation. In the anticipatory stimulation group, BR recovered in 7/10 kittens compared to 1/9 kittens in the reactive stimulation group (p=0.015)(Table 3). Similarly, HR recovered in 5/10 kittens in the anticipatory stimulation group versus 1/9 kittens in the reactive stimulation group (p=0.091). Two minutes after the onset of stimulation, both BR and HR were still significantly higher in the anticipatory stimulation group (17.3 ±13.7 vs 2.9 ±1.8 breaths/min, p=0.009, 123.9 ±55.8 vs 64.7 ±15.5 bpm, p=0.009) (Table 3, Figure 4b). FRC values were not different between groups (anticipatory: 27.7 (22.1–29.7) vs reactive: 19.1 (16.8–28.0) mL/kg, p=0.315), although tended to be lower in the reactive group during the entire study.

Table 3. Comparisons with respect to start stimulation

	Anticipatory approach (n=10)	**Reactive approach** (n=9)	**p-value**
BR 120s after stimulation onset (breaths/min)[a]	17.3 ± 13.7	2.9 ±1.8	0.009
Incidence of BR recovery within 120s after stim. onset[c]	7/10 (70)	1/9 (11)	0.015
HR 120s after stimulation onset (bpm)[a]	123.9 ± 55.8	64.7 ±15.5	0.009
Incidence of HR recovery within 120s after stim. onset[c]	5/10 (50)	1/9 (11)	0.091
FRC 120s after stimulation onset (ml/kg)[b]	27.7 (22.1 – 29.7)	19.1 (16.8 – 28.0)	0.315

Data is presented as mean ± SE (a), median (IQR) (b) or n(%) (c). BR: breathing rate, HR: heart rate, FRC: functional residual capacity.

DISCUSSION

In this study we have shown that vibrotactile stimulation can significantly reduce the incidence and duration of apnoea and increase breathing rate if it is applied when breathing becomes irregular instead of waiting until after apnoea onset. Together with the statistically insignificant but greater cardiorespiratory stability these data suggest that stimulating in anticipation of an impending apnoea is considerably better than waiting for apnoea to occur. With respect to the start of stimulation, anticipated stimulation led to recovery of breathing rate more often and resulted in a significantly higher breathing rate two minutes after stimulation onset when compared to reactive stimulation. Similarly, the heart rate two minutes following the start of stimulation was significantly higher when anticipatory stimulation was given. Interestingly, the FRC values were similar in both groups with little variability over the analysed periods, despite the changes and differences in breathing rate between groups.

Our results support the generally accepted view that tactile stimulation can promote breathing and counteract apnoea in preterm infants. Previous experimental studies have shown that stimulation of somatosensory receptors can trigger spontaneous foetal breathing [16, 17], enhance respiratory drive after birth [18] and shorten the duration of induced apnoea [19]. Our study also confirmed earlier reports that not all forms and methods of mechanical stimulation are (equally) effective [19-21]. In addition to stimulation characteristics such as type, intensity and location, we have now demonstrated that the effectiveness of stimulation is also influenced by timing. Although both groups were treated in exactly the same manner prior to the onset of IB, the majority of kittens in the anticipatory stimulation group increased breathing activity following stimulation and increase in FiO2 while most of the kittens in the reactive stimulation group became apnoeic despite the

increase in FiO2. Furthermore, although the reactive stimulation group received a 5-fold larger stimulus amplitude, we found that it was less effective than the gentler stimulation that was applied in anticipation of apnoea. This could indicate that central processing of these stimuli is rapidly modified as the period of IB increases, where the gradually increasing level of hypoxia blocks or modifies somatic inputs arising from tactile stimulation [22], thereby impairing the resumption of breathing and resolution of apnoea. Indeed, it is well established that a foetus/newborn gradually stops breathing and becomes bradycardic, but also loses tone and becomes unresponsive to tactile stimuli, as hypoxia increases [23, 24]. However, it is also possible that, although the stimulation location and vibratory frequency were the same, the difference in stimulation amplitude that we decided to use for the anticipatory and reactive stimulation triggered different sensory receptors or afferent inputs into the brain leading to potentially dissimilar responses.

It is important to note that in the reactive approach group, 2/11 kittens did not develop apnoea and thus did not receive stimulation, despite developing an IB pattern that was similar to all other kittens. This type of biological variability is not unexpected and suggests that, in these cases, the respiratory centre was able to stabilize breathing in response to the increase in FiO2 without additional stimuli. Indeed, we would expect a similar number of kittens in the anticipatory approach group to have not required stimulation to prevent apnoea. Although applying stimulation in the anticipation of apnoea is likely to be considerably more effective, it is unknown whether this approach outweighs the possible adverse effects of unnecessary stimulation.

Anticipatory mechanical stimulation had a less pronounced and consistent effect on heart rate than breathing rate in this study. As there is a close link between the onset of apnoea, hypoxia and bradycardia in preterm infants [25, 26], we had expected a stronger interdependency with regard to recovery. Our results might suggest that tactile stimulation primarily targets the respiratory centre and that recovery of heart rate is a secondary response which arises, for example, from a chemoreceptor mediated increase in oxygenation. Perhaps the kittens from our experiment remained sufficiently hypoxic to suppress their heart rate, even though anticipatory stimulation enhanced breathing.

The low variability in FRC during the experiment and the lack of difference in FRC between groups indicate that lung aeration, at this level, is not necessarily related to decreased or increased respiratory effort resulting from the change in FiO2 or the presence or absence of stimulation. These results are consistent with previously published data showing similar lung aeration in two groups of preterm rabbits despite significantly different breathing rates resulting from different levels of FiO2 [13]. As we only included kittens that were breathing regularly at the start of the experiment, lung aeration had already occurred, as can be seen

by the FRC levels measured. We have previously shown that within a few minutes of birth we would expect a FRC of 15-20 mL/kg in normal spontaneously breathing term kittens without CPAP [27, 28]. However, with a CPAP 8 cmH2O (initially 15 cmH2O) our preterm kittens had FRCs of >20 mL/kg, which they were able to sustain even after the initiation of IB and apnoea. Presumably, closure of the glottis (active adduction) in between breaths and during apnoea helped to maintain FRC in kittens that developed apnoea [29]. However, it is unclear how long the glottis stays adducted when apnoea persists, because as the hypoxia deepens muscle tone and reflexes are lost.

To compare the effect of different stimulation approaches in this study, irregular breathing was induced by hypoxia. Although irregular breathing and apnoea in preterm infants are not necessarily induced by hypoxia, using this approach gave us the opportunity to enforce a consistent starting point in all kittens within a comparable amount of time. It is unclear why the breathing rate appeared to decrease faster in kittens in the reactive group following the induction hypoxia, although there was no statistical difference between groups. It could have resulted from lower FRC values in the reactive group, which reduced their oxygen exchange capacity and increased the rate of decrease in oxygenation following the initial reduction in FiO2. However, as FRC values are well within the expected range for both groups during the entire experiment, we would not expect this to significantly influence their response to stimulation. In addition, our study was limited by our inability to measure oxygen saturation in our kittens as our oximeter (Oximeter Pod ML320/F, AD Instruments, Sydney, Australia) is unable to read SpO2 values below 70% and so it is unknown whether the oxygenation level differed between groups. As the FiO2 used to induce IB was similar and the FiO2 provided in response to IB was exactly the same, we would expect that the oxygenation levels in both groups were similar at the onset of IB. However, as our results indicate that the degree of hypoxia impacts on the effectiveness of tactile stimulation, it would be desirable to include oxygen saturation measurements in further studies.

In conclusion, we confirmed that mechanical vibratory stimulation can prevent apnoea and stimulate breathing effort in preterm rabbit kittens after birth. Timing proved to be a key factor in the effectiveness of stimulation, which is more successful when apnoea is imminent rather than present. Based on our results it appears possible that anticipated automated tactile stimulation can improve current clinical care, provided that the benefits outweigh the possible drawbacks. The challenge of improving apnoea treatment in preterm infants with automated tactile stimulation depends on finding the right balance between enhancing excitatory inputs and attenuating inhibitory inputs into the respiratory centre while limiting the interference with other regulatory processes in the brain. However, anticipated stimulation can only exist in combination with yet to be developed predictive

algorithms for impending apnoea. Thus far, these algorithms have only been studied using pre-recorded physiological data [30-32] and have not been evaluated in combination with a tactile response. Further studies are warranted to define the most beneficial closed-loop strategy for providing tactile stimulation to treat apnoea of prematurity.

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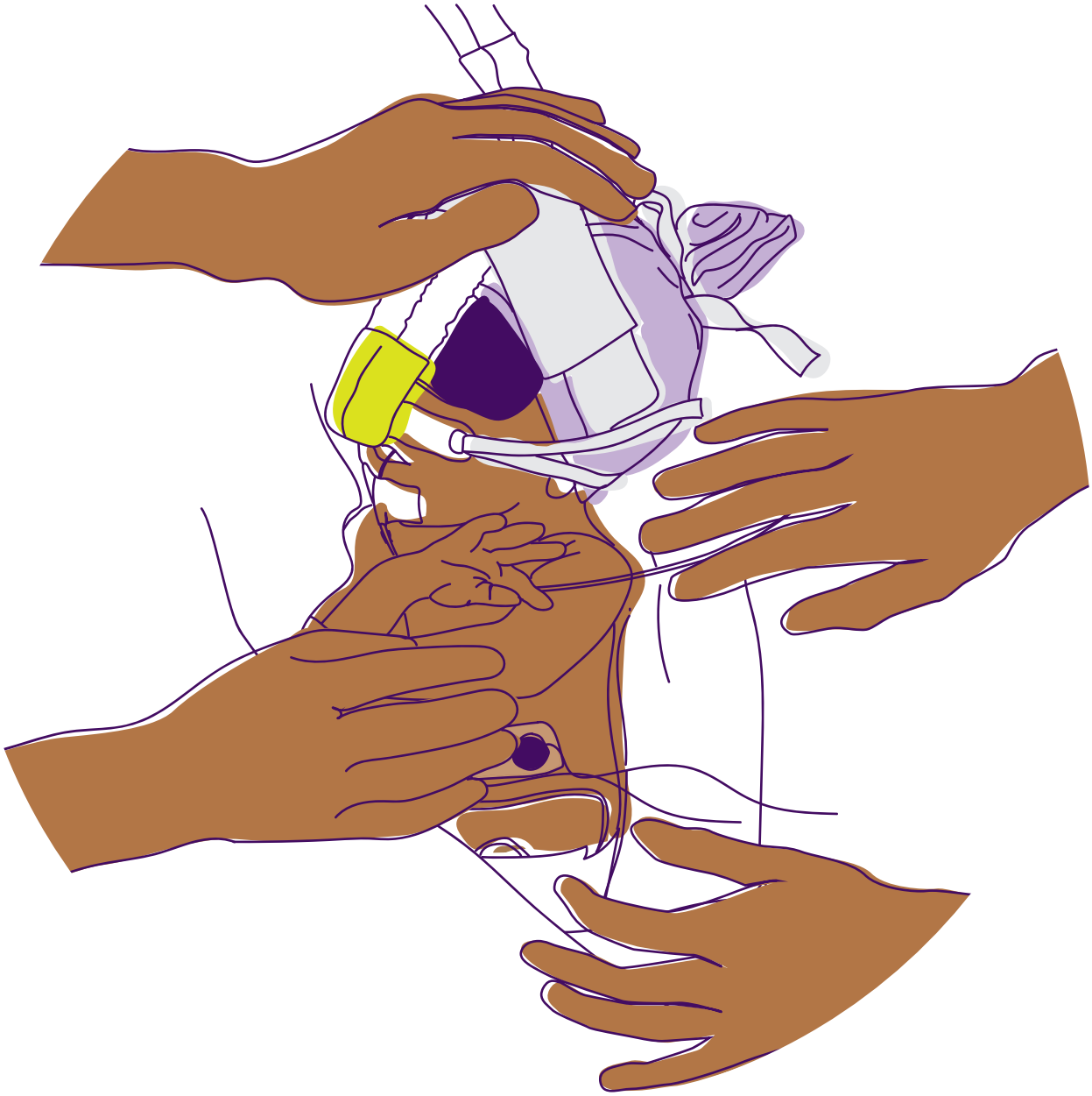

PART 4

CHAPTER 5

Development of the Breathing Operator for BaBY (BOBBY): an automated tactile stimulation device to facilitate breathing in preterm infants

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Submitted to BMJ Innovations

ABSTRACT

OBJECTIVE

Preterm infants have difficulty breathing unassisted because their lungs and respiratory control systems are immature, resulting in frequent respiratory pauses. Manual tactile stimulation provided by the nurse is effective but also selective and comes with response delays. This prompted us to develop a purpose-built automated tactile stimulation device (ATSD) to address these challenges by providing a reliable and direct response.

METHODS

The development process followed an iterative design approach incorporating five phases. The discover-phase consisted of various studies to gain a deeper understanding of the challenges and context of the problem. The knowledge gained was integrated into user needs and requirements in the define-phase, which in turn provided input for the ideate-phase. Ideas, concepts and prototypes were generated and built during multiple co-creation sessions. Iterative evaluation took place to select the most promising concepts.

RESULTS

Insights from all phases guided the development of Breathing Operator for BaBY (BOBBY), the first purpose built ATSD for preterm infants. In the design, we prioritized safety and efficacy, ensuring separation of electronic components from the infant. We have employed an apparent tactile motion technique, that simulates the stimulation performed by the nurse when responding to cardiorespiratory monitor alarms, to enhance neural excitation while minimizing irritation or damage to the skin.

CONCLUSION

BOBBY can potentially advance neonatal care using automation and address the challenges associated with breathing pauses in preterm infants. Clinical trials are warranted to validate its safety, efficacy and added value in the NICU.

INTRODUCTION

Worldwide, an estimated 15 million infants are being born prematurely each year [1] and this number is increasing [2]. Although the survival rate and overall outcome of these infants have markedly improved over the last decades, premature birth remains the single major cause of neonatal mortality and morbidity in both developed and developing countries.

One of the challenges facing preterm infants is the ability to maintain a rhythmic, stable spontaneous breathing pattern for effective ventilation and gas exchange. Their lungs and respiratory control systems are immature and their control of breathing can be unstable, represented by periods of irregular breathing and frequent periods of apnoea [3]. Although apnoea of prematurity (AOP) is, by definition, an age-specific and self-limiting disorder that resolves with maturation, it can result in adverse events and worse long-term outcomes. The major pathophysiological consequences of apnoea are presumably caused by the accompanying hypoxia and bradycardia, which have been associated with increased mortality, oxidative stress, serious cerebral injury and long-term neurodevelopmental impairment [4-7].

Although existing preventative therapies such as the administration of respiratory stimulants or non-invasive respiratory support are beneficial, most preterm infants still experience respiratory pauses, including apnoea's. To avoid the harmful consequences associated with apnoea, an adequate response consisting of a sequence of interventions is required. This sequence usually commences with tactile stimulation such as rubbing the foot of back of the infant, but can escalate to providing increased supplemental oxygen, positive pressure ventilation and, eventually, intubation [8].

Although tactile stimulation is the first, most frequently used and arguably the most important intervention that has been recommended and applied for years, treatment of apnoea on demand remains an ongoing challenge. Most nurses take care of multiple infants, leading to a large number of tasks and alarms, which requires them to respond selectively and can lead to response delays [9]. Nurses mainly focus on longer apnoeic episodes, as these will increase the risk, duration and severity of subsequent hypoxia and bradycardia [10-12]. However, given their numerical preponderance, brief respiratory pauses also substantially contribute to physiological instability [13, 14] and so are clinically significant and should be treated [15].

We hypothesized that these challenges can be addressed by providing automated mechanical tactile stimulation, offering a reliable and direct response to AOP. Although attempts have been made previously [16, 17], there are currently no commercially available automated tactile stimulation devices (ATSD) that can be implemented in a Neonatal Intensive Care

Unit (NICU). We aimed to develop a purpose-built ATSD prototype by following an iterative design approach.

METHODS

This design project was conducted at the Leiden University Medical Center (LUMC), the Netherlands. The hospital contains a 25-bed level-III NICU divided among two units, with in total 17 single-patient rooms and 4 twin-rooms.

The ATSD was developed by following an iterative design process, containing elements from the Design Thinking methodology of the Stanford d.school, the Stanford Biodesign Innovation process [18] and the Waterfall Method described by the FDA [19]. It consisted of five phases which alternately brought divergence and convergence in the design process (Figure 1): Discover, Define, Ideate, Prototype and Evaluate.

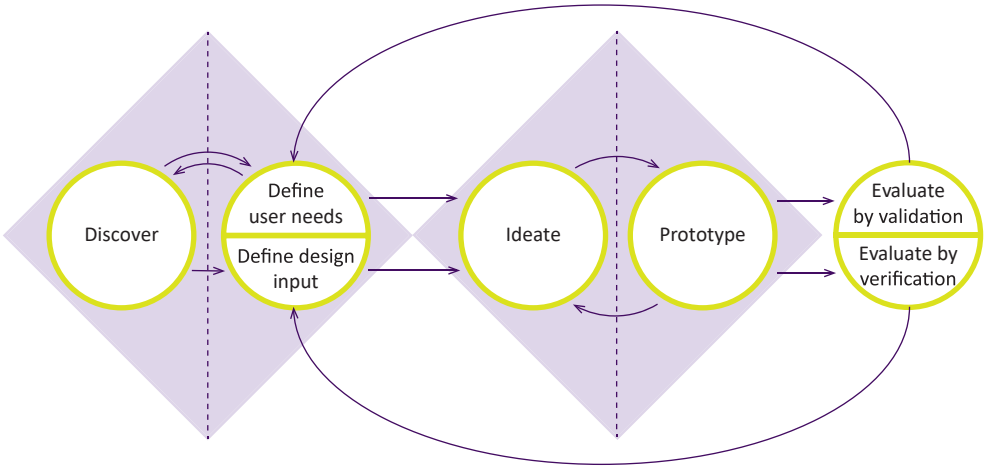


Figure 1. Overview of design methodology that was used for the development of the ATSD

DISCOVER

The goal of this initial phase was to gain a deeper understanding of the problem, the current situation and context as well as greater insights into the needs, motivations and challenges of preterm infants and nurses on the NICU. Several different research methods were used:

1. Several observations were conducted within the NICU. Nurses were shadowed during their shift in order to obtain a better understanding of their routine care practices. These observations were then used as foundational data and provided insights for the development of an interview protocol.

2. In-depth semi-structured interviews were organized with nurses (n=3) and with external experts (n=2). The nurses were selected by the nursing team leader and the questions were focused on the most important aspects of neonatal intensive care and the current AOP treatment process. Both external experts have conducted studies examining the effect of mechanical stimulation on AOP in preterm infants and were asked about their findings, knowledge and opinion on this topic. All interviews were audio-recorded and transcribed for analysis.
3. Two focus groups were conducted in which nurses engaged in a guided discussion exploring how they perform and experience the current treatment process of AOP. The focus groups took place before the start of the evening shift, both times with 8-10 nurses participating. The discussions were audio-recorded and transcribed for analysis.
4. A contextual field study was performed in other to map the stimulation methods nurses currently use, which involved direct observation in a simulated setting. Data collection focused on the location and type of tactile stimulation administered. Subsequently, short semi-structured interviews were conducted with nursing staff to gain further understanding of their rationale behind the chosen tactile stimulation methods.
5. A systematic literature search was conducted to identify the existing evidence for the effects of manual and mechanical tactile stimulation on the termination and prevention of apnoea in preterm infants. Relevant studies were identified through searches of electronic databases and references of the included articles.
6. A preliminary risk assessment was conducted using the Healthcare Failure Mode and Effects Assessment (HFMEA) methodology to identify potential failure modes associated with the concept of an ATSD. The assessment involved a cross-functional team composed of two neonatologists, two nurses, two technicians and one medical engineer.

DEFINE

Based on the first findings of the discover-phase, user needs were identified and functional requirements of the ATSD were defined. By going back and forth between the discover and define-phases in an iterative way, these needs were further specified into design inputs, capturing and defining the intended use of the device and the technical requirements the device must meet.

IDEATE & PROTOTYPE

Guided by the user needs and design inputs, two co-creation sessions were organized by the research team to explore and generate a wide range of potential solutions. Both sessions took approximately 1.5 hours and were attended by one or two NICU nurses, one neonatologist, one researcher, two technicians and two (medical) engineers from our hospital. In between and after the two brainstorm sessions, there were many smaller half-hour sessions in which the technician and engineers discussed the technical possibilities and feasibility of the concepts. All sessions were followed by the development of prototypes, which were tested against the predefined requirements to select the most promising design direction or concept. In this way, the design was further fine-tuned by each session.

EVALUATE

In addition to the iterative evaluations of concepts and prototypes, the final design was verified by evaluating whether all predefined design inputs were met, using different tests and checks. Final validation will occur in the future as it requires clinical evaluation and so will not be included in this report.

RESULTS

The results from the abovementioned phases served as input for the ATSD. Below we provide a description of the accompanying findings of each phase and a description of the final design.

DISCOVER

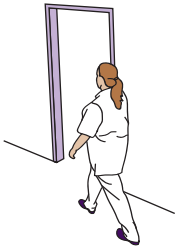
The observations from the NICU and information derived from interviews and focus groups resulted in a broad overview and deeper understanding of the NICU environment, important aspects in the care for preterm infants and the current treatment of AOP (Figure 2). In addition to the insights from the treatment process, the following items were taken into account: (1) preterm infants are placed in incubators in order to provide a warm and humid environment, (2) preterm infants are extensively monitored and supported by variety sensors and devices, such as pulse oximetry sensors, ECG leads, phototherapy devices and intravenous (IV) lines, (3) preterm infants often require medical interventions and checks such as line placements, IV insertions or routine ultrasound examinations and (4) preterm infants benefit from skin to skin contact with parents.

Figure 2. Overview of and insights from the current apnoea treatment process

Be alarmed
Alarms are visible and audible on the patient monitor in question and at the central post. A selection is transferred to the pager of the nurse to minimize alarm fatique.

The nurse will accept the alarm on their pager if he/she has time and otherwise try to actively deny, so the alarm will be redirected immediately to a buddy nurse. In case the nurse does not respond within 30 seconds, the alarm will be redirected automatically to ensure a timely response.

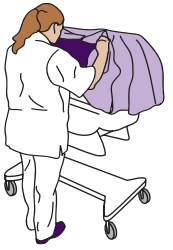
To ensure a timely response, nurses must actively decide to acknowledge the alarm or not and are therefore always interrupted. For caregivers there is a fine line between clinical awareness and alarm fatique.



Decide to act
The nurse who accepts the alarm will consider whether to act or not, depending on amongst others the event type and severity, the course of previous events the clinical status of the infant.

In most cases the nurse will wait and (remotely) monitor the patient for a while to see whether the event is brief and self-resolved or if intervention is required.

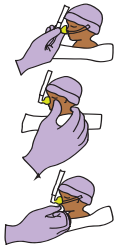
Nurses can only respond to a selection of events and are usually not in the position to respond immediately. In addition, nurses try not to disturb the infant unnecissarily.



Find the cause
At the bedside the nurse will silence the alarm, open the cover and turn on the light above the incubator to inspect the infant and find the possible cause for the event.

This involves inspecting the thorax on breathing movements, the respiratory support interface on pressure leaks, the position of the head for possible obstruction, the skin colour for signs of reduced blood flow or oxygenation and the mouth for vomit or mucus. If it is hard to see, the incubator is opened and the blanket is removed or the infant is slightly turned over.

Finding the cause of the event already disturbs the infant in the form of sound and light.



Intervene
In some cases cleaning the mouth, replacing the respiratory support interface or replace the head is a sufficient remedy. However, if the event is very serious or there is no evident cause for the event, the nurse will apply tactile stimulation. FiO2 is automatically controlled based on the oxygen saturation.

If stimulation does not help, the nurse will turn the infant around to ensure arousal. Ultimately, if all attempts fail and no progress is made, the nurse will call assistance and ventilate the infant. In the worst case, the neonatologist will intubate the infant.

Nurses use different interventions depending on the cause of the event but tactile stimulation is the most applied intervention.

Report
Most of the nurses only report events where they had to intervene. Based on their observations and data from the patient monitor they mark an event as an A (apnea), B (bradycardia), C (cyanose) or a combination.

The documentation is used by both doctors and nurses to keep track on the status of the infant over a longer period of time. Details about the events, the assumed causes and the response to the interventions are shared during the handover with the next nurse on duty.

Events are reported manually, resulting in subjective and potentially inconsistent clincial references.

Our contextual study showed that the tactile stimulation approaches currently used by nurses are highly variable, particularly the stimulation technique and the targeted locations on the infant's body [20]. We observed ten different stimulation techniques, with the application of pressure or the rubbing of skin the most common, which were mainly applied to the torso (thorax, side or abdomen). Stimulation methods were based on either prior training or intuition, which is a logical consequence of the lack of evidence-based recommendations.

A systematic literature study revealed that several systems and devices have been developed to provide mechanical and automated intervention of AOP [21], again with large variations in stimulation characteristics. Studies focusing on the termination of apnoea showed that this is possible with a closed-loop mechanical pulsating or vibrating device and that mechanical vibratory stimulation of 250 Hz is equally effective as manual stimulation. Studies investigating the effect of tactile stimulation on the prevention of apnoea mainly used oscillating or vibrating stimuli, the latter of which showed the best results by consistently reducing apnoea, hypoxia, and bradycardia. The added value of a direct response however remains unclear as there are no comparisons between automated systems and the current manual approach. Similarly, the most effective form of tactile stimulation is unclear, which stems from the lack of knowledge about the exact working mechanism and the sensory neuronal pathways. These findings were confirmed in the expert interviews.

Finally, the preliminary risk assessment for an ATSD, regardless of its design and shape, identified 7 general risks that need to be considered during development. These included: (1) risk of electrical shock of patient/user, (2) risk of skin damage, (3) risk of interference with other devices, (4) risk of hampering breathing, (5) risk of overstimulation/agitation, (6) risk of habituation and (7) risk of cross contamination/infection.

DEFINE

Initially, we defined five important user needs that the ATSD should fulfil to be of added value. These included; the device should (A) provide effective automated mechanical stimulation, (B) be safe, (C) suitable for preterm infants at risk for AOP, (D) user friendly and (E) maintain clinical awareness of the nurse. These user needs were further broken down in technical requirements originating from the findings of the discover-phase (Table 1).

As there is currently no standardized stimulation method that has shown to be effective, we will have to demonstrate that our device provides stimulation that is at least as effective as that provided by a nurse. As a result, a protocol for clinical evaluation was developed in parallel with the list of requirements, which was adapted accordingly. In order to perform this evaluation it must be possible to assess whether and when tactile stimulation (either

manual or mechanical) has been applied; a sixth user need that the ATSD should meet (F, Table 1).

As is it not yet possible to accurately predict cardiorespiratory events, we decided that the ATSD should respond to the clinical alarms the nurses receive. This enables evaluation of the effect of a direct response without affecting the initiation of alarms and thus the clinical awareness of the nurse.

IDEATE, PROTOTYPE & EVALUATE

In both brainstorm sessions, brainwriting and braindrawing were used to come up with solutions to a variety of problems. These included; (i) identification of existing devices that can provide tactile stimulation (e.g. toothbrush, game controller, massage chair and blood pressure cuff), (ii) clarification of the different forms of tactile stimulation that can be applied (e.g. pulling, pressing, stroking, massaging, tapping, squeezing, scratching, vibrating and shaking), (iii) different techniques for providing tactile stimulation (f.e. vibration motors, speakers, air pulses, squeezing inflatables, rotating balls in bearing, rolling cylinder and waterbed) and (iv) different ways to attach stimulating devices to a preterm infant (f.e. sticking or sucking to skin, clamping, knotting or clicking to diaper, ECG sensors, mattress, blankets or the incubator itself or keep in place by gravity). The ideas were combined into concepts and prototypes, ranging from simple sketches at the start to detailed physical models at the end, and were evaluated and compared through discussion with nurses using a selection of requirements (Table 1). Finally, several different test methods were used to verify that the final design met all the technical requirements specified (Table 1). This confirmation served as input for formal clearance of the ATSD for clinical evaluation, which was granted.

END RESULT

The final version of our ATSD, called BOBBY (Breathing Operation for BaBY), provides automated vibratory stimulation on the thorax of the infant directly after the onset of a clinical alarm from the patient monitor. BOBBY consists of multiple parts that are connected to each other in the following order: (1) a light sensor placed on the patient monitor, (2) a control-box consisting of a mini computer (Raspberry Pi 3, Raspberry Pi Foundation, UK) a camera and infrared lights placed on the back of the incubator, (3) an activation-box, housing an amplifier and two speakers placed near the incubator (4) a silicon strap with integrated air cavities placed on the thorax of the infant and (5) a fabric belt with small pieces of Velcro that keeps the strap in place (Figure 3).

Table 1. List of requirements including user needs (A-F) and underlying technical requirements, origin and purpose.

	Description	Origin	Purpose
A	**Provide effective automated mechanical stimulation**		
1	Start stimulation at onset cardiorespiratory alarm	Study protocol	Verification: bench test
2	Stimulate the thorax	Contextual study, interviews	Verification: physical check
3	Enable variable stimulation intensity/frequency	FMEA: risk of habituation	Verification: bench test
4	Enable stimulation site alteration	FMEA: risk of habituation/skin damage	Verification: physical check
5	Gentle stimulus	Focus group, interviews	Concept comparison
6	Stimulate large area	Focus group, interviews	Concept comparison
B	**Safe for preterm infants at risk for AOP**		
1	Stop stimulation at end cardiorespiratory alarm	FMEA: risk of overstimulation/agitation	Verification: bench test
2	Electrically safe according to IEC60601	FMEA: risk of electrical shock patient/user	Verification: electrical safety test
3	Electrical parts completely insulated	FMEA: risk of interference other devices	Verification: electrical safety test
4	Non-sticky material	FMEA: risk of skin damage	Verification: physical check
5	Soft material with rounded edges	FMEA: risk of skin damage	Verification: physical check
6	Medical grade material	FMEA: risk of skin damage	Verification: material documentation check
7	Temperature of device <38°C	FMEA: risk of skin damage	Verification: endurance test with temperature check
8	Resistant to disinfection according to hospital standard or disposable	FMEA: risk of infection	Verification: material documentation check
9	Noise within incubator <45dBA	FMEA: risk of agitation/discomfort patient	Verification: sound test
10	Minimal pressure when stimulating	FMEA: risk of skin damage, hampering breathing	Concept comparison
11	Minimal pressure when not stimulating	FMEA: risk of skin damage, hampering breathing	Concept comparison
12	Minimal contact area	FMEA: risk of skin damage	Concept comparison

	Description	Origin	Purpose
C	**Suitable for preterm infants at risk for AOP**		
1	Fits on infants of 23-38 weeks gestational age	Target group	Verification: physical check
2	Fits in/on an incubator or crib	Focus groups, observations	Verification: physical check
3	Resistant to temperatures of 20-50 degrees	Focus groups, observations	Verification: Endurance test
4	Water resistant	Focus groups, observations	Verification: bench test
5	Resistant to 80% humidity	Focus groups, observations	Verification: bench test
6	Fits in combination with sensors/lines/breathing interfaces	Focus groups, observations	Concept comparison
7	Works during kangaroo care	Focus groups, observations	Concept comparison
8	Works during ultrasound examination	Focus groups, observations	Concept comparison
9	Works during placement of lines/IV	Focus groups, observations	Concept comparison
10	Minimal blockage of phototherapy	Focus groups, observations	Concept comparison
D	**User friendly**		
1	Max two additional wires	Interviews, observations	Verification: physical check
2	Attach/detach to the infant within 10 seconds	Interviews, observations	Verification: User test
3	Set up at bedside within 3 minutes	Interviews, observations	Verification: User test
4	Easy to transport	Interviews, observations	Concept comparison
5	Easy to use and understand - minimize amount of settings	Interviews, observations	Concept comparison
6	Minimize cleaning time	Interviews, observations	Concept comparison
7	Minimize total size	Interviews, observations	Concept comparison
E	**Maintain clinical awareness**		
	N/A		
F	**Asses applied interventions**		
1	Log start and end of stimulation	Study protocol	Verification: bench test
2	Videorecord inside incubator	Study protocol	Verification: bench test

The work flow for BOBBY commences with the detection of a clinical alarm, usually a flashing light on the patient monitor, which is detected by a light sensor. Upon detection, the computer activates both speakers by playing an audio file, causing the cones of the speakers to oscillate. The speakers are airtight connected to two thin-walled air cavities in a silicon strap, positioned on the infants skin. The pressure signal of the speakers is transmitted via silicon tubes to the air cavities, which start to vibrate and stimulate the infant's skin without producing sound. In addition to the stimulation, the computer also activates the camera, capturing a video of the inside of the incubator. The videorecording is stored on the computer and the start and end time of the stimulation is logged to enable evaluation of the intervention afterwards.

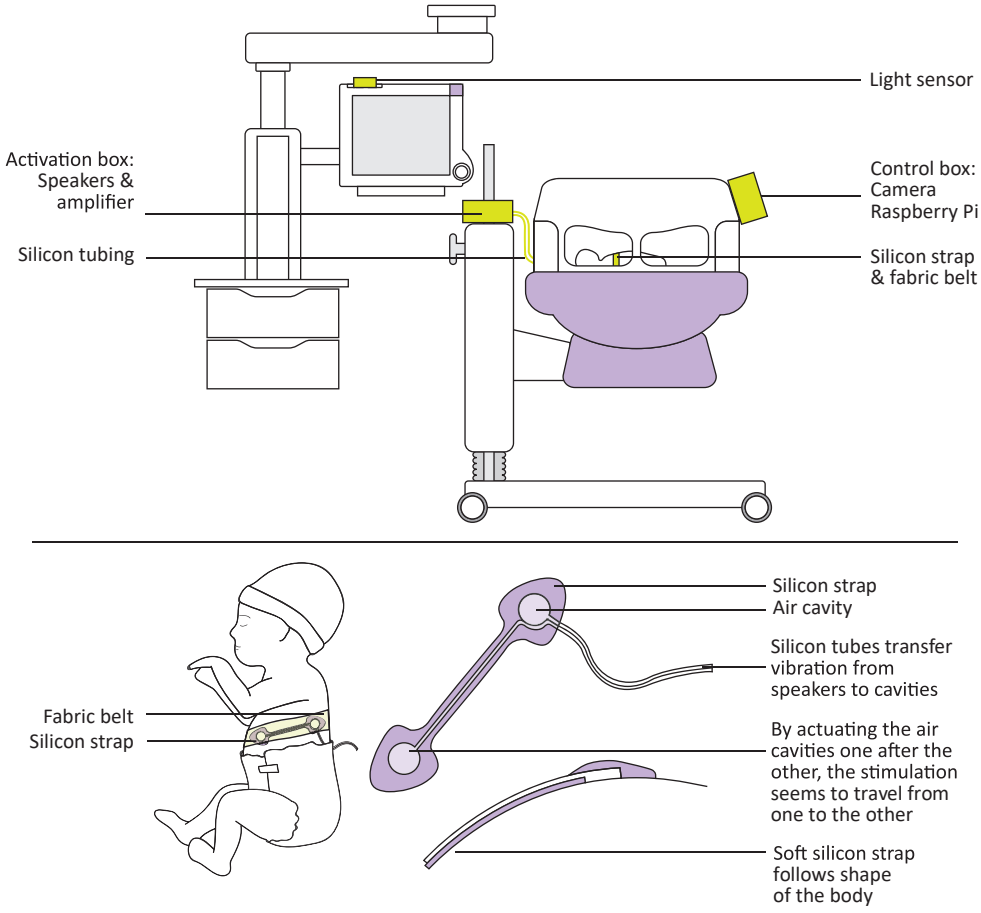


Figure 3. Overview of set-up and embodiment of BOBBY

The distinctive features of BOBBY include the activation of stimulation using speaker-like pressure actuators, enabling separate amplitude and frequency control. It also allows the separation of electronic parts from the incubator, preventing possible heat, electrical or acoustic injury to the infant. Furthermore, the soft and flexible strap that is easily attached, detached and replaced, makes BOBBY usable in different scenario's including kangaroo care. However, the ingenuity of the design is mainly in the way the stimulation is provided. In order to stimulate a large area of the skin without the need for a large and cumbersome probe, BOBBY provides apparent tactile "motion" [22], which provides the sensation of vibration that travels in a continuous motion from one actuator to another. This illusion is created by controlling the length and delay (onset asynchrony) of actuation between the two pressure actuators. This implies that once an alarm is detected, the computer first activates one speaker and then the other after a varying delay. As a result, the infant will experience a soft stroking sensation underneath the silicon strap, moving from the position of one cavity to the other.

BOBBY is patented under EP4103042A1 [23].

DISCUSSION

Although the idea of using mechanical and/or automated tactile stimulation to reduce or shorten breathing pauses in preterm infants is not new, our approach and development process is unique. These previous studies primarily applied existing tools [11, 16, 17, 24, 25], whereas we developed a device specifically for the application by using an iterative design process. This ensured that factors such as user needs, contextual requirements and potential risks were considered in the early stage and continually reconsidered, directing the design of a safe, effective and desirable solution.

The biggest challenges for developing this device were defining requirements and making design decisions regarding the effectivity of the stimulus, caused by two main obstacles: (1) despite existing evidence of tactile stimulation to (re)initiate breathing, the precise mechanism of action and therefore the most effective way of stimulation are unclear and (2) conducting explorative or interim tests of various ways of stimulation in preterm infants to enable quick iterative steps were not feasible due to ethical and safety considerations.

Rather than starting fundamental research to find out the mechanisms of action, we opted for a pragmatic approach and drew insight from existing literature, clinical experiences and expert opinion to design a device that is most likely to be effective. Additionally, we retained flexibility in the design (e.g., the ability to adjust amplitude and frequency independently) to allow for further refinement of the stimulus through future clinical research.

Although we used several research methods to gain insights into the problems and potential solutions, the process was limited by the fact that nurse input came from a relatively small group of people from our own ward. Furthermore, parents of preterm infants were not yet included in the developmental process, as the primary goals was to establish a scientific foundation for the design. However, recognizing the important role of parents in the eventual success and usability of the design, we plan to involve them in future iterations of the device. Although the device is currently tailored to function correctly in our department in order to evaluate its safety, feasibility and effectiveness, we believe the concept of BOBBY can be easily refined to make it suitable for other units and accepted and embraced by parents.

Assuming its stimulation is equally effective as manual stimulation, BOBBY will be able to reduce BRP's and apnoea and thereby reduce the onset or exacerbation of associated hypoxia and bradycardia by providing an automated and direct response. In the future, combining BOBBY with a predictive algorithm may provide a preventative solution that potentially avoids cardiorespiratory instability in this vulnerable cohort of infants. By logging and visualizing the required tactile intervention in the future, BOBBY could also aid objective clinical assessment of the infant and therefore benefit both patient and nurse.

CONCLUSIONS

We aimed to address current challenges in the treatment of breathing pauses in preterm infants by developing an automated tactile stimulation device that enables a direct and reliable response. This was accomplished using an iterative design process, culminating in the creation of BOBBY, which is a novel stimulation device that is ready for clinical validation. Ultimately we consider that it will be integrated in standard neonatal care.

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CHAPTER 6

Automated tactile stimulation in response to cardiorespiratory events in preterm infants: a feasibility study

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ABSTRACT

OBJECTIVE, DESIGN & SETTING

Assess the feasibility and safety of a purpose-built automated tactile stimulation device (ATSD) responding to cardiorespiratory events in preterm infants in a randomized cross-over study at a level-III Neonatal Intensive Care Unit in the Netherlands.

PATIENTS & INTERVENTIONS

Infants born between 24-30 weeks gestational age, receiving non-invasive respiratory support and experiencing apnoea, bradycardia and/or hypoxia for >10 seconds. Infants underwent two study periods of 24 hours. In the control period, the ATSD was attached but inactive. In the intervention period, ATSD was activated and used in addition to standard care, providing direct vibratory stimulation in response to clinical alarms.

MAIN OUTCOME MEASURE

Feasibility of using ATSD, expressed by the number of infants completing the study, the ability to provide stimulation on the skin and the perceived feasibility by the nurses.

RESULTS

Sixteen infants were included, of which 14 (88%) completed both study periods. Two infants were withdrawn from the study prematurely: one infant required intubation for cyanotic spells and the other developed local non-blanching erythema consistent with a mild pressure ulcer, upon which the device was removed. During the intervention period, ATSD correctly detected 84% of the cardiorespiratory events, with automatic stimulation following 100% of the events. Nurses found the ATSD easy to use and rated the clinical utility neutral to positive.

CONCLUSION

Applying automated tactile stimulation in preterm infants using a purpose-build device is feasible, was well tolerated by infants and nurses considered our device useful and easy to use.

INTRODUCTION

Most very preterm infants experience apnoea, defined as respiratory pauses of 10-20 seconds, that are a result of lung and brain immaturity [1, 2]. Apnoeic events are often accompanied with hypoxia and/or bradycardia, which, especially if prolonged, severe or frequent, contribute to adverse short- and long-term outcomes, including neurodevelopmental impairment [3-5]. Reactive treatment of these events primarily involves tactile stimulation and entirely depends on caregivers' actions. Its execution is therefore subject to human factors such as the perceived workload, perceived importance, walking distances and cultural norms [6, 7]. These factors delay, or can even avert, effective action to counteract apnoea, causing potential injury to the infant [8].

Automated mechanical stimulation has the potential to shorten apnoea, hypoxia and bradycardia experienced by preterm infants by enabling a reliable and direct response. Studies have shown that mechanical stimulation is effective in preventing and/or terminating these events [9] but there are currently no devices commercially available that provide automated tactile stimulation systems and can be used in the Neonatal Intensive Care Unit (NICU). This prompted us to develop an automated tactile stimulation device (ATSD) that generates and applies vibrotactile stimulation on the thorax of a preterm infant in response to adverse cardiorespiratory events. The aim of this study was to assess the feasibility, including safety, of this device in the NICU.

METHODS

STUDY SETTING

This randomized cross-over study was conducted in the NICU of the Leiden University Medical Center (LUMC), a tertiary-level, perinatal centre with a single-room design, divided into two units with a total of 25 beds. The Institutional Review Board of the LUMC (METC LDD) approved the protocol (P21.034) and the study was registered in the Dutch national trial register (registration number NL9606). Written informed parental consent was acquired prior to participation of each infant in the study.

All infants who are admitted to the unit are continuously monitored via a patient monitor at the bedside (Philips Intellivue MP70 or MX750, Philips Medical Systems, the Netherlands). All modes of ventilatory support are provided using the SLE6000 ventilator (SLE Ltd, Croydon, UK) and can be supplemented with automated titration of the fraction of inspired oxygen (FiO2) using the embedded "OxyGenie" option, which adjusts FiO2 based on SpO2 values

from a pulse oximeter (Masimo Corporation, Irvine, California, USA). The patient monitor displays cardiorespiratory alarms from directly connected sensors, such as electrocardiogram ECG, as well as from the ventilator, which is coupled via Philips EC5-EC10 modules. Default activated cardiorespiratory alarms include: low heart rate and bradycardia directly via the patient monitor and desaturation, high FiO2 requirement and steep FiO2 increase from the ventilator. Apnoea alarms based on impedance via ECG leads are disabled but apnoea alarms originating from the ventilator's pressure breath detection module are occasionally activated on discretion of the caregiver. More information about the alarm settings in our unit is provided in the supplemental material of Chapter 4.

STUDY POPULATION

Preterm infants born between 24 and 30 weeks of gestation who were receiving respiratory support in the form of continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV) were assessed for eligibility. Infants were considered eligible when they experienced at least one apnoeic, bradycardic and/or hypoxic episode of >10 seconds in the previous hour, but were otherwise clinically stable and expected to be on non-invasive respiratory support for the next 48 hours. Infants with major congenital anomalies affecting breathing or ventilation were excluded as were infants suspected or proven to have sepsis with apparent discomfort, as indicated by a comfort score >14. The predefined goal was to include 16 infants. Inclusion took place in two phases, starting with eight infants of 27-30 weeks gestation, followed by 8 infants of 24-26 weeks gestation.

AUTOMATED TACTILE STIMULATION DEVICE

Various forms of (mechanical) tactile stimulation have been shown to positively impact breathing in preterm infants [9, 10]. While it is reasonable to assume that differences in effectiveness exist, a direct comparison of their effectiveness is not yet feasible, and the most optimal method of stimulation remains unknown.

Instead of pursuing fundamental research to find out, we adopted a pragmatic, iterative design approach, incorporating insights from our research, existing literature, clinical experience, and feedback from NICU nurses and neonatologists. This approach led to the development of BOBBY, an ATSD designed to be both effective and safe, providing a soft stroking sensation that mimics a caregiver's touch.

The device consists of multiple parts that are connected to each other in the following order: (1) a light sensor, used to detect the alarm light of the patient monitor, (2) a control-box consisting of a mini computer (Raspberry Pi 3, Raspberry Pi Foundation, UK), a camera

and infrared lights, used to control automated stimulation and enable video recording of the infant, (3) an activation-box housing an amplifier and two speakers, used to generate vibration, (4) a silicon strap with integrated air cavities that are airtight connected to the speakers, used to transfer the vibration from the speakers to the skin of the infant and (5) a fabric belt with small pieces of Velcro, used to keep the silicon strap in place (Figure 1). A more detailed description can be found elsewhere (Chapter 5).

For this study, the ATSD was programmed to detect all clinical alarms (yellow and red) from our patient monitor and connected ventilator. The selected stimulation was filtered white noise in the 2- to 30-Hz band, with a moving stimulation of 1-10 cm/seconds as this was perceived as most comforting [11-13]The distance between the two stimulation points on the strap was 4 cm and the length of each stimulation was 1.2 seconds with an onset asynchrony 0.4 seconds, resulting in a total stimulus duration of 1.6 seconds. The stimulation was repeated for long as the alarm was active, with pauses of 0.8 second between each stimulus.

STUDY PROCEDURES

A crossover design was used to study each infant with and without receiving automated tactile stimulation. Infants underwent two consecutive study periods of 24 hours each, resulting in a total study duration of 48 hours.

Before the study started, the ATSD was attached to the infant and activated to finetune the required strength of the stimulation (soft, medium or strong) in a patient specific manner. This was done by evoking multiple stimulations and evaluating the response of the infant accordingly, starting with the softest stimulation. If the infant responded with body movements [14], that amplitude was selected and used throughout the study. If the infant did not respond, the procedure was repeated with the normal, and eventually the strong stimulus. If the infant did not respond to any of the stimulations, the strong amplitude was selected.

Castor EDC (Castor, Amsterdam, The Netherlands), a web-based data management platform was used to randomize the order of the two study periods using variable block sizes (2,4). In the control period the ATSD was attached but only the camera was activated. In the intervention period, the ATSD was fully activated and used in addition to standard care, providing direct vibratory stimulation in response to the clinical alarms. The ATSD remained attached during the entire study, including kangaroo care time, but was replaced at every routine care round and placed on top of the infant to prevent pressure ulcers. All included infants received their own silicon strap to prevent cross contamination. Alarm settings for

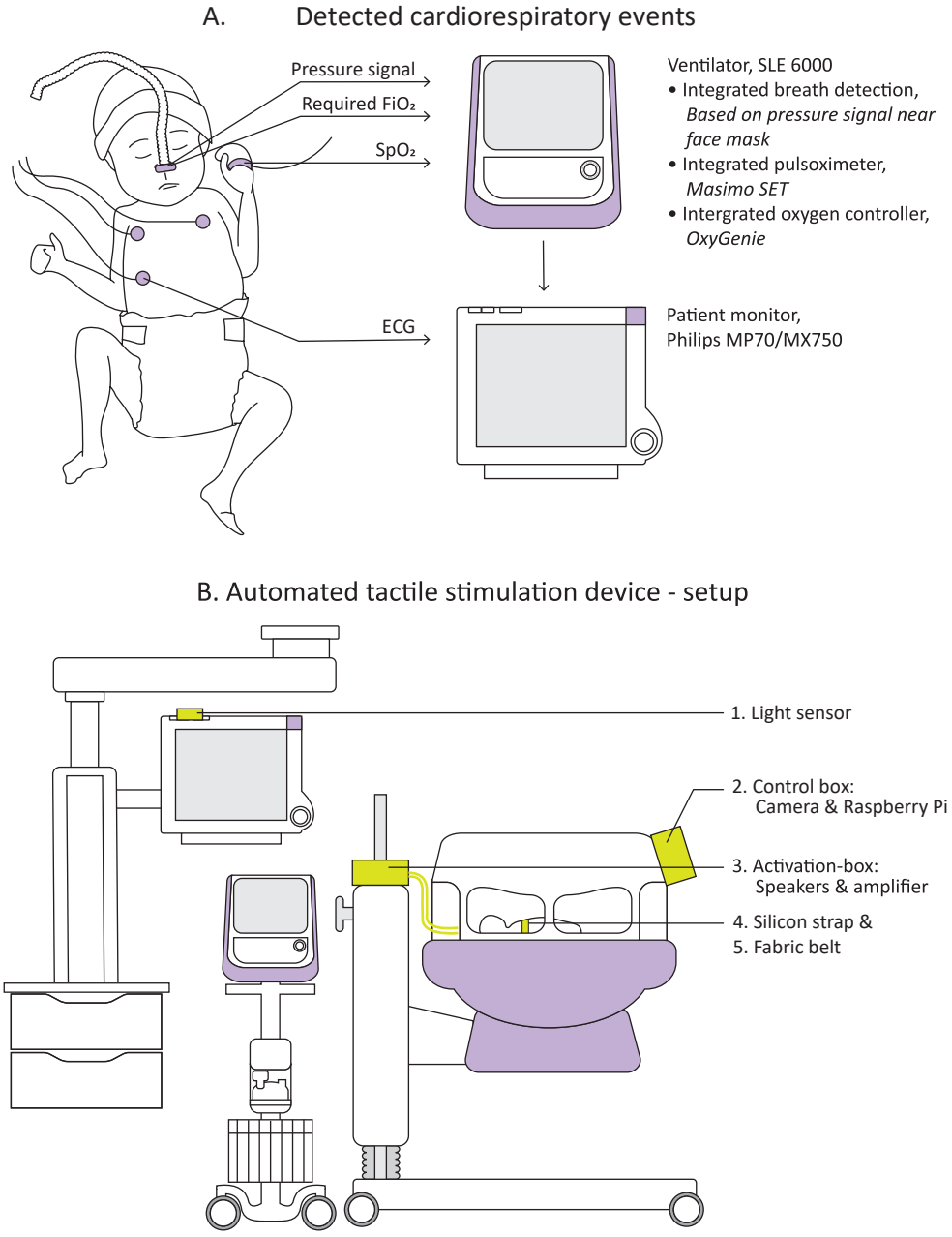

Figure 1. Overview of set-up (A, B) and embodiment (C) of the ATSD

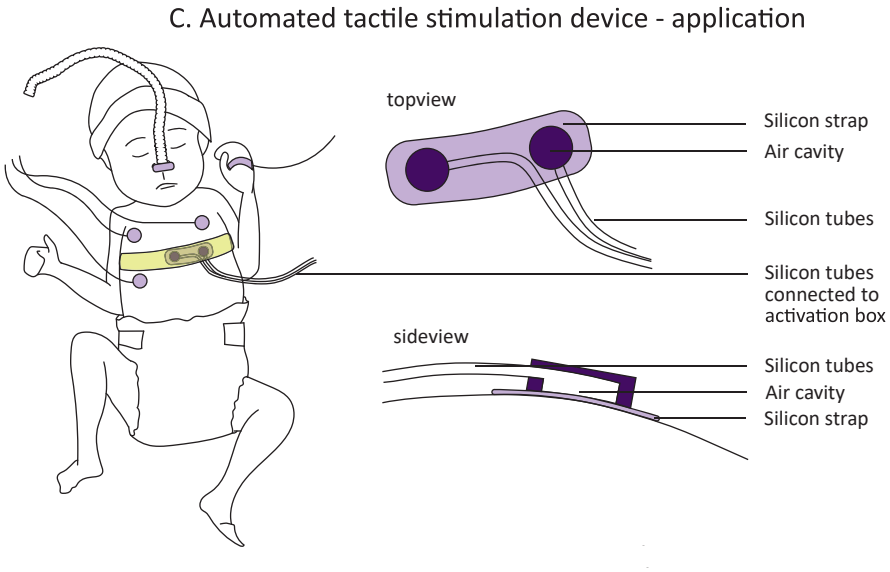

Figure 1. Overview of set-up (A, B) and embodiment (C) of the ATSD

cardiorespiratory monitoring were not modified for the purpose of this study.

To evaluate safety, nurses were asked to assess the skin underneath BOBBY during routine care and record the COMFORTneo score [15] every four hours. In addition, they were asked to fill in a digital questionnaire regarding the perceived ease of use. Nurses who worked during the intervention period were asked to fill in an additional questionnaire regarding the perceived clinical utility of the ATSD. The questionnaires are based on the Technology Acceptance Model (TAM)[16] and have been included in the supplemental material.

The study was terminated prematurely if the comfort score exceeded 14, indicating discomfort, if the infant developed pressure ulcers or if other (serious) adverse events occurred that were expected to be related to BOBBY.

DATA COLLECTION AND ANALYSIS

Baseline characteristics from each infant were collected from our Patient Data Management System (PDMS Metavision, IMDsoft, Tel Aviv, Israel), including demographics, details on respiratory support and clinical state. Vital parameters (1Hz) and alarm details were collected using Philips Data Warehouse (DWH) Connect software. Video recordings of the infant in the incubator and logfiles with timestamps for the automated stimulation were retrieved from the ATSD itself.

The primary outcome was feasibility, including safety, of using ATSD in preterm infants. Feasibility was expressed by the number of infants finishing the protocol, the ability to

provide stimulation in response to a cardiorespiratory event and the perceived feasibility and clinical utility by nurses. An event was defined as a single alarm or a cluster of different alarms that followed each other directly. Correct application was assessed by the video recordings of the infant.

Secondary outcomes included: (1) proportion of time with oxygen saturation (SpO2) values <90%, (2) proportion of time with heart rate (HR) <100 and (3) average oxygen exposure (fraction of inspired oxygen; FiO2) using the vital parameters from the DWH, (4) average comfort score, (5) occurrence, (6) timing and (7) duration of manual stimulation using the video recordings of the ATSD and the (7) occurrence and (8) duration of automated stimulation from the logfiles of the ATSD.

STATISTICAL ANALYSIS

Continuous data are presented as median (IQR) or mean ± SD as appropriate, with standard tests for normality. Time within specific SpO2 ranges were collated for each infant and expressed as proportion of usable recorded time. Comparisons between the control and intervention period were assessed with the Wilcoxon matched-pairs test using IBM SPSS Statistics V.25 (IBM, Armonk, New York, USA). The intention-to-treat principle was applied and a p value <0.05 was considered statistically significant.

RESULTS

The study was conducted from July 2021 to March 2022. Consent was sought from 18 parent couples, of which 16 agreed to participate and whose infants were included in the study (baseline characteristics in table 1).

The cross-over comparison could be completed in 14 infants (88%). In two infants the study was stopped prematurely for different reasons: one infant required intubation for cyanotic spells and one infant developed a small non-blanching erythema without broken skin, consistent with pressure ulcer grade 1, after which we removed the ATSD and stopped data collection (after 4.5 respectively 3.5 hours in the study). No other (serious) adverse events were observed. The comfort score of all patients remained <14 during the entire study.

The ATSD correctly detected 84% of the events in the 14 infants that finished the study (Table 2). In the intervention period, 1426/1429 (100%) of the correctly detected events were automatically followed by mechanical stimulation. From the video recordings it became clear that the silicon strap was correctly positioned on the skin in 47% of events, intentionally removed because of (routine) care in 15% of events and unintentionally removed in 3% of events. In the remaining 35% of events the position of the strap could not

Table 1. Patient characteristics

	n=16
Gestational age (weeks.days)[a]	26.2 (± 1.2)
Birth weight (grams)[a]	880.0 (± 174.5)
Gender (female/male)[a]	7/9
Postnatal age at study entry (days)[b]	8.5 (4.0 – 11.0)
Weight at study entry (grams)[a]	873.7 (± 167.6)
Ventilation mode (CPAP/CPAP+back-up ventilation /NIPPV)	4/11/1
Allocation (intervention first/control first)	8/8
Amplitude of stimulation (soft/medium/strong)	0/4/11
Comfort score before start study[a]	11.0 (± 1.4)

Data is presented as mean ± SD for normally distributed data (a) or median (IQR) for data that were not normally distributed (b)

Table 2. Feasibility outcomes

Total event detection	**Control** (n=1930)	**Intervention** (n=1706)	**Total** (n=3636)
Correct detection, n(%)	1613 (84)	1429 (83)	3060 (84)
False detection, n(%)	28 (2)	10 (1)	38 (1)
Missed detection, n(%)	271 (14)	267 (16)	538 (15)
Automated stimulation following correct detection		**Intervention** (n=1429)	
Stimulation following detection, n(%)		1426 (100)	
No stimulation following detection, n(%)		3 (0)	
Silicon strap positioned on the skin, n(%)		666 (47)	
Silicon strap position unknown, n(%)		507 (35)	
Silicon strap unintentionally removed, n(%)		37 (3)	
Silicon strap intentionally removed, n(%)		219 (15)	

be assessed due to for example covering blankets.

Figure 2 shows the responses of nurses to the perceived ease of use (A) and clinical utility (B) questionnaire. Questionnaire A was filled in by 74/82 (90%) nurses during either the intervention or the control period. The majority (strongly) agreed that the ATSD was easy to use. Questionnaire B was completed by 32/35 (91%) nurses during the intervention period. Most nurses found the ATSD suitable for use in the NICU and would like to see it being further developed. Overall, clinical utility of the ATSD in its current form was rated neutral to positive.

Figure 2. Results of the survey on perceived ease of use and clinical utility of the ATSD

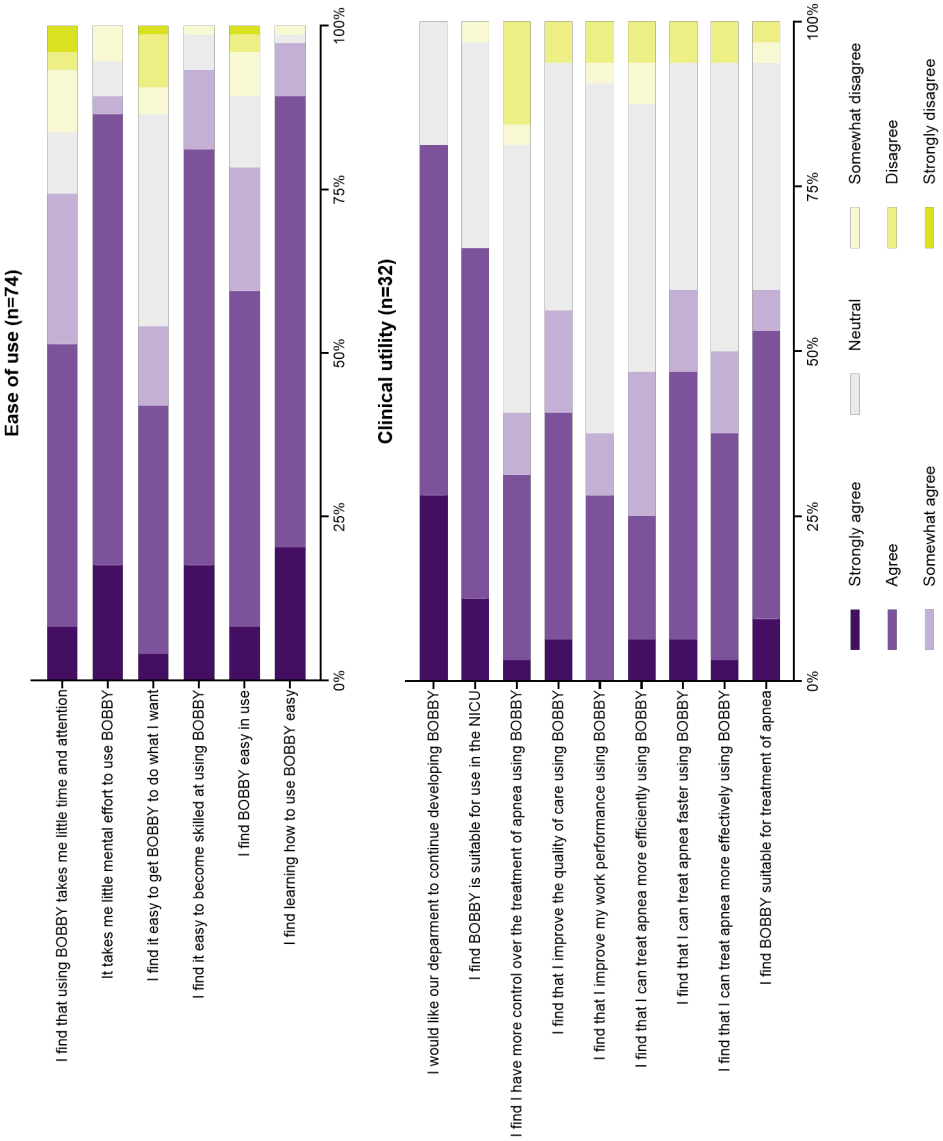

Table 3. Secondary outcomes

	Control	Intervention	p-value
SpO2:			
Proportion of time SpO2 <90%	9.3 (2.6 – 13.7) %	8.2 (2.7 – 12.0) %	0.10
Heart rate:			
Proportion of time HR < 100 bpm	0.6 (0.1 – 1.0) %	0.5 (0.2 – 0.9) %	0.66
FiO2:			
Average FiO2 delivery	26.7 (22.4 – 35.1) %	24.9 (22.0 – 33.3) %	0.12
Manual stimulation:			
Number of manual stimulations	2.5 (1.0 – 5.3)	2.0 (0.8-4.3)	0.55
Average response time	20.0 (2.1 – 27.1) s	16.7 (2.6 – 45.9) s	0.75
Average stimulation duration	30.8 (14.8-48.3) s	19.1 (7.0-30.4) s	0.35
Automated stimulation:			
Number of automated stimulations*	-	79.0 (38.5-100.3)	-
Average automated stimulation duration*	-	19.1 (14.8-30.2) s	-
Comfort score:			
Average comfort score	10.1 (10.6-11.2)	10.3 (10.3-11.0)	0.66

Data is presented as median (IQR). Excluding stimulations that were generated when BOBBY was (un) intentionally not attached*

For the analysis of secondary outcomes, data of 14/16 infants that completed the study were used. On per patient analysis the time spent in SpO2<90% tended to be lower in the intervention period, but the differences did not reach significance (Table 3). The time spent in HR<100 bpm, average provided FiO2, number of manual stimulations, response time of the nurse as well as the manual stimulation duration was similar in both periods. Additional automated stimulation was provided 79 times in the intervention period with a mean duration of 19.1 seconds. Despite the large differences in total amount of stimulation, the average comfort score did not differ between periods.

DISCUSSION

This randomized cross-over study was designed to assess the feasibility, including safety, of using a purpose-built ATSD that responds to cardiorespiratory events in preterm infants. The results show that our device, BOBBY, was able to provide automated tactile stimulation following most adverse cardiorespiratory events, was well tolerated by the infants and considered feasible by nursing staff. Apart from a single case of a mild pressure ulcer (grade 1), which resolved upon removal of the device, no adverse events were observed.

This study contributes to a growing body of literature demonstrating the potential benefit of using mechanical tactile stimulation to stabilize breathing in preterm infants [9]. Previous studies have primarily utilized mechanical stimulation that was either activated by caregivers or provided continuously. In contrast, our study has examined the usability of a fully automated mechanical tactile stimulation device that detected and responded to adverse events in preterm infants over an extended period of time.

Initially, the ATSD was successfully applied in all included infants and in 14/16 infants (87.5%) the full 48-hour study period was completed. In two infants the study was stopped within a few hours because of clinical deterioration, unrelated to the study, and development of non-blanching erythema (pressure ulcer grade 1). This occurred in the control period of the youngest participating infant (GA 25+6, 2 days old) and may have been caused by the silicon strap being pressed too firmly to the skin. It is well known that this patient group is susceptible to developing iatrogenic skin injuries [17] and that erythema also occurs after placing pulse oximeter probes. Nevertheless, measures to prevent this should be included in the next design iteration of the device.

The ATSD in its current form was able to provide automated stimulation in 83% of the events in the intervention period, of which most were directly applied to the skin of the infant. Successful application was mainly hampered by the error-prone detection method. Although the light sensors were tested and adjusted at the start of each study, the installation of new patient monitors (MP70 was replaced by MX750, Philips Medical Systems, Best, the Netherlands), which automatically dimmed screen and alarm light brightness in low light, resulted in numerous missed alarms in several infants.

In addition, using these alarms as a trigger was a suboptimal approach since they inherently occur relatively late during the adverse cardiorespiratory event, due to built-in delays and averaging. Indeed, in preterm rabbit kittens we showed that an early, anticipatory stimulation was more effective in counteracting apnoea than a reactive response [18], a finding that underscores the importance of response time in resolving cardiorespiratory events [8, 19]. We hypothesize that the increasing level of hypoxia, which results from longer-lasting

apnoea's, blocks or modifies somatic inputs arising from tactile stimulation [20], thereby impairing the resumption of breathing and resolution of apnoea. The main limitation of this study is the inability to accurately detect, and therefore evaluate, the onset and duration of apnoea. Impedance monitoring has not been used in our unit since the transition from an open-bay to a single room unit due to its insensitive and non-specific nature and its significant contribution to alarm fatigue and the pressure breath trigger of the ventilator is used on discretion of the caregiver for the same reasons. While our current approach for triggering stimulation was suitable for the purposes of this study, when designing a follow-up study to assess effectiveness, quicker and more reliable detection or even prediction methods should be considered in order evaluate the full potential of ATSD.

The opinion and experience of nurses, the primary users of the device, play a crucial role in evaluating feasibility. Nurses rated the ATSD favourably in terms of usability and were neutral to positive in terms of clinical utility, which is noteworthy given that the device was not yet optimally utilized in this study. The TAM questionnaires are however somewhat biased towards positive responses and potentially encouraged favourable perceptions of the technology. There was unanimous support for continuing its development and nurses will continue to be involved, as they were in the initial development phase (Chapter 5).

In this feasibility study no significant differences in physiological parameters were observed, but the study was not powered for these comparisons. It is furthermore possible that the routine use of automatic oxygen titration in our centre contributes to relatively greater stability in infants [21], making the possible positive effect of tactile stimulation less evident. However, even with an automated controller, effectively addressing intermittent hypoxia resulting from central apnoea remains challenging due to (1) the rapid onset of hypoxia after apnoea, with SpO2 reaching its lowest point within approximately 18–20 seconds [22], and (2) the fact that FiO2 adjustments only become effective once breathing resumes. A recent study demonstrated that increasing FiO2 in anticipation of hypoxia can reduce the severity of hypoxia following apnoea, but also results in SpO2 overshoot upon resumption of breathing [23]. The combination of automated oxygen control with automated stimulation holds the potential to prevent or shorten apnoea, thereby facilitating more precise titration of FiO2 to maintain the infant within target oxygenation ranges.

However, we could demonstrate that an ATSD can respond directly and is unaffected by alarm fatigue, unlike caregivers. This makes it possible to respond even to frequent short-lasting and self-limiting events, which could potentially enhance physiological stability of preterm infants [24, 25]. On the other hand, the infants will receive considerable more stimulation - nearly 40 times more than manual stimulation according to our results – as it will respond to all alarms. The performance of the device is highly dependent on the detection method and

its associated limitations, with false alarms, for instance, potentially resulting in unnecessary stimulation. There is evidence that excessive exposure to stimuli can have short- and long-term adverse consequences [26-28]. However, other studies have shown beneficial effects of repetitive, dynamic and/or even continuous tactile stimulation in preterm infants [29-33] and we observed that the infants in our study remained comfortable in both periods. Further research should aim to establish a sound benefit-risk assessment of ATSD in the NICU. These assessments should include, the effectiveness of automatic stimulation on reducing apnoea, hypoxia and bradycardia in preterm infants, possible adverse effects and the workload and user-experience of the nursing staff. Additionally, the results and feedback from all studies will help to refine our ATSD into a clinically useful and user-friendly medical device.

CONCLUSION

The use of our purpose built ATSD (BOBBY) was shown to be feasible in our NICU. Automated tactile stimulation was successfully applied, there were no serious adverse events and the nurses considered the device suitable and easy to use. Addressing the current knowledge gaps and continuing to refine the technology will be key steps in realizing the full potential of automated tactile stimulation for preterm infants in the NICU.

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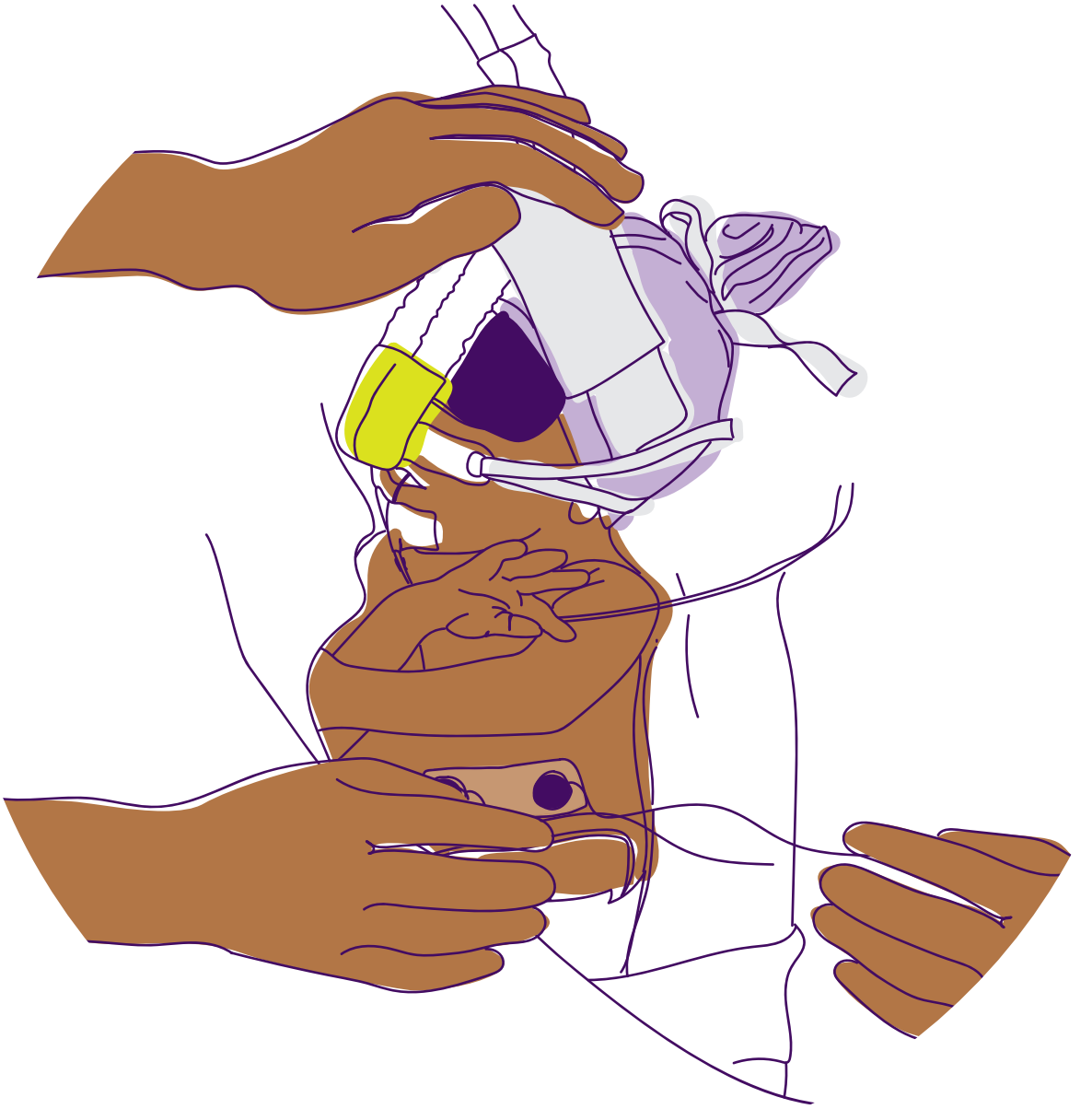

PART 5

CHAPTER 7

Technology in the delivery room supporting the neonatal healthcare provider's task

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ABSTRACT

Very preterm infants are a unique and highly vulnerable group of patients that have a narrow physiological margin within which interventions are safe and effective. The increased understanding of the foetal to neonatal transition marks the intricacy of the rapid and major physiological changes that take place, making delivery room stabilisation and resuscitation an increasingly complex and sophisticated activity for caregivers to perform. While modern, automated technologies are progressively implemented in the neonatal intensive care unit (NICU) to enhance the caregivers in providing the right care for these patients, the technology in the delivery room still lags far behind. Diligent translation of well-known and promising technological solutions from the NICU to the delivery room will allow for better support of the caregivers in performing their tasks. In this review we will discuss the current technology used for stabilisation of preterm infants in the delivery room and how this could be optimised in order to further improve care and outcomes of preterm infants in the near future.

INTRODUCTION

Because of their immaturity, very preterm infants are a unique and highly vulnerable group of patients that have a narrow physiological margin within which interventions are safe and effective. A large amount of scientific research along with technological innovations have improved care for preterm infants in the neonatal intensive care unit (NICU). In the NICU, infants are monitored meticulously and devices are used to provide treatment in a safe and sophisticated manner. The arrival of automated technologies, whether or not in combination with artificial intelligence (servo-controlled incubator, algorithm driven ventilators, automated oxygen titration, predictive monitoring) has decreased the manual work in the NICU and improved care and outcome in the last twenty years.

While these automated technologies are increasingly being used in the NICU, technology in the delivery room still lags far behind. Preterm infants can be difficult to manage in the intensive care unit, but this task is considerably more complex at birth due to the infant's rapidly changing physiology. Particularly at birth, automated technologies and/or artificial intelligence could be highly relevant, since the infant's physiology is undergoing large and rapid changes. We now start to understand that the transition to life after birth is an extremely critical phase of life which greatly impacts an individual's risk of death, injury [1, 2] or life-long disability [3, 4], particularly infants born very preterm.

Stabilisation of preterm infants in the delivery room is usually brief, but many interventions need to be performed in order to stabilise the infant's temperature, (spontaneous) ventilation and oxygenation in a time sensitive manner. It has been shown that some interventions are not as effective as caregivers assumed and that the provision of an optimal and safe treatment during this stressful moment is a major challenge for caregivers. [5-8] It also has been demonstrated that caregivers have difficulty in assimilating the complex and rapidly changing physiological information that is required to make accurate strategic decisions with regard to assisting preterm infants as they transition to newborn life [6-10].

In this review we will discuss the current technology used for stabilisation of preterm infants in the delivery room and how this could be optimised by the provision of purpose-built devices and technology that assimilates all of the physiology data and supports decision making processes.

TEMPERATURE MANAGEMENT

The first step of neonatal stabilisation is the prevention of heat loss, which easily occurs in the exposed and wet infants through convection, conduction, radiation and evaporation, resulting in a decreased body temperature. Hypothermia after birth has been recognised as a significant contributor to neonatal morbidity and mortality. [11, 12] Although less is known about the acute and long-term impact of hyperthermia after birth, the potential risks for both hypothermia and hyperthermia are currently recognised in the international resuscitation guidelines with the advice to keep the body temperature of the infant between 36.5 and 37.5°C. [13, 14] While measures to prevent hypothermia – such as increased room temperature and the use of a head cap, a wrap, a radiant heater, a thermal mattress and heated and humidified gases - are commonly performed, keeping the body temperature within the normal range during stabilisation at birth proves to be challenging. [15-18]

Currently, the temperature is often only measured at NICU admission, which does not allow us to take correcting measures until that moment. Although standardised thermoregulation protocols, training, and audits have shown to improve our temperature management [19-21], frequent or continuous measurement of temperature, in combination with a temperature dependent protocol, can further improve this. [22, 23] However, temperature management based on continuous measurements requires constant attention and is more labour intensive. Technology could assist in this process by providing visual or audible cues when the recommended ranges are exceeded in order to capture the attention of the caregiver or by providing decision support on the timing and type of heat loss measures to take. Technology could even further assist caregivers by enabling automated regulation via servo-controlled mattresses and radiant warmers, which are commonly used in the NICU.

Although a recent multi-centre study reported that the use of servo-controlled radiant warmers on the delivery room showed no benefits over the use of radiant warmers on maximal output [24], studies implementing servo-controlled radiant warmers combined with a temperature dependent protocol for additional measures show the highest overall scores of normothermia at NICU admission, ranging from 74% to 100%. [25-28] As infants are much more exposed in the delivery room as compared to the NICU, full automation of thermoregulation in the delivery room probably asks for completely different closed-loop solutions minimising the effects of the environment on their temperature.

TACTILE STIMULATION

As of 2005, local and international resuscitation guidelines recommend tactile stimulation in the form of warming, drying and rubbing the back or soles of the feet to evoke spontaneous breathing in newborn infants. [13, 14, 29] While experimental studies demonstrated tactile stimulation to increase respiratory effort [30, 31], the clinical guidelines are still largely based on many years of experience and expert opinion as there is lack of data on this topic in human infants.

Several retrospective studies recently evaluated current practice, showing a wide variation between caregivers and between centres concerning timing, duration and method of stimulation. [32-36] In addition, stimulation turned out to be often omitted, in particular in preterm infants placed in a polyethylene bag. [34-36] A recent randomised trial showed that repetitive tactile stimulation in preterm infants increased oxygenation, while less oxygen was needed, and improved respiratory effort. [37] However, the trial also led to a high incidence of stimulation in the standard group. This effect could be attributed to the Hawthorne effect and/or the increased focus on tactile stimulation during the study, which in turn implies that omission of stimulation happens because it is simply forgotten.

Albeit the most optimal way of stimulation remains unclear, automated mechanical stimulation could ensure tactile stimulation to be provided, in a more consistent way. [38] Several closed-loop vibratory stimulation devices to treat apnoea's of preterm infants admitted to the NICU have been described in literature, but currently none of these are commercially available. [39-42] No studies have been performed in the delivery room, but mechanical vibratory stimulation in preterm infants in the NICU proved to be as effective as manual stimulation in aborting apnoeic episodes in two preliminary studies, [42, 43] and two other observational studies reported that their closed-loop pulsating and vibrating devices were able to terminate 90% of all apnoea's. [44, 45] Applying this technique in the delivery room has the potential to replace manual intervention, eliminating the chance that stimulation will be forgotten.

OXYGENATION

Currently, oxygen administration is guided by predefined oxygen saturation (SpO2) target ranges. [46] Caregivers manually titrate the fraction of inspired oxygen (FiO2) accordingly to avoid hypoxia and hyperoxia. At birth, hypoxia can lead to suppression of spontaneous breathing, and hypoxia that persists for more than 5 minutes after birth is associated with an increased risk of mortality and the development of intraventricular haemorrhages. [47-50] On the other hand, hyperoxia needs to be avoided as this increases the production of

free radicals, but also can inhibit the respiratory centre. [51, 52] As such, it is critical to adequately control oxygenation during this period. However, this is an incredibly difficult and complex task given the fact that immediately after birth, the lung is constantly and rapidly changing.

It has been shown that maintaining SpO2 values within a predefined target range with manual titration is extremely difficult in the delivery room as well as in the NICU. [53-59] Randomised trials demonstrated the potential of closed-loop titration of FiO2 in the NICU, increasing the time spent within the SpO2 target range with a decrease in extreme deviations in oxygenation, including both the duration and the number of episodes. [60-69] The use of a closed-loop oxygen controller in the delivery room has so far only been studied once in a preterm lamb model. [70] In this study, the effect of a closed-loop oxygen controller with timeout restrictions of 30s after each titration step was compared to manual titration of oxygen after evaluation of SpO2 to be performed every 30s. Results show similar time within the SpO2 target range and below the target range, while time above the target range was significantly shorter in the automatic titration group. [70]

However, this technique cannot just simply be extrapolated to the delivery room, as there are considerable differences with regard to target ranges, physiology and devices used. In the NICU, the SpO2 target range is static, while this is dynamic in the first minutes after birth. Oxygen exchange in the lungs is largely determined by the surface area available for gas exchange and the oxygen concentration gradient between the alveoli and adjacent capillaries. At birth, when the airways are mostly liquid-filled, the surface area available for gas exchange is small and a high oxygen concentration is required for adequate exchange (Figure 1A). As the lungs aerate, the surface area available for gas exchange increases exponentially and as such a much lower oxygen concentration is needed for adequate oxygenation (Figure 1B). The oxygen concentration administered after birth should thus be adjusted according to the degree of lung aeration. This would require the closed-loop titration mechanism to adjust the SpO2 target range continuously based on the time after birth. In addition, the algorithm of the closed-loop oxygen controller should also be calibrated based on the factors present at birth which influence the position of the oxygen-haemoglobin dissociation curve.

Furthermore, titration of oxygen using a T-piece ventilator, which is commonly used for respiratory support at birth [14], can result in a delay between the moment of titration and the delivery of the corresponding FiO2 at the face mask of the infant. [71] The algorithm used by the closed-loop oxygen controller that is used with the T-piece resuscitator should therefore reckon with this delay.

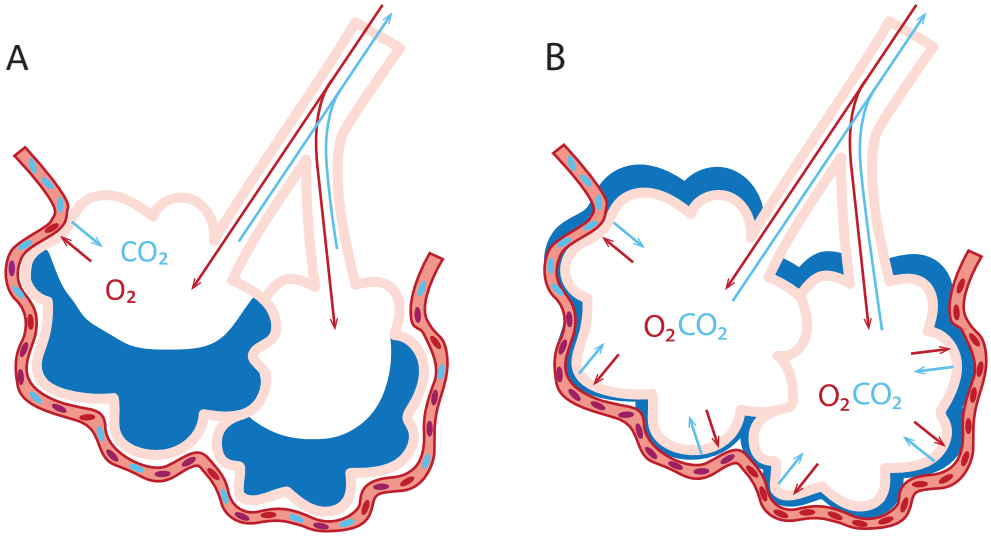

Figure 1. Overview of the alveoli, surrounded by capillaries. A: Directly at birth, lung liquid needs to be replaced with air. The movement of liquid into the interstitial tissue causes a high airway resistance and the partially liquid-filled alveoli reduces the surface area available for gas exchange. B: As the liquid moves into the interstitial tissue surrounding the alveoli, the airway resistance decrease while the interstitial pressure and lung recoil increase. This causes alveolar collapse and liquid re-entry at end-expiration. Nevertheless, the surface area available for gas exchange increases.

CONTINUOUS POSITIVE AIRWAY PRESSURE

Although most preterm infants breathe at birth, the breathing effort is often insufficient to ensure the large pulmonary physiological changes that are needed to survive the foetal to neonatal transition. While continuous positive airway pressure (CPAP) is often used to support the infant's breathing, there is no data on the optimal pressure level. The CPAP level of 4-8 cmH2O that is currently used is predominantly extrapolated from data from CPAP later in the NICU, while the underlying physiology during the neonatal transition is strikingly different. [13, 72]

Considering the physiological changes that need to occur during transition, it would be more logical to use a dynamic CPAP strategy wherein the CPAP levels suit the different phases of the transition. In the first phase of the transition (Figure 1A), the role of CPAP is to promote lung aeration and assist movement of lung liquid across the distal airway wall into the interstitial tissue. As a result, the resistance in the airways is high due to the high viscosity of liquid (compared with air) moving across the airway epithelium requiring higher CPAP levels to overcome this. [73-77] Once the lungs become more aerated and liquid is accumulated in the interstitial tissue, the lung characteristics change quickly and the role of CPAP converts to maintaining lung aeration. During this phase of the transition (Figure

1B), airway resistance is considerably lower (~100 fold), but lung recoil and interstitial tissue pressure increase which promote alveolar collapse and liquid re-entry at end-expiration. [73-81] Lower CPAP levels are likely sufficient to maintain aeration and support breathing, while decreasing the risk for lung overexpansion and/or adverse effect on pulmonary blood flow. This dynamic CPAP approach, following the pulmonary physiological changes during transition, has been called physiological based (PB)-CPAP.

Experimental studies in spontaneously breathing preterm animal models demonstrated that PB-CPAP should ideally start with CPAP of 15 cmH2O which is stepwise decreased to 8 cmH2O. These studies also showed that PB-CPAP promotes lung aeration (functional residual capacity; FRC)), breathing effort and pulmonary blood flow, without causing bulging of the lungs or pneumothoraxes. [82, 83] These results were translated into a small randomised controlled trial wherein PB-CPAP was compared to 5-8 cmH2O CPAP. This feasibility study demonstrated that PB-CPAP led to a quicker restoration of heart rate and shorter duration of mask ventilation, likely reflecting lung aeration. Nevertheless, post-trial evaluations indicated that caregivers found it difficult to combine standard care with a CPAP protocol that requires constant evaluations and changes in CPAP levels. [84]

This is where technological innovation could help the caregiver in assimilating complex physiological changes and fine-tuning and optimising the respiratory support. Mathematical modelling with currently available physiological data could be used to create algorithms, which will allow us to develop a decision or even automated pressure support system in the delivery room.

POSITIVE PRESSURE VENTILATION

If preterm infants fail to clear their lung liquid, establish FRC and initiate spontaneous breathing to facilitate gas exchange [85], manual non-invasive positive pressure ventilation (NIPPV) is provided by occluding the aperture of a T-piece resuscitator with a thumb or finger. The sufficiency of the provided tidal volumes is confirmed by adequate chest rise, auscultation or, indirectly, by an increase in heart rate. [86] However, due to rapidly changing pulmonary physiology and inconsistent respiratory drive of infants at birth, variable tidal volume are administered that might be inadequate or excessive. Large tidal volumes could overstretch the delicate alveoli and airways (volutrauma), while small tidal volumes could lead to loss of lung volume or cycling between collapse and recruitment (atelectotrauma) thereby injuring the lungs. [87, 88] A recent multicentre trial evaluating tidal volume monitoring during manual ventilation reported that, despite using a respiratory function monitor (RFM)(Figure 2), ineffective ventilation <4 mL/kg and potentially harmful ventilation >8 mL/kg was provided 40.7% and 20.0% of the time, respectively. [89]

The high percentage of ineffective manual ventilation could be caused by pharyngeal ventilation as the glottis is predominantly closed after birth and only opens when a spontaneous breath is taken. [90] When ventilation is provided to a closed glottis, no air is able to enter into the lungs. [90] Providing inflations which coincides with spontaneous breaths would be more effective, but also increases the risks of high tidal volumes and thus the risk of lung and/or cerebral injury. [91] As it is difficult for caregivers to evaluate the presence and quality of spontaneous breathing at birth [8], especially during manual ventilation [7], this hampers safe and effective ventilation at birth.

Again, automation can offer a solution. In this case, several solutions already exist and are being applied as features of a neonatal ventilator. Replacing the T-piece resuscitator for a regular neonatal ventilator in the delivery room therefore brings several opportunities to prevent inappropriate ventilation. The first solution is automated synchronised NIPPV (sNIPPV). Caregivers can only detect breathing after a breath has been taken, while a ventilator can detect the start of a breath. This enables ventilators to synchronise their ventilation. In addition, caregivers have to keep overview of the clinical condition of the infant and are, therefore, not able to continuously focus on the infant's breathing while a ventilator can. Although there is no evidence for the effectiveness of synchronised ventilation in the delivery room, it has shortened the duration and improved the effectiveness of ventilation in the NICU. [92, 93]

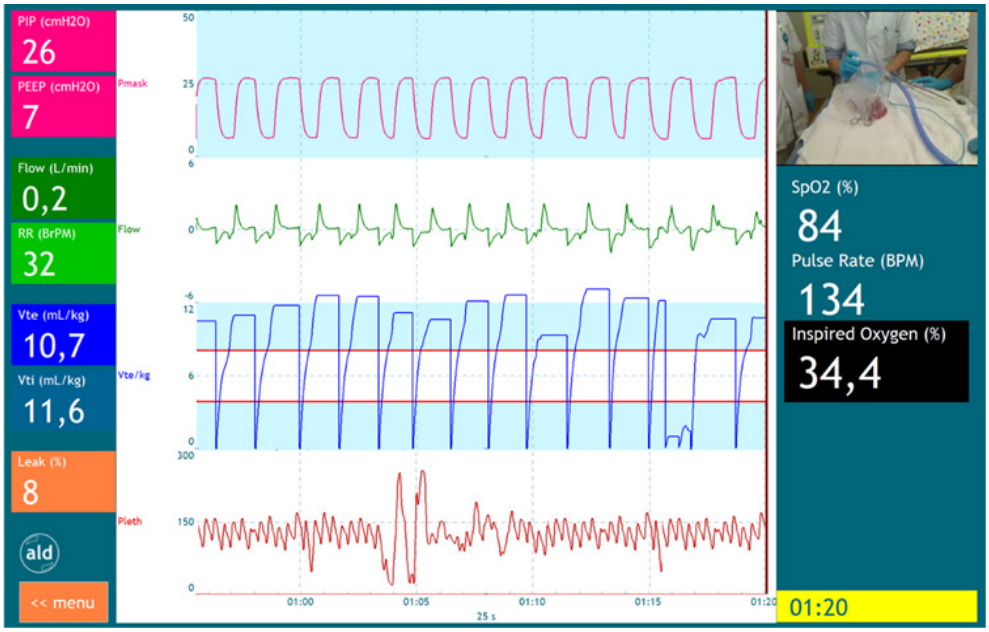

Figure 2. Respiratory Function Monitor Display

Even with sNIPPV, it remains difficult to provide tidal volumes in a safe target range. To date, caregivers are only able to apply pressure-limited manual ventilation in the delivery room due to the lack of appropriate technology. However, a recent neonatal resuscitation simulation study showed it is feasible to use a ventilator with RFM in the delivery room as it increased the proportion of tidal volumes within the target range and reduced the number of large tidal volumes during different simulated scenarios of changing pulmonary mechanics commonly encountered at birth. [86] Also, the delivery of consistent tidal volumes during changing pulmonary mechanics could be improved by implementing volume-targeted ventilation. While, this ventilation mode showed to improve outcome and is a widely accepted in the NICU, there is no data on using this mode in preterm infants at birth. [87, 94, 95] This effect might even be increased when using a ventilator with synchronised ventilation and/or volume-targeted ventilation.

MONITORING

Regular feedback on the patient's physiological state is a pivotal element of neonatal stabilisation after birth, guiding corrective actions and clinical decision making of the caregivers. Despite its importance, monitoring in this critical period is still relatively basic compared to the continuous and extensive monitoring techniques used in the NICU.

The current guidelines recommend the use of pulse oximetry and/or ECG for physiological feedback instead of rudimentary methods such as auscultation, palpation of the umbilical cord and assessment of skin colour, as these methods proved to be prone to subjectivity [96, 97]. The same applies to the assessment of administered tidal volumes by observing chest excursions [98] but the evidence for using a RFM instead remains conflicting. Although manikin studies demonstrated that providing continuous feedback on ventilation pressures, tidal volumes, mask leak, SpO2, heart rate and FiO2 via a RFM improved the performance of the caregiver during PPV [86, 99-101], a recent multicentre randomized controlled trial showed no difference between neonatal resuscitation with or without integrated feedback by RFM. [89] This result might be explained by previous findings that the use and interpretation of a RFM in the delivery room is experienced as challenging and therefore not helpful to all caregivers in critical decision making. [7], [102]

Although continuous, objective and accurate data acquisition is necessary to further implement modern technological innovations such as closed-loop interventions and prediction models, the question is whether presenting all this data directly to the caregivers is always useful. Future research should also be focused on which data to present, and in particular in what manner, to facilitate quick assimilation and easy interpretation by caregivers so that they can recognize and act upon abnormalities or changes in physiology.

In other words, in the design or development of monitoring methods, one should consider carefully whether the data is processed by algorithms or a human brain.

MAN AND MACHINES

Our understanding of the foetal to neonatal transition and the underlying physiological changes has evidently increased in the recent decades, facilitating clear opportunities aiming to improve clinical outcome. However, these insights also underscore the eminent complexity of the transition process, especially in ill or preterm infants who cannot meet the required physiological challenges on their own.

Whilst the expansion of monitoring solutions and intervention strategies and the finetuning of protocols and target ranges can definitely aid caregivers in providing the right support, it makes the resuscitation process increasingly sophisticated. As of today, caregivers continuously have to assimilate and interpret many physiological parameters from different devices in order to decide if, when and which intervention is required, in just a small-time window. The more difficult, dynamic and versatile the process, the more prone it becomes to human errors such as forgetfulness and lack of continued focus.

Over the last decades the development and adoption of automated medical technology has tremendously increased and accordingly revolutionised medical practice, but not yet in the delivery room. We argue that the development and implementation of automation, closed-loop systems and artificial intelligence could serve as a next iteration in improving resuscitation management by reducing human error and unwanted variability in human behaviour. However, this can only be achieved if we critically validate the added value using a holistic approach; not only taking into account the patient but also the caregivers. This means that we should not blindly use existing solutions for new problems but find new ones fitting the entire context. We should not use or implement innovations because it is technically feasible, but because it is desirable and we should not endlessly extend and expand existing solutions but come up with solutions that replace a bundle of existing ones.

Although some might dream, and others fear, a completely automated transition support system, it is more likely that technology will take on an integral part of resuscitation management, resulting in an increased caregiver-machine interaction. Given the growing complexity of automated systems, the poor explainability of artificial intelligence and the consequences of possible erroneous automated interventions, a paradigm shift is necessary. Caregivers should not only be clinically aware, understanding the status of the patient with regard to the interlinked physiological changes, but be situational aware, also understanding the status of all automated devices, systems and software during the transition process.

Shaping this role is however not the sole responsibility of the caregivers. To make the most out of it, designers and developers should indeed focus on the explainability and interpretability of automated systems and error prone interfaces including clear user feedback. Managers and medical engineers should moreover ensure that caregivers are trained like pilots; focussing on the capabilities to identify and respond to system errors or failure. As it is utopian to think that capitalising some strength of computers will fully replace human weaknesses, caregivers have to accept that improvement of care will always remain an iterative process.

CONCLUSION

Although the complexity of stabilisation after birth increases by our growing understanding of the complex physiology, the development and implementation of technology to assist in this process lags behind. Implementing state-of-the-art technology during the neonatal stabilisation would enable us to i) prevent hypo- and hyperthermia through closed-loop temperature management, ii) stimulate spontaneous breathing by providing automatic repetitive tactile stimulation to all infants , iii) control oxygenation in relation to neonatal transition through closed-loop oxygenation, iv) support spontaneous breathing during

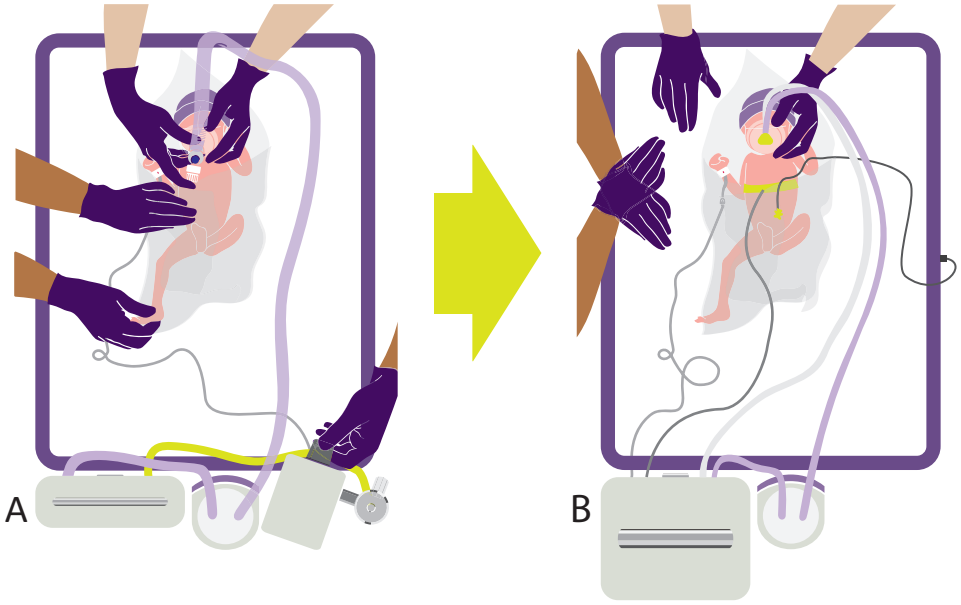

Figure 3. Visualisation of evolving technologies for use in the delivery room. From providing manual heat loss measures, manual tactile stimulation, manual supplemental oxygen control and manual CPAP and NIPPV with a T-piece resuscitator (A) to automated thermoregulation, automated tactile stimulation, automated oxygen control and automated ventilation using a ventilator (B).

neonatal transition by automated PB-CPAP algorithms and v) provide safe and effective ventilation by using synchronised volume targeted ventilation (Figure 3). By using technology to assist caregivers to provide the optimal care, caregivers would be able to comprehend an overview of the infant's clinical condition more easily and finetune the stabilisation where appropriate.

Although most of the technology discussed in this review is already used in the NICU, it cannot simply be extrapolated to the delivery room because of the difference in physiology, environment and situation. The adoption of automation has great potential to improve the care we provide in the delivery room, as long as we put humans, not technology, first. Above all, we must realise that technology does not make man superfluous: the clinical view remains necessary.

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PART 6

GENERAL DISCUSSION

INTRODUCTION

Apnoea of prematurity (AOP) and the resulting intermittent hypoxia (IH) and bradycardia it causes are exceedingly common in preterm infants and have been recognized as such with the advent of technology capable of continuous heart rate and oxygen saturation measurement [1, 2]. The definition of a true apnoeic event has also evolved significantly over the last several decades: from 2 minutes in 1956 [3], to 1 minute in 1959 [4], 30 seconds in 1970 [5] and finally 20 seconds or shorter if accompanied by bradycardia or cyanosis in 1978 [6].

While it is well understood that treating prolonged apnoea's is important as these episodes will increase the risk, duration and severity of subsequent hypoxia and bradycardia [7-9], accumulating evidence indicates that brief respiratory pauses (BRP) also significantly contribute to physiological instability due to their high frequency and cumulative burden [10-12]. However, despite the potential benefits of addressing these short events, the definition of apnoea has not changed anymore for the last 45 years [13, 14]. We postulate that this is due to concerns regarding the practical feasibility of responding to short events and expected increased caregiver workload and risk of alarm fatigue.

While this limitation may be true for human caregivers managing the shorter events in the current care setting, a mechanical and automated "caregiver" has the ability to respond immediately to any respiratory pause without difficulty. The use of an automated stimulation system could improve treatment as it could prevent the onset or exacerbation of hypoxia and bradycardia following respiratory pauses by providing a reliable and direct response, which potentially improve the outcome in preterm infants.

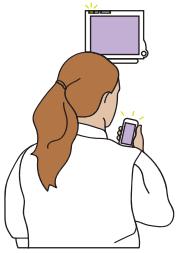
Although various sensory stimuli have been reported to enhance respiratory effort and/or decrease apnoea incidence in small studies [15], we chose to focus solely on tactile stimulation, as it is the first, most frequently used and arguably the most important intervention currently used in response to apnoea in preterm infants. In this chapter, we will discuss the steps taken to investigate the potential of automated tactile stimulation in the treatment of apnoea in preterm infants, which was also the aim of this thesis.

STEP 1: DESCRIBE CURRENT CARE

In order to find out whether automation of reactive tactile intervention could actually lead to improvement of care, a good understanding the current treatment method is essential. Although tactile stimulation in response to apnoea is recommended and standard care for many years, there are no guidelines available defining when, where, how or how long

to stimulate. Data on actual application in clinical practice are also lacking. We therefore performed several studies aiming to provide a data-driven overview of the current manual reactive treatment process in our Neonatal Intensive Care Unit (NICU). In combination with existing literature and studies repeated our work, we categorized the treatment process in three phases, each with its own challenges:

1. APNOEA DETECTION



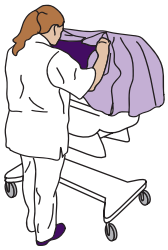
As caregivers in the NICU are not continuously present at the bedside, the routine method for detecting AOP consists of different types of alarms from continuous cardiorespiratory monitoring, typically involving transthoracic impedance (TTI), electrocardiography (ECG) and pulse oximetry. The combination of the frequent, unpredictable occurrence of IH and bradycardia and the insensitivity and non-specific nature of TTI [16-20] can quickly evoke sensory overload in caregivers and/or a lack of trust in the alarm veracity [21, 22]. Both forms of alarm desensitisation can result in reduced or selective response rates and increased response times [23].

In addition to this, the architectural layout of NICU's worldwide shows a transition from the traditional open-bay units (OBU's) to single room units (SRU's), to provide infants with a suitable developmental environment and promote family cantered care [24]. However, where an OBU allows for all alarms to be visible and audible for several patients simultaneously, a SRU does not. Alarm distribution systems are therefore put into place to forward alarms from the patient monitors to handheld devices. If the designated nurse does not respond in time, alarms are forwarded to a larger number of nurses, which leads to increased alarm pressure [25, 26].

As alarm overload is a significant concern, several measures have been researched and/or implemented in the NICU. Studies evaluating these measures often include outcomes related to both alarm pressure and patient safety, as many alarm reducing strategies come at a cost. Increasing the alarm thresholds reduces the number of alarms but, but if set too wide or loose, it may lead to overlooking critical incidents [27, 28]. Increasing the averaging time for calculating a parameter can mask short drops or peaks outside the limits, but also results in underestimation of the severity of events and in a delayed representation of the measured parameter [29-31]. Furthermore, most devices allow users to add or increase a delay in

the announcement of the alarms [32]. While this scenario is considered more transparent than a longer averaging time – as alarms that are activated within the delay time are visible but silent –, it could still lead to a delayed response in critical situations [29].

2. APNOEA INTERVENTION



It is up to the caregiver to decide if an alarm from the patient monitor mandates clinical action. In **Chapter 2** we demonstrated that caregivers in our NICU refrain from intervention in the majority (>90%) of cardiorespiratory events. Similar findings have been reported in previous studies examining NICU caregivers' response rates to alarms in general [33, 34], as well as to hypoxia [35] and bradycardia [36] alarms specifically.

Building on the findings of these studies, we propose four potential explanations for the low response and/or intervention rate:

1. *There is no intervention required:* Although alarms are put into place to enable healthcare providers to quickly respond to critical situations, alarms that are invalid or do not even require clinician awareness appear to comprise the majority of alarm burden [21].
2. *Caregivers are physically unable to intervene:* In all aforementioned studies (including **Chapter 2**) that examined alarm duration and/or response time, the average alarm duration was significantly shorter (around 10 seconds [34, 37]) than the nursing staff's response time (20 to 50 seconds [34, 35, 37]). Although response time is influenced by various factors, this data demonstrates that it is impossible for nurses to respond or intervene to every event before it resolves on its own.
3. *Caregivers are cognitively unable to intervene:* Research indicates that the tendency to respond to an alarm increases with longer-lasting events [33, 37], presumably because these alarms are perceived as more credible and indicative of a sustained issue, making them more urgent. However, the absence of a response in 40% of the longer events (>60 seconds) seen in **Chapter 2** indicates that unintentional non-responses, due to alarm fatigue or heavy workload, may occur frequently.
4. *Caregivers are reluctant to intervene:* Caregivers do not perceive

every alarm as valid, urgent, important and/or actionable [34]. Various factors influence the assessment of an alarm and the decision to respond, including for example the infants' demographics, medical history and current clinical condition, as well as the context and technical reliability of the alarm, established protocols and agreements, and the training, beliefs and availability of the assigned nurse [38, 39]. In **Chapter 2** we found that 20% of active responses involved pausing the alarms at the bedside without further intervention. This, combined with the observation that the duration of intervention (on average 19 seconds) was typically shorter than the remaining time to event resolution (on average 31 seconds) suggests that caregivers are cautious or reluctant to intervene.

When caregivers do decide to respond to apnoea, they usually provide an escalating sequence of interventions including tactile stimulation, increasing supplemental oxygen (FiO2) delivery, providing non-invasive positive pressure ventilation (NIPPV) and, in more severe cases, intubation and mechanical ventilation [40]. In our observational study described in **Chapter 2** we identified three other responses in addition to tactile stimulation, including: (a) pausing the patient monitor alarm without further intervention, (b) adjusting or replacing medical devices (e.g., CPAP mask or saturation probe) and (c) combining device adjustment with tactile stimulation. Application of NIPPV, manual titration of supplemental oxygen (FiO2) as well as intubation were not observed in response to cardiorespiratory events in our study. This is likely the result of utilizing the OxyGenie algorithm in most patients, acting directly on a fall in SpO2. Although nurses can manually override the FiO2 settings of the algorithm, a previous study in our centre showed that this is rarely done [41]. In contrast, a German study found that 25% of the documented interventions following apnoea involved supplemental oxygen administration and additionally also reported aspiration of nasopharyngeal secretions and body position changes [42]. Although this study, like ours, demonstrated that various interventions are applied in response to apnoea, tactile stimulation remains most commonly applied intervention.

In our study (**Chapter 2**), the median response time to any of the interventions was 25.4 (13.8-35.9) seconds, which was similar to a previous study where the median response time for providing tactile intervention

in response to IH was 20.5 (16.6-25.5) seconds [35]. In contrast, Joshi et al reported considerable longer response times to cardiorespiratory events, ranging from 39 to 56 seconds depending on the type of alarm [34]. However, due to a different study set-up, they could only measure the response time when caregivers were not already present in the room, which may account for the observed differences. Nevertheless, it is clear that a response delays to apnoea's indeed occur.

Using a simulated scenario, described in **Chapter 1**, we observed considerable variability in stimulation methods applied, both in terms of stimulation technique as well as location. Our findings were recently confirmed by a multicentre study conducted across five hospitals in Italy, Burkina Faso, and Mozambique, in which they replicated our simulation study protocol [43]. Their study not only showed heterogeneity in stimulation methods but also reported notable differences between centres. In addition, a German study extended these findings by quantifying the intensity of stimulation, showing a wide range of applied pressures from 11 to 227 mbar [44]. Evaluation of actual applied stimulation methods in the unit (**Chapter 2**) showed that pressing and rubbing were the most frequently employed techniques but this time predominantly applied to the trunk (back and sides) and to a lesser extent on the feet, which was similar to the findings in our simulation study (**Chapter 1**).

To our knowledge, no other studies have examined the application of tactile stimulation in the NICU and potential differences in effectiveness between various techniques and locations are therefore also unknown. However, tactile stimulation used to initiate and support breathing directly after birth, recently gained attention. Studies in this context also show significant variability in both method and timing of tactile stimulation across caregivers and institutions [45-51]. Three of these studies indicated a potential benefit of rubbing the trunk compared to other stimulation methods, though these findings were not significant and have not yet been scientifically substantiated [45-47]. While medical staff members seem to intuitively adjust tactile stimulation methods and pressure in response to the intensity of apnoea, the question remains which type of stimulation is necessary or most sufficient.

The interventions provided in response to cardiorespiratory events are commonly performed with bare hands, making proper hand hygiene

practices important. To our knowledge, only one study has investigated this aspect of the nurse response to cardiorespiratory event [36]. They reported that in nearly half of the cases, nurses neglect hand hygiene before performing interventions. While this may reduce the time to intervention, it increases the risk of cross-contamination and the spread of infections to preterm babies.

3. APNOEA REGISTRATION

NICU nurses typically document episodes of apnoea when they consider them clinically significant, based on their visual assessment of the infant, patient monitoring data and any interventions provided. Neonatologists routinely rely on this information to determine the initiation, continuation, or discontinuation of pharmacologic therapy and respiratory support. Additionally, these observations help assess the infant's readiness for transfer or discharge home. However, there is general consensus that AOP is underreported [42, 52-54]. Moreover, critical details such as event duration, heart rate change and oxygen saturation are not documented, making it difficult to accurately assess the severity of the events at a later stage. While data from bedside patient monitoring has better sensitivity and specificity than nursing documentation, it has also limitations. Obstructive apnoea's go often undetected [53] and monitors do not capture information about the intervention that are performed in response to the event. In conclusion, the current methods for apnoea registration are either subjective or incomplete, leaving room for improvement.

STEP 2: REDEFINE THE CHALLENGE

The challenge of treating apnoea in preterm infants presents a paradox: the inherent physiological instability in this patient group leads to frequent and unpredictable episodes of apnoea, bradycardia, and desaturation, placing a considerable strain on the nurses responsible for monitoring and managing these events. In turn, the high workload, compounded by factors such as alarm fatigue, creates a challenging environment where timely intervention and accurate documentation may be compromised, hindering the effectiveness of nursing care and potential further exacerbating the infant's instability.

Expanding the current repertoire of management tools for apnoeic events in preterm infants through the application of automated tactile stimulation may help avoid apnoea-associated physiological instability and minimizing the potentially life-long consequences of frequent

or long-lasting apnoeic episodes, whilst at the same time reducing nursing workload. By eliminating alarm fatigue and response delays, an automated system could ensure a timely and consistent intervention while allowing for real-time documentation of administered stimulation intensity. However, this approach is contingent on the condition that the automated stimulation proves to be at least as effective and safe as manual intervention, ensuring that the balance of benefits outweighs any potential risks.

STEP 3: FIND OUT WHAT IS KNOWN

Throughout history, applying manual physical stimulation has been common practice to initiate or support spontaneous breathing in newborn infants. The impulse to stimulate an apnoeic infant may be driven by instinct, as tactile manoeuvres such as nudging, licking and biting are also observed in animals assisting their newborn pups to breath [55, 56]. Despite its long-standing use, there is a surprising lack of evidence regarding its effectiveness. The first study on manual tactile stimulation in preterm infants indicates that providing prophylactic stimulation for 5 minutes every 15 minutes significantly reduces the incidence of apnoea compared to the control period [57]. A similar study recently confirmed these findings, showing a difference in apnoea rate between the intervention group, which received 10-minute stimulation three times a day for 7 days, and the control group [58]. However, there are no studies that address the effectiveness of manual stimulation in response to apnoea.

In contrast, the effectiveness of mechanical stimulation has been more extensively investigated, as discussed in our literature review (**Chapter 3**). Two studies demonstrated that nurse-activated, mechanical vibratory stimulation applied to the foot or thorax is as effective in resolving apnoea as manual stimulation [8, 59]. Additionally, automated mechanical stimulation was shown to resolve over 90% of apnoea's [60, 61], though these results were not directly compared to manual or other mechanical tactile stimulation methods. The majority of studies included in our review however focussed on the preventive effects of mechanical stimulation, comparing the incidence of apnoea in periods of continuous stimulation to periods without stimulation. While studies utilizing oscillating stimuli failed to obtain consistent results [62-67], all studies that employed vibratory [65, 68-70] or pulsating [71] stimuli reported a significant reduction in apnoeic episodes and/or breathing pauses compared to control periods, despite considerable variability in study designs, patient characteristics, stimulation devices, stimulation parameters, and outcome measures.

Various mechanisms have been proposed to explain how tactile stimuli influence respiratory control. Some theories suggest that tactile stimuli activate the brainstem [72], while others

argue that specific vibration frequencies stabilize breathing by activating proprioceptors in the joints and the inherent reflexive coupling between limb movements and breathing [68]. Additionally, it has been hypothesized that continuous small noisy inputs, generated by low-frequency vibrations, can stabilize respiratory rhythms through stochastic resonance. Although this hypothesis is most extensively explained and substantiated by computational models [73, 74], the ideal stimulation strategy and stimulation characteristics to elicit a response in infants are unknown.

The heterogeneity among the studies published to date make it impossible to directly compare the effectiveness of different stimulation methods, although it is reasonable to assume that variations in effectiveness may exist. For instance, experimental research has shown that direct electrical stimulation of somatic afferent nerves triggers breathing in foetal and newborn animals [72, 75], whereas electrical stimulation of the intercostal muscles has been shown to have an inhibitory effect on breathing [76]. As another example, a study in foetal lambs found that breathing responses persisted longer when the skin was electrically stimulated compared to manual scratching and rubbing, while vibratory stimulation failed to elicit any response [77]. Conversely, vibratory stimulation applied to the abdomen or ankles of adult rate shortened induced apnoea and electrical stimulation had no effect [78].

Several factors may explain these differences. Somatic afferents comprise various types of sensory fibres that transmit signals related to touch, pressure, temperature, pain, and proprioception. These fibres can involve different neurotransmitters and interact with the medullary respiratory rhythm generator at distinct sites, making it difficult to determine which specific fibres are responsible for inhibitory or excitatory effects on breathing and why. Additionally, the skin contains a wide range of (mechano)receptors, each sensitive to different frequencies, pressures, stimulation methods and types, differing in density across various body regions [79], and changing over time due to functional maturation [80, 81]. Finally, respiratory responses may be influenced by sleep state, with certain stages of sleep potentially enhancing or attenuating the effect of somatic stimulation [82].

In summary, the findings of our literature review (**Chapter 3**) suggest that various forms of mechanical tactile stimulation positively affect breathing. However, the exact neural pathways, as well as the most effective form, location, and timing of stimulation for regulating respiratory control, remain unclear.

Additionally, the review (**Chapter 3**) has highlighted that to date, only nurse-activated or continuous mechanical stimulation strategies have been systematically compared to standard care. Nurse-activated mechanical stimulation offers limited benefits, as it only eliminates the need to perform hand hygiene without addressing any of the other issues we

identified. In contrast, continuous stimulation represents a completely different approach to treating apnoea, as it bypasses most of the challenges related to detection, response, and registration. While easy to implement, continuous exposure to stimulation carries a higher risk of habituation or other short- or long-term adverse effects [83-86]. Moreover, it complicates the assessment of the patient's clinical status, as it becomes unclear how many apnoea events are prevented by the stimulation and to what extent stimulation is required. As a result, gradual discontinuation is necessary before the infant can be safely transferred or discharged. Automatic responsive stimulation, as we have proposed, could serve as a promising compromise between these two strategies; however, its potential added value in relation to current care has yet to be investigated.

STEP 4: PROOF THE PRINCIPLE

In **Chapter 4**, we present a study in which we aimed to investigate whether an early, anticipatory stimulation approach is more effective in promoting breathing and preventing apnoea compared to a reactive stimulation approach in preterm rabbit kittens. We compared the effect of soft mechanical vibrotactile stimulation in response to hypoxia-induced irregular breathing (IB) to the effect of stronger stimulation in response to apnoea and showed that both the incidence and duration of apnoea were significantly reduced. With respect to the start of stimulation, anticipated stimulation led to recovery of breathing rate more often and resulted in a significantly higher breathing rate two minutes after stimulation onset when compared to reactive stimulation.

The results, including the statistically insignificant but greater cardiorespiratory stability, suggest that stimulating in anticipation of an impending apnoea is considerably better than waiting for apnoea to occur. Furthermore, earlier stimulation seemed to require a less intense stimulus, a finding that aligns with the fact that even subtle continuous stimulation can lead to a reduction in apnoea (68, 70). We hypothesize that the central processing of tactile stimuli undergoes rapid modification as the duration of IB prolongs, where the gradually increasing level of hypoxia blocks or modifies somatic inputs arising from stimulation [87], thereby impeding the resumption of breathing and resolution of apnoea. This hypothesis parallels the well-known response in newborns, where increasing hypoxia leads to a gradual cessation of breathing, bradycardia, loss of muscle tone and diminished responsiveness to tactile stimuli [88, 89].

It is important to note that, in both preterm rabbits and infants, IB does not always progress to apnoea, and the respiratory centre does not always require stimulation to restore or stabilize breathing. Automated devices are likely to intervene more often – and in some cases, potentially unnecessarily – compared to the delayed and more selective approach

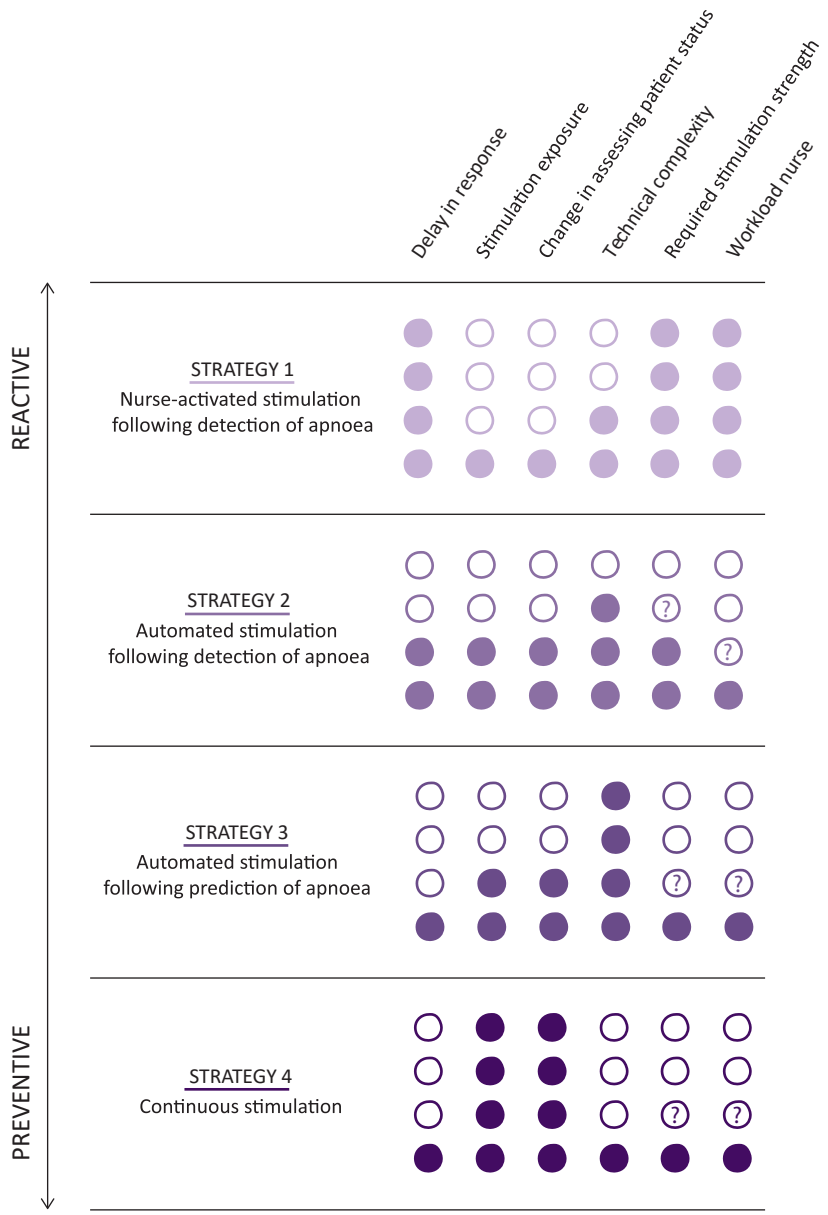


Figure 1. Different stimulation approaches with expected pro's and con's.

of caregivers, due to their rapid and consistent response upon detection of (imminent) apnoea. However, when compared to continuous stimulation, the frequency of intervention remains relatively low.

Devices that automatically stimulate in response to apnoea seem offer advantages over a nurse-triggered or continuous approach (Figure 1). Additionally, a predictive automated

approach presents benefits over a detection-based approach, albeit technically more complex. Thus far, predictive algorithms have only been studied using pre-recorded physiological data [90-92] and have not been evaluated in conjunction with an automated tactile response. Clinically viable prototypes are needed to facilitate studies with the aim to determine which approach offers the optimal overall balance between benefit and burden for both the infant and the caregivers.

STEP 5: DEVELOP AND EVALUATE A SOLUTION

Although various automated tactile stimulation devices (ATSDs) have been described [93-96], there are currently no devices commercially available that can be implemented or evaluated in a NICU. We therefore decided to develop a purpose-built ATSD prototype that responds to the current detection/alarm system for cardiorespiratory events and allows for feasibility assessment in clinic.

As it became clear that performing fundamental research to find out the most optimal method and location of stimulation would be immensely time and resource consuming, we opted for a pragmatic and iterative design approach, drawing insights from our own research, existing literature, clinical experiences and opinions of NICU nurses and neonatologists, as described in **Chapter 5**. This data informed the design of a device that is both likely to be effective and safe. As a result, our device, named BOBBY, provides a soft stroking sensation through asynchronously triggered vibrations at both ends of a silicone strap that that fits over the infants' chest (Patent EP4103042A1 [97]). In doing so, we aimed to mimic the stimulation provided by nurses over a large area of the skin without imposing excessive strain. Additionally, we incorporated flexibility into the design, allowing for independent adjustments of amplitude and frequency to facilitate further refinement of the stimulus through future research.

In a randomised cross-over study we evaluated feasibility and short term safety of automated tactile stimulation with our device in preterm infants of 24-30 weeks gestational age in our NICU (**Chapter 6**). We demonstrated that the device was successfully applied to all infants, with 14 out of 16 completing the full 48-hour study period. In one infant, the study was terminated early due to the need for intubation resulting from clinical deterioration unrelated to the study, while in the other infant, the study was stopped due to the development of a non-blanching erythema (pressure ulcer grade 1) resulting from the strap being applied too tightly. Previous studies described in our literature review in Chapter 3 did not report skin damage or patient dropout. However, most of these studies were much shorter in duration, and the included infants were on average at least a month older at study entry, reducing the likelihood of intubation and skin damage [98].

During the intervention period the device achieved a detection rate of 83% to cardiorespiratory alarms and an automated and direct response rate of 100%, resulting in a 30 to 40 fold increase in stimulation frequency. Given the facts that no discomfort was observed the participating infants, no adverse events were reported, and nurses considered the device to be suitable and easy to use, we concluded that it is feasible to provide automated tactile stimulation in response to cardiorespiratory events using our device.

It is important to acknowledge that the device utilized in this study is still in the prototype phase and differs in several key aspects from the ideal version we envision. This discrepancy primarily concerns the detection method and two specific design choices made in this context: (a) responding to existing alarms and (b) detecting these alarms through a light sensor. The advantage of the first choice is that the automated stimulation minimally interferes with clinical workflows, does not require additional alarms and prevents the device from intervening unnoticed by the care team. However, the downside is that the automated response occurs relatively late, due to inherent alarm delays and averaging, but primarily because all apnoea alarms in our unit are disabled. Consequently, we were unable to accurately detect or respond to the onset of apnoea, nor assess the effect of automated stimulation on its duration. No significant differences were observed in the other physiological parameters; however, the study was not powered for these comparisons. We chose to use a light sensor for its technical simplicity and our positive experience in the study described in **Chapter 2**, where the light sensor demonstrated a near-perfect detection rate. However, a switch in patient monitors, which dimmed the screen brightness and alarm lights at night, resulted in a much lower detection rate in our feasibility study (**Chapter 6**). The limitation of this technique is its poor specificity, as alarms can only be discriminated by colour rather than, for example, by label.

Ideally, the device would respond more promptly, with vital parameters averaged over shorter periods or even incorporating predictive capabilities, as shown in **Chapter 4**. However, such improvements would necessitate a feedback feature to inform nurses, as the stimulation might otherwise go unnoticed, potentially delaying the recognition of patient deterioration. The focus of our current design, as described in **Chapter 5**, was primarily on developing the stimulus mechanism and we intentionally chose a pragmatic approach to assess feasibility and short-term safety with a simple yet functional prototype before further developing more advanced detection and reporting functions.

NEXT STEPS: FUTURE PERSPECTIVE

Further development and refinement of our stimulation device should enable faster responses to brief respiratory pauses and apnoea, while maintaining the caregiver's situational awareness regarding the status of the infant. At the start of 2025, we founded BOBBY Neonatal, a start-up company aimed at translating our prototype into a commercially available product. This will make it possible to conduct further research into the full potential of automatic tactile stimulation, including its effectiveness and long-term safety for the infant, as well as its impact on the workload of caregivers. To ensure that the system truly assists caregivers, it is crucial that they remain involved in the development and implementation of the technology. This involvement helps ensure that the technology meets their needs and addresses any potential barriers to acceptance.

In addition to the potential for automating tactile stimulation as an individual intervention to improve care, we believe the technology could also enhance the effectiveness of existing automated interventions for respiration, such as automatic oxygen control (AOC) and back-up positive pressure ventilation (PPV). Although AOC has been shown to improve the time spent within the desired SpO2 target range [41, 99], effectively addressing intermittent hypoxia caused by brief respiratory pauses and apnoea remains challenging due to (a) the rapid onset of hypoxia after apnoea, with SpO2 dropping to its lowest point within approximately 18–20 seconds [100], and (b) the fact that preterm infants close their vocal cords during respiratory pauses [101-103], which makes automated back-up FiO2 and PPV ineffective unless the infant is stimulated to re-start breathing. A recent study demonstrated that increasing FiO2 in anticipation of hypoxia can reduce the severity of hypoxia following apnoea, but also results in SpO2 overshoot upon resumption of breathing [104]. The combination of automated oxygen control with automated stimulation holds the potential to prevent or shorten apnoea, thereby facilitating effective PPV and enabling more precise titration of FiO2 to maintain the infant within target oxygenation ranges.

Finally, we propose that automated tactile stimulation might be beneficial in other settings and for different patient populations. For example, in preterm infants immediately after birth, as repetitive tactile stimulation has been shown to improve oxygenation and enhance respiratory effort, yet is often omitted (**Chapter 7**). Also older infants admitted to the hospital as they developed apnoea's due to viral infection could benefit.

CONCLUSION

Manually applied tactile stimulation is arguably the most frequent and important intervention in response to apnoea in preterm infants and has been recommended and applied in clinical practice for many years. This thesis demonstrates that, despite its simplicity, timely intervention is hindered by various human factors and is burdensome to caregivers, leading to delays or even non-response. Automating this intervention could ensure a timely and consistent response to apnoea, but also to brief respiratory pauses, potentially reducing physiological instability while simultaneously reducing the workload of caregivers.

Existing literature indicates that several forms of mechanical tactile stimulation, in particular vibratory and pulsatory stimuli, have a beneficial effect on respiration and can help terminate and/or prevent apnoea. While the precise underlying mechanisms as well as the most optimal stimulation method remain unclear, we demonstrated that early application of a vibratory stimulation was considerably more effective than delayed stimulation, requiring a less intense stimulus.

As there are no automated tactile stimulation devices available for research or clinical care, we developed a purpose-built prototype by following an iterative design approach and showed that is it feasible to provide automated tactile stimulation in response to cardiorespiratory events in preterm infants.

This thesis forms a scientific basis for further advancements of automated tactile stimulation and emphasizes that research and development are closely intertwined, wherein research forms the foundation for technological advancements, while the resulting technology facilitates the practical application and scalability of the research. Addressing the current knowledge gaps and continuing to refine the technology will be crucial steps in realizing the full potential of automated tactile stimulation in the treatment of apnoea in preterm infants.

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ENGLISH SUMMARY

One of the challenges preterm infants face is maintaining a rhythmic and stable spontaneous breathing pattern to ensure effective ventilation and gas exchange. Their lungs and respiratory control systems are immature and their control of breathing can be unstable, represented by periods of irregular breathing and frequent periods of apnoea. Although *Apnoea of Prematurity* is, by definition, an age-specific and self-limiting disorder that resolves with maturation, it can result in adverse events and worse long-term outcomes. The major pathophysiological consequences of apnoea are presumably caused by the accompanying hypoxia and bradycardia, which have been associated with increased mortality, oxidative stress, serious cerebral injury and long-term neurodevelopmental impairment.

In order to avoid potentially harmful invasive ventilation, spontaneous breathing is commonly supported by providing continuous positive airway pressure (CPAP) and/or administration of caffeine. Although these interventions are proven effective, most preterm infants still experience respiratory pauses, including apnoea's. In order to restore breathing, caregivers must promptly intervene by providing an escalating sequence of interventions. This sequence usually commences with tactile stimulation such as rubbing the foot of back of the infant, but can escalate to providing increased supplemental oxygen, positive pressure ventilation and, eventually, intubation. Manually applied tactile stimulation is arguably the most common and important intervention used in response to apnoea and has been recommended and applied in clinical practice for many years. However, manual interventions come with response delays, which makes treatment of apnoea on demand an ongoing challenge.

We hypothesized that this challenge can be addressed by providing automated mechanical tactile stimulation, offering a reliable and direct response to AOP. The general aim of this thesis was to explore the potential added value of automating tactile stimulation treatment for apnoea, as well as shorter respiratory pauses, in preterm infants admitted to the Neonatal Intensive Care Unit (NICU).

The thesis begins with two studies that were conducted to gain a deeper understanding of the challenges associated with manual tactile stimulation. These are followed by studies investigating the potential of automated tactile stimulation. Subsequently, the design and development process of an automated system is described, along with a clinical evaluation of the resulting custom-made system. The final chapter offers an overview of the challenges in the care of preterm infants immediately after birth and explores how technology – and in particular automation – can offer potential solutions.

UNDERSTANDING CURRENT CARE

Although tactile stimulation in response to apnoea is recommended and standard care for many years, there are no guidelines available specifying when, where, how or how long to apply it. Additionally, data on its actual application in clinical practice is also scarce. To address this gap, we comprehensive quantitative and qualitative data were collected on the current manual reactive treatment process in the Neonatal Intensive Care Unit (NICU) of the Leiden University Medical Center (LUMC).

Chapter 1 focused exclusively on the tactile stimulation methods currently employed by nurses. A prospective observational study was carried out in which nurses were invited to demonstrate and describe their current approaches for stimulating preterm infants using a simulated scenario. A total of 47 nurses performed three consecutive demonstrations each, with the manikin positioned in either prone, supine, or lateral position. Following the demonstrations, nurses were asked to explain how they adopted the stimulation methods they used. The stimulation methods were logged in chronological order by describing both the technique and the location. Explanation by the nurses were transcribed and categorized.

Nurses used 10 different stimulation techniques - press, massage, rub, scratch, shake, squeeze, stroke, tap, tickle and vibrate – applied to 10 different locations: arms, back, abdomen, buttocks, cheek, feet, hands, head, legs and side. Three additional interventions that involved a tactile component and a specific location were observed: supporting the neck or chin to obtain an open airway, lifting the thorax and turning the infant into either a lateral or prone position. In total, 57 different combinations of stimulation techniques and locations were identified. The most frequently used methods included rubbing the feet, turning the infant over to supine position, applying gentle pressure to the head, opening the airway via neck support, and back rubbing.

The majority of nurses (40/47, 85%) reported learning how to stimulate during formal training, although 15 of those 40 (38%) had modified their approaches over time. The remaining 7 nurses (15%) developed their stimulation methods independently.

The findings underscore the absence of a clearly established standard stimulation method. Both the high variability in stimulation methods and the way nurses develop their methods reflect the lack of detailed protocols, and, in turn, the lack of knowledge about the most effective way to activate the respiratory centre in the brain.

Chapter 2 describes a second study conducted in the NICU of the LUMC, where caregivers were observed in order to quantify their responsiveness to cardiorespiratory events. Video recordings of the inside of the incubator were made for a maximum of 72 in 19 preterm

infants (28 ± 2 weeks). The recording started at the onset of a clinical alarm and stopped 5 minutes after the most recent alarm ended. Caregivers' responses to these alarms were then identified from the videos.

A total of 1851 cardiorespiratory events were recorded and assessed, with a median duration of 11.0 (5.0-23.0) seconds. In the vast majority of the events (91.5%), no active response was provided, although longer event durations were associated with an increased likelihood of response. When caregivers did respond, the average response time was 25.4 (13.8-35.9) seconds. Responses included pausing the alarms, checking and adjusting medical devices on the infant, providing stimulation or a combination of the latter two. Stimulation was the most frequently observed response and was applied in 38 different ways. Contrary to the demonstrations on the manikin (**Chapter 1**), stimulation was most commonly applied to the torso and in the majority of cases consisted of at least providing static pressure. More vigorous interventions, such as turning over the infant or lifting the thorax, were less common. On average, the stimulation duration (18.7 (11.6-44.6) seconds) was shorter than the completion time of the event (30.6 (19.5-47.6) seconds), which seems to imply that caregivers are reticent in providing stimulation.

The results of this study emphasize that caregivers – whether consciously or unconsciously - often fail to intervene during cardiorespiratory events, particularly when these events are brief. Furthermore, the findings highlight once again that the indication, timing and execution of responses are highly subjective, and that the optimal response to such events remains unknown.

In summary, treating apnoea in preterm infants presents a paradox: the inherent physiological instability in this patient group leads to frequent and unpredictable episodes of apnoea, bradycardia, and desaturation, placing a considerable strain on the nurses responsible for monitoring and managing these events. High workload, compounded by factors such as alarm fatigue, creates a challenging environment where timely intervention may be compromised, hindering the effectiveness of nursing care and potential further exacerbating the infant's instability.

THE POTENTIAL OF AUTOMATED TACTILE STIMULATION

One possible way to resolve this paradox is through automation. An automated tactile stimulation device could aid caregivers in maintaining or restoring the patient's cardiorespiratory stability as it is able to provide a timely and consistent response to every cardiorespiratory event. This hypothesis, however, only holds true if mechanical stimulation proves to be at least as effective and safe as manual stimulation.

In **Chapter 3** presents a systematic review of the existing literature to provide an overview of the effectiveness of manual and mechanical tactile stimulation in terminating and preventing apnoea of prematurity. Four studies investigating tactile stimulation in order to terminate apnoea were included, involving a total of 13 preterm infants. Two of the studies demonstrated that nurse-activated mechanical vibratory stimulation applied to the foot or thorax was equally effective in resolving apnoea as manual stimulation. The other two showed that automated mechanical stimulation was able to resolve over 90% of apnoea's, although these results were not directly compared to manual or other mechanical tactile stimulation methods.

The preventative effect of tactile stimulation was evaluated in 11 studies, including 290 preterm infants. These studies compared the incidence of apnoea during to control periods of repetitive or continuous stimulation to periods without stimulation. One study applied manual stimulation by rubbing the infant's extremities for five minutes every 15 minutes. All other studies employed mechanical methods to provide continuous stimulation, such as a pulsating cuff placed under the thorax (1 study), little vibration motors attached to the hands or feet (1 study), vibrating mattresses (2 studies), or oscillating water mattresses (6 studies). While studies using oscillating stimuli failed to produce consistent results, all studies employing manual, vibratory, or pulsating stimulation reported a significant reduction in apnoeic episodes and/or breathing pauses compared to control periods, despite considerable variability in study designs, patient characteristics, stimulation devices, stimulation parameters, and outcome measures.

This chapter demonstrates that, although manual tactile stimulation has long been a common practice to initiate or support spontaneous breathing in newborn infants, its effectiveness has been scarcely investigated. Nonetheless, the available evidence suggests that various forms of mechanical tactile stimulation can positively influence breathing, though they are likely not equally effective. The heterogeneity among published studies makes it impossible to directly compare the effectiveness of different stimulation methods, leaving the most optimal form of (mechanical) stimulation unclear. To date, only two studies have been conducted using automated tactile stimulation devices, but its potential added value compared to manual stimulation has not yet been explored.

Chapter 4 describes a study investigating whether an early, anticipatory stimulation approach – a strategy that can be enabled by an automated system - is more effective in promoting breathing and preventing apnoea compared to a reactive stimulation approach, which represents the current standard of care. Therefore, the effect of soft mechanical vibrotactile stimulation in response to hypoxia-induced irregular breathing was compared to the effect of stronger stimulation in response to apnoea in preterm rabbit kittens.

The results showed that both the incidence and duration of apnoea were significantly reduced (anticipatory vs reactive; incidence of rabbits with apnoea 3/10 vs 9/11, p=0.030; duration apnoea 7.7 (5.1–30.8) vs 38.4 (15.5–73.9) seconds, p=0.014). With respect to the start of stimulation, anticipated stimulation led to recovery of breathing rate more often and resulted in a significantly higher breathing rate two minutes after stimulation onset when compared to the reactive stimulation approach (anticipatory vs reactive; recovery of breathing rate 7/10 vs 1/9 rabbits, p=0.015; breathing rate 17.3 ±13.7 vs 2.9 ±1.8 breaths/min, p=0.009).

These findings suggest that stimulating in anticipation of impending apnoea is considerably more effective than waiting for apnoea to occur. Earlier stimulation also appeared to require a less intense stimulus, a finding that aligns with the fact that even subtle continuous stimulation can lead to a reduction in apnoea (**Chapter 3**). However, it is important to note that in both preterm rabbits and infants, irregular breathing does not always progress to apnoea, and the respiratory centre does not always require stimulation to restore or stabilize breathing. Although applying stimulation when apnoea is imminent rather than present seems to offer several benefits, it remains unknown whether this approach outweighs the potential adverse effects of unnecessary stimulation. Further studies with automated tactile stimulation devices are necessary to identify the most beneficial closed-loop strategy for providing tactile stimulation for treating apnoea of prematurity.

A PURPOSE-BUILT AUTOMATED TACTILE STIMULATION DEVICE

The absence of commercially available devices suitable for use or evaluation in the NICU necessitated the development of a new, purpose-built automated tactile stimulation device (ATSD).

As conducting fundamental research to determine the most optimal method and location of stimulation was deemed immensely time and resource consuming, a pragmatic and iterative design approach was used. This approach drew insights from research described above, existing literature, clinical experiences and opinions of NICU nurses and neonatologists, as described in **Chapter 5**. These inputs informed the design of a device expected to be both effective and safe, while offering flexibility to apply various forms of stimulation.

The resulting device, named BOBBY, delivers a soft stroking sensation through asynchronously triggered vibrations at both ends of a silicone strap that that fits over the infants' chest. Activation occurs upon detection of a cardiorespiratory event via the existing patient monitoring system. The goal was to mimic the stimulation typically provided by nurses across a large skin surface area without imposing excessive strain. Flexibility in the design

was ensured by enabling independent adjustment of amplitude and frequency, allowing for future refinement of the stimulus in ongoing research.

The feasibility and short term safety of our ATSD was evaluated in a randomised cross-over study in preterm infants of 24-30 weeks gestational age the NICU of the LUMC (**Chapter 6**). Infants underwent two consecutive study periods of 24 hours each: one intervention period in which the ATSD was fully activated and used in addition to standard care, providing direct vibratory stimulation in response to every clinical alarm and one control period in which the ATSD was attached but only the camera that recorded the nurses' response to the clinical alarms was activated. The ATSD remained attached during the entire study, including kangaroo care time, but was replaced at every routine care round and placed on top of the infant to prevent pressure ulcers.

The study demonstrated that the device was successfully applied to all enrolled infants, with 14 out of 16 completing the full 48-hour study period. In one infant, the study was discontinued early due to the need for intubation resulting from clinical deterioration unrelated to the study, while in the other infant, the study was stopped due to the development of a non-blanching erythema (pressure ulcer grade 1) resulting from the strap being applied too tightly. During the intervention period the device achieved an 83% detection rate of for cardiorespiratory alarms and an automated and direct response rate of 100%, resulting in a 30 to 40 fold increase in stimulation frequency. Importantly, no signs of discomfort were observed in any of the participating infants, no adverse events were reported and nurses considered the device to be suitable and easy to use. These findings support the feasibility of using this device to provide automated tactile stimulation in response to cardiorespiratory events.

In the per-patient analysis, no significant differences were found in the total duration of hypoxia, total duration of bradycardia, the average additional administered oxygen, number of manual stimulations, nurse response time, or duration of manual stimulation. However, these were secondary outcomes, and the study was not powered for these comparisons. Follow-up studies are required to assess effectiveness, in which quicker, more reliable detection—or even prediction—methods should be considered evaluate the full potential of ATSDs.

FURTHER OPPORTUNITIES FOR AUTOMATION

Chapter 7 outlines the potential benefits of automated tactile stimulation in other clinical settings and across different patient populations. For example, it could aid in initiating breathing in preterm infants immediately after birth, as repetitive tactile stimulation has

been shown to improve oxygenation and enhance respiratory effort - yet is often omitted in practice. The review also presents other examples where automation could directly improve care for preterm infants immediately after birth, such as automated ventilation and oxygen titration.

CONCLUSION

In conclusion, tactile stimulation is a common and essential intervention in response to apnoea in preterm infants, but human factors and circumstances can lead to delays or inconsistencies in response. While clinical focus has traditionally been on longer-lasting events, shorter and self-limiting events may also warrant active intervention, as their numerical preponderance contributes substantially to physiological instability of preterm infants.

Replacing manual tactile stimulation with an ATSD, which provides a direct and consistent response, has the potential to improve patient outcomes and reduce the workload of healthcare providers. Evidence indicates that mechanical stimulation—particularly vibratory and pulsatory—can help shorten or prevent apnoeic episodes, with early application proving more effective and requiring lower intensity. In the absence of existing automated devices for clinical use, a purpose-built prototype was developed and its feasibility and short-term safety were demonstrated in a clinical context. This thesis lays the foundation for future advancement of automated tactile stimulation devices, offers initial insights into the balance between the burden and benefit of automated stimulation, and highlights the importance of integrating research and development of new technology to improve neonatal care.

NEDERLANDSE SAMENVATTING

Te vroeg geboren baby's hebben vaak moeite met het tot stand brengen en behouden van een ritmisch en stabiel spontaan ademhalingspatroon, wat nodig is voor een effectieve ventilatie en gasuitwisseling. Zowel hun longen als de delen in de hersenen die de ademhaling regelen zijn nog onrijp, wat leidt tot periodes van onregelmatige ademhaling en frequente apneus - adempauzes van langer dan 10 seconden. Hoewel *Apneu bij Prematuriteit* per definitie een leeftijdsspecifieke aandoening is die verdwijnt naarmate een baby ouder wordt, kan het toch leiden tot nadelige effecten en slechtere uitkomsten op de lange termijn. De belangrijkste pathofysiologische gevolgen van apneu worden vermoedelijk veroorzaakt door de bijbehorende hypoxie en bradycardie, die geassocieerd zijn met een verhoogde mortaliteit, oxidatieve stress, ernstige hersenschade en ontwikkelingsachterstand.

Apneus kunnen worden voorkomen door de ademhaling volledig over te nemen met een beademingsmachine. Intubatie en mechanische beademing kunnen echter schadelijk zijn voor de kwetsbare, nog ontwikkelende longen. Daarom wordt bij prematuren doorgaans gekozen voor ondersteuning van de spontane ademhaling met continue positieve luchtwegdruk via een neuskapje en/of wordt de ademdrive gestimuleerd door het toedienen van cafeïne. Hoewel deze interventies bewezen effectief zijn, hebben de meeste prematuren nog steeds last van apneus. Wanneer zich een apneu voordoet is het van belang dat zorgverleners snel ingrijpen om de ademhaling weer op gang te brengen en zo hypoxie en bradycardie te voorkomen of verkorten. Tactiele stimulatie, zoals het wrijven over de voet of rug van de baby, is de meest gebruikte en belangrijkste interventie in reactie op apneu en wordt al jarenlang aanbevolen en toegepast in de klinische praktijk. Het is echter erg lastig voor zorgverleners om deze interventie bij iedere apneu zo snel mogelijk toe te passen.

Dit proefschrift is ontstaan vanuit de hypothese dat dit probleem aangepakt kan worden door de tactiele interventie te automatiseren, wat het mogelijk maakt om bij iedere apneu direct te reageren. Het algemene doel van dit proefschrift is om de potentiële meerwaarde van het automatiseren van tactiele stimulatie bij prematuren die opgenomen zijn op de Neonatale Intensive Care Unit (NICU) en last hebben van instabiele ademhaling en apneus in kaart te brengen.

De eerste twee onderzoeken in dit proefschrift zijn uitgevoerd om een beter inzicht in de uitdagingen van de huidige, handmatige behandeling van apneu te krijgen. In de daaropvolgende twee studies is de potentie van geautomatiseerde tactiele stimulatie onderzocht. Hierop volgt een studie waarin het ontwerp- en ontwikkelproces van een automatisch tactiel stimulatie apparaat is beschreven, gevolgd door een klinische evaluatie van het resulterende product. In het laatste hoofdstuk wordt een overzicht gegeven van uitdagingen in de zorg voor prematuren direct na geboorte, waarvoor wordt verkend hoe

technologie - en in het bijzonder automatisering – mogelijke oplossingen kan bieden.

HET BEGRIJPEN VAN DE HUIDIGE BEHANDELING

Tactiele stimulatie bij apneu wordt aanbevolen en valt onder standaardzorg, maar de huidige richtlijnen geven geen details over wanneer, waar, hoe en hoe lang stimulatie toegepast moet worden. Data over hoe stimulatie in werkelijkheid wordt ingezet in de klinische praktijk zijn daarnaast ook schaars.

Hoofdstuk 1 richt zich uitsluitend op de tactiele stimulatie methoden die verpleegkundigen momenteel toepassen. In een prospectieve observationele studie werd aan 47 verpleegkundigen gevraagd om in een gesimuleerd scenario drie opeenvolgende demonstraties te geven van hun gebruikelijke stimulatie methoden, met de baby pop in buik-, rug- of zijligging. Na afloop werd gevraagd naar de herkomst van hun methodes. De demonstraties werden opgenomen met een videocamera. Bij het terugkijken van de video's werden de toegepaste technieken en locaties waar de stimulatie werd uitgevoerd in chronologische volgorde genoteerd. De toelichtingen over de herkomst van de methodes werden getranscribeerd en gecategoriseerd.

De verpleegkundigen bleken tien verschillende stimulatietechnieken toe te passen: drukken, masseren, wrijven, krassen, schudden, knijpen, aaien, tikken, kriebelen en trillen. Deze technieken werden uitgevoerd op 10 verschillende lichaamslocaties: armen, benen, buik, billen, wangen, voeten, handen, hoofd, benen en in de zij. Daarnaast werden drie interventies geïdentificeerd met een tactiele component die specifiek gericht waren op een bepaalde locatie: het ondersteunen van de nek of kin om de luchtweg te openen, het optillen van de hele borstkas en het omdraaien van het kind naar rug- of zijligging. In totaal werden 57 verschillende combinaties van technieken en locaties waargenomen, waarbij wrijven over de voeten, het omdraaien naar de rugligging, uitoefenen van druk op het hoofd, het openen van de luchtweg door het ondersteunen van de nek en wrijven over de rug het meeste voorkwamen.

De meeste verpleegkundigen (40/47, 85%) gaven aan de toegepaste stimulatiemethodes geleerd te hebben tijdens hun opleiding, hoewel 15 van hen (38%) hun methode in de loop der tijd ook weer hadden aangepast. De overige 7/47 (15%) verpleegkundigen ontwikkelden hun methode geheel zelfstandig.

De grote variatie in methoden en de wijze waarop verpleegkundigen hun methodes ontwikkelen onderstrepen het ontbreken van een duidelijke standaard voor de manier van stimuleren, evenals het gebrek aan kennis over de meest effectieve manier om het ademhalingscentrum in de hersenen te activeren.

Hoofdstuk 2 beschrijft een tweede studie binnen de NICU van het LUMC, waarin het gedrag van zorgverleners werd geobserveerd om de manier waarop ze op cardiorespiratoire incidenten reageren te kwantificeren. Bij 19 prematuren (28 ± 2 weken) werden videobeelden gemaakt van de binnenkant van de couveuse, gedurende maximaal 72 uur. De opname werden geactiveerd bij een klinisch alarm op de patiënt monitor en stopte vijf minuten nadat het laatste alarm was geëindigd. De videobeelden werden vervolgens gebruikt om de reactie van de zorgverleners op deze alarmen te identificeren en beschrijven.

In het totaal werden 1851 cardiorespiratoire incidenten geregistreerd met een mediane duur van 11.0 (5.0-23.0) seconden. In de overgrote meerderheid van incidenten (91,5%) werd geen actieve reactie geregistreerd. Hoe langer het incident duurde, hoe groter de kans dat er op gereageerd werd. Wanneer er wel gereageerd werd, bedroeg de gemiddelde reactietijd 25.4 (13.8-35.9) seconden. De reacties bestonden uit het pauzeren van de alarmen, het controleren en eventueel aanpassen van de medische apparatuur aan het kind, tactiele stimulatie of een combinatie van de laatste twee. Stimulatie was de meest voorkomende interventie en werd op 38 verschillende manieren toegepast. In tegenstelling tot de demonstraties op de pop (**Hoofdstuk 1**) werd de stimulatie vooral toegepast op de romp, meestal door lichte druk uit te oefenen met de hand. De duur van de stimulatie (18,7 (11,6-44,6) seconden) was gemiddeld korter dan de resterende duur van het incident (30,6 (19,5-47,6) seconden), wat lijkt te suggereert dat zorgverleners terughoudend zijn met stimuleren.

De resultaten van deze studie benadrukken dat zorgverleners – bewust of door omstandigheden –vaak niet ingrijpen bij cardiorespiratoire incidenten, vooral wanneer deze van korte duur zijn. Daarnaast benadrukken de bevindingen opnieuw dat de indicatie, het tijdstip en de methodes van tactiele stimulatie subjectief zijn, en dat de optimale interventiestrategie onbekend is.

Samengevat vormt de behandeling van apneu bij prematuren een paradox: de fysiologische instabiliteit in deze patiëntenpopulatie leidt tot frequente, onvoorspelbare episoden van apneu, bradycardie en hypoxie, waardoor de behandeling hiervan een aanzienlijke belasting vormt voor verpleegkundigen. De hoge werkdruk in combinatie met factoren zoals alarmmoeheid, vergroten het risico dat er niet tijdig en adequaat gereageerd wordt met als gevolg dat de instabiliteit van de patiënt verder toeneemt.

DE POTENTIE VAN GEAUTOMATISEERDE TACTIELE STIMULATIE

Een mogelijke manier om deze paradox op te lossen is automatisering. Een geautomatiseerd

tactiel stimulatieapparaat zou zorgverleners kunnen ondersteunen bij het behouden of herstellen van de cardiorespiratoire stabiliteit van premature doordat op elk cardiorespiratoir incident tijdig en consistent gereageerd kan worden. Deze hypothese houdt echter alleen stand als mechanische stimulatie even effectief en veilig is als handmatige stimulatie.

In **Hoofdstuk 3** wordt een systematische review gepresenteerd van de bestaande literatuur over de effectiviteit van handmatige en mechanische tactiele stimulatie bij het beëindigen en voorkomen van apneu bij premature. Vier studies, waarbij in totaal 13 premature werden geïncludeerd, onderzochten de effectiviteit van tactiele stimulatie op het beëindigen van apneu. Twee van deze studies tonen aan dat mechanische vibrerende stimulatie op de voet of romp, die ter plekke door zorgverleners werd geactiveerd, net zo effectief is als handmatige stimulatie door de zorgverlener. De twee andere studies rapporteren dat geautomatiseerde mechanische stimulatie meer dan 90% van de apneus kan beëindigen, maar hierin ontbreekt directe vergelijking met andere mechanische of handmatige methoden.

Het preventieve effect van tactiele stimulatie werd geëvalueerd in 11 studies, waarbij in het totaal 290 premature werden geïncludeerd. Deze studies vergeleken het aantal apneus tijdens periodes van repetitieve of continue stimulatie met periodes zonder stimulatie. Eén studie paste handmatige stimulatie toe door elke 15 minuten, 5 minuten over de ledematen van de patiënten te wrijven. Alle andere studies gebruikten mechanische methoden: een pulserende ballon onder de borstkas (1 studie), trilmotortjes op de handen of voeten (2 studies), vibrerende matrassen (2 studies) of oscillerende watermatrassen (6 studies). De studies met oscillerende stimuli geven geen consistente resultaten, maar alle studies met handmatige, vibrerende of pulserende stimulatie rapporteren wel een significante vermindering in het aantal apneus in de periodes waarin stimulatie plaatsvond - ondanks grote variatie in studieopzet, patiënten en meetmethoden.

Hoewel handmatige tactiele stimulatie al sinds jaar en dag gebruikt wordt om spontane ademhaling bij premature te initiëren of te ondersteunen, toont deze review aan dat de effectiviteit hiervan nauwelijks is onderzocht. De resultaten suggereren desondanks wel dat verschillende methoden van mechanische stimulatie een positief effect op de ademhaling kunnen hebben, hoewel de mate van effectiviteit tussen de methoden naar alle waarschijnlijkheid verschilt. Door de heterogeniteit van de studies is directe vergelijking van methoden niet mogelijk en is ook de optimale vorm van mechanische stimulatie onbekend. Tot op heden zijn er slechts twee studies uitgevoerd met geautomatiseerde apparaten, en in die studies is de potentiële meerwaarde ten opzichte van handmatige stimulatie niet direct onderzocht.

Hoofdstuk 4 beschrijft een studie waarin onderzocht is of een vroege, anticiperende

stimulatiestrategie – mogelijk gemaakt door automatische stimulatie – effectiever is in het ondersteunen van de ademhaling en het voorkomen van apneu dan een reactieve stimulatiebenadering, wat nu standaardzorg is. Daarvoor is bij premature konijnen het effect van milde mechanische vibrotactiele stimulatie bij door hypoxie geïnduceerde onregelmatige ademhaling (IB) vergeleken met het effect van sterkere stimulatie als reactie op apneu.

De resultaten tonen aan dat zowel de incidentie als de duur van apneu significant afnemen bij anticiperende stimulatie ten opzichte van reactieve stimulatie (optreden apneu: 3/10 vs. 9/11 konijnen, p=0.030; duur apneu: 7.7 (5.1–30.8) vs. 38.4 (15.5–73.9) seconden, p=0.014). Wanneer geanalyseerd wordt vanaf de start van de stimulatie, blijkt anticiperende stimulatie in vergelijking met reactieve stimulatie vaker te leiden tot herstel van het ademhalingsritme, en ook te resulteren in een significant hogere ademhalingsfrequentie na twee minuten (herstel van ademhalingsritme: 7/10 vs. 1/9 konijnen, p=0.015; ademhalingsfrequentie: 17.3 ±13,7 vs. 2.9 ±1.8 ademhalingen/min, p=0.009).

Deze bevindingen suggereren dat stimuleren bij dreigende apneu aanzienlijk effectiever is dan stimulatie die start bij het optreden van een apneu. Bovendien blijkt vroegtijdige stimulatie een minder intensieve prikkel te vereisen, wat overeenkomt met het feit dat heel subtiele continue stimulatie al kan leiden tot vermindering van apneu (**Hoofdstuk 3**). Het is echter belangrijk op te merken dat zowel bij premature konijnen als bij premature of pasgeboren baby's onregelmatige ademhaling niet altijd resulteert in apneu en dat het ademhalingscentrum niet altijd stimulatie nodig heeft om de ademhaling te hervatten. Hoewel anticiperende stimulatie diverse voordelen lijkt te bieden, blijft het onduidelijk of deze aanpak opweegt tegen mogelijke nadelen van overmatige of onnodige stimulatie. Verdere studies met geautomatiseerde tactiele stimulatieapparaten zijn nodig om de meest effectieve closed-loop strategie voor de behandeling van apneu bij prematuren vast te stellen.

EEN NIEUW GEAUTOMATISEERD TACTIEL STIMULATIEAPPARAAT

Het ontbreken van commercieel verkrijgbare apparaten die geschikt zijn voor gebruik of evaluatie op de NICU maakte het noodzakelijk om zelf een nieuw, speciaal gemaakt geautomatiseerd tactiel stimulatieapparaat (GTSA) te ontwikkelen. Omdat fundamenteel onderzoek naar de optimale methode en locatie voor stimulatie bijzonder tijdrovend en kostbaar zou zijn, is er gekozen voor een pragmatisch en iteratief ontwerpproces, waarbij gebruikt is gemaakt van inzichten uit het hiervoor beschreven onderzoek, bestaande literatuur, klinische ervaring en ideeën van NICU-verpleegkundigen en neonatologen. In

Hoofdstuk 5 staat beschreven hoe deze input geleid heeft tot het ontwerp van een apparaat dat zowel effectief als veilig is, en voldoende flexibiliteit heeft om verschillende vormen van stimulatie toe te passen.

Dit ontwerp, genaamd BOBBY, geeft een zacht strelende sensatie op de huid door middel van asynchroon getriggerde vibraties aan beide uiteinden van een silicone bandje dat over de borst van de prematuur wordt geplaatst. De stimulatie wordt geactiveerd na detectie van een klinisch alarm via het bestaande patiëntbewakingssysteem. Het doel is om de stimulatie die verpleegkundigen doorgaans geven na te bootsen en een groot huidoppervlak te stimuleren, zonder daarbij overmatige belasting te veroorzaken. De amplitude en frequentie van het GTSA zijn onafhankelijk instelbaar, zodat de optimale stimulatie in toekomstig onderzoek verder uitgezocht kan worden.

De toepasbaarheid en korte-termijn veiligheid van dit GTSA werden geëvalueerd in een gerandomiseerde cross-over studie met 16 prematuren van 24–30 weken zwangerschapsduur op de NICU van het LUMC (**Hoofdstuk 6**). De studie bestond uit twee opeenvolgende periodes van elk 24 uur: een interventieperiode waarin het GTSA werd toegevoegd aan de standaardzorg en geactiveerd na elk klinisch alarm, waardoor direct stimulatie werd toegediend, en een controleperiode waarin het GTSA wel werd bevestigd maar niet actief was. Het apparaat bleef gedurende de gehele studie bevestigd, ook tijdens buidelen, en werd bij elke verzorging verplaatst om drukplekken te voorkomen. In beide periodes registreerde een camera de interventies van de zorgverleners.

De resultaten tonen aan dat het apparaat succesvol kan worden toegepast: 14 van de 16 geïncludeerde patiënten voltooiden het volledige 48-uurs studieprotocol. Bij één patiënt werd de studie voortijdig beëindigd vanwege noodzaak tot intubatie door klinische achteruitgang die niet gerelateerd was aan het onderzoek, en bij een andere patiënt werd de studie gestopt na het ontstaan van niet-wegdrukbaar erytheem (doorligwond graad 1) veroorzaakt door te strakke bevestiging van het bandje. Tijdens de interventieperiode detecteerde het apparaat 83% van de cardiorespiratoire alarmen van de patiëntmonitor, wat in 100% van de gevallen gevolgd werd door automatische stimulatie. In de interventieperiode werd daardoor een 30- tot 40-voudige toename van de stimulatiefrequentie waargenomen ten opzichte van de controleperiode. Geen van de deelnemende patiënten vertoonde ongemak tijdens de studie, er werden geen bijwerkingen gerapporteerd en verpleegkundigen beschouwden het apparaat als geschikt en eenvoudig in gebruik Deze bevindingen ondersteunen de toepasbaarheid van dit apparaat voor geautomatiseerde tactiele stimulatie als reactie op cardiorespiratoire events in prematuren.

Zowel de totale duur van hypoxie, totale duur van bradycardie, de hoeveelheid extra

toegediende zuurstof, het aantal manuele stimulaties, de responstijd van de verpleegkundige als de duur van de manuele stimulatie verschilden niet significant tussen de twee periodes. Deze vergelijkingen waren echter meegenomen als secundaire uitkomsten, omdat de omvang van de studie te klein was om verschillen hierin aan te tonen. Om de effectiviteit van automatische stimulatie te beoordelen zijn dus vervolgstudies nodig, waarbij snellere en betrouwbaardere detectie methodes – of zelfs predictie methodes - overwogen zouden moeten worden om het maximale potentieel te kunnen evalueren.

VERDERE KANSEN VOOR AUTOMATISERING

Hoofdstuk 7 bespreekt de potentiële voordelen van geautomatiseerde tactiele stimulatie in andere klinische situaties en bij diverse patiëntengroepen. Automatische stimulatie zou bij kunnen dragen aan het op gang brengen van de ademhaling bij prematuren direct na de geboorte. Onderzoek heeft aangetoond dat herhaalde tactiele stimulatie de zuurstofvoorziening verbetert en de ademdrive versterkt, maar desondanks niet vaak wordt toegepast. De review presenteert ook andere voorbeelden waarbij automatisering de zorg voor prematuren direct na de geboorte kan verbeteren zoals geautomatiseerde beademing en zuurstoftoediening.

CONCLUSIE

Tactiele stimulatie is een veelgebruikte en essentiële interventie in reactie op apneu bij prematuren, maar menselijke factoren en omstandigheden kunnen leiden tot vertragingen en inconsistenties in de respons. Hoewel de focus altijd op de langere ademhalingspauzes heeft gelegen, is er steeds meer bewijs dat prematuren ook bij kortere en zelflimiterende incidenten baat kunnen hebben bij actieve interventie. Korte pauzes komen relatief vaker voor waardoor ze bij elkaar opgeteld aanzienlijk bijdragen aan de fysiologische instabiliteit van prematuren.

Het vervangen van de handmatige tactiele interventie door een GTSA, die een directe en consistente respons aanbiedt, heeft de potentie om patiëntuitkomsten te verbeteren en de werkdruk van zorgverleners te verlagen. Er is bewijs dat mechanische stimulatie – met name vibrerende en pulserende – kan helpen om apneu te verkorten of te voorkomen, waarbij vroege toepassing effectiever lijkt te zijn en een lagere intensiteit vereist. Bij gebrek aan bestaande geautomatiseerde apparaten voor klinisch gebruik is een eigen prototype GTSA ontwikkeld waarvan de toepasbaarheid en korte termijn veiligheid in een klinische context zijn aangetoond. Dit proefschrift legt hiermee een basis voor toekomstige ontwikkeling van geautomatiseerde tactiele stimulatieapparaten, biedt eerste inzichten in het spanningsveld

tussen de baten en lasten van automatische stimulatie, en benadrukt het belang van integratie van onderzoek en ontwikkeling van nieuwe technologie ter verbetering van de neonatale zorg.

PART 7

APPENDICES

LIST OF ABBREVIATIONS

AF	Nasal airflow
AUC	Area under the curve
AOP	Apnoea of Prematurity
ATSD	Automated tactile stimulation device
BOBBY	Breathing Operator for BaBY
BR	Breathing rate
BRP	Brief respiratory pause
COV	Coefficient of variation
CPAP	Continuous positive airway pressure
EEG	Electroencephalogram
ECG	Electrocardiogram
EMG	Electromyogram
FiO2	Fraction of inspired oxygen
FRC	Functional Residual capacity
GA	Gestational age
HFMEA	Healthcare Failure Mode and Effects Assessment
HFNC	High flow nasal cannula
HR	Heart rate
IB	Irregular breathing
IBI	Inter-breath interval
IH	Intermittent hypoxia
IPPV	Intermit tent positive pressure ventilation
IQR	Interquartile range
LUMC	Leiden University Medical Center
NICU	Neonatal Intensive Care Unit
NIPPV	Non-invasive positive pressure ventilation

OBU	Open Bay Unit
PB-CPAP	Physiological based (PB)-CPAP
PMA	Post menstrual age
PR	Pulse rate
RFM	Respiratory function monitor
RR	Respiratory rate
RRI	RR interval
SD	Standard deviation
sNIPPV	Synchronised NIPPV
SpO2	Peripheral oxygen saturation
SRU	Single Room Unit
WHO	World Health Organisation

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CURRICULUM VITAE

Sophie Josephine Elisabeth Cramer was born on February 2, 1992, in Veldhoven, the Netherlands and grew up in Eindhoven with her parents and two younger siblings; Dirk and Olivia. In 2010 she completed grammar school at the Van Maerlant Lyceum in Eindhoven and moved to Delft for her studies. It was during her bachelor in Industrial Product Design that she got interested in healthcare. She was selected for a minor in medicine at the Leiden University Medical Center (LUMC) and the Erasmus Medical Center and subsequently took bridging courses to transition to a master in Biomedical Engineering. As part of the master's program, Sophie visited the technical workshop at LUMC where she encountered the first prototype of the Concord Birth Trolley. She applied for an internship to contribute to the development of this prototype and was introduced to the initiator and inventor promotor prof.dr. A.B. te Pas. Their collaboration during this project served as the foundation for her subsequent research trajectory. In the summer of 2016, Sophie commenced her graduation project under his supervision, focusing on automating tactile stimulation.

Sophie graduated at the Delft University of Technology in 2017 and continued her project as part of a Professional Doctorate in Engineering (PDEng) program at Eindhoven University of Technology and the LUMC. During this two-year program, she completed various technical oriented projects in the department of neurosurgery, in the operating rooms and the technical department of the LUMC. Additionally she spent three months in Hobart, Australia conducting neonatal research the Royal Hobart Hospital's NICU under the supervision of prof. dr. P. Dargaville. Her PDEng thesis was nominated for Best Thesis in the Qualified Medical Engineer program and her accompanying two-minute video pitch received the Audience Award on the 2020 TU/e Thesis Awards.

Following her graduation, Sophie was appointed as a medical engineer in the NEONWISE project at the LUMC NICU. In 2019, she was awarded the Gisela Thier Grant by the Willem-Alexander Children's Hospital, enabling her to pursue a part-time PhD alongside her clinical engineering work. Since September 2023, she has held a permanent position at the departments of Neonatology and Medical Technology at LUMC and serves as an expert in medical devices on the Medical Ethics Review Committee.

During her PhD Sophie has visited national and international scientific conferences, where she presented her research using oral and poster presentations. In 2019, she received the Young Investigator Award at the 10th Dresden Symposium on Delivery Room Management. The automated tactile stimulation device developed during her PhD project, in collaboration with prof. Dr. A.B. te Pas and prof. dr. S.B. Hooper, is patented and a startup company, BOBBY Neonatal, has been established to bring the device to market.

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