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

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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 ( $28 \pm 2$  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  $17.3 \pm 13.7$  vs  $2.9 \pm 1.8$  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 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.

