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

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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.

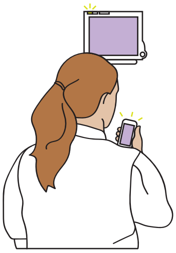
While this limitation may be true for human caregivers managing the shorter events in the current care setting, a mechanical and automated "caregiver" has the ability to respond immediately to any respiratory pause without difficulty. The use of an automated stimulation system could improve treatment 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

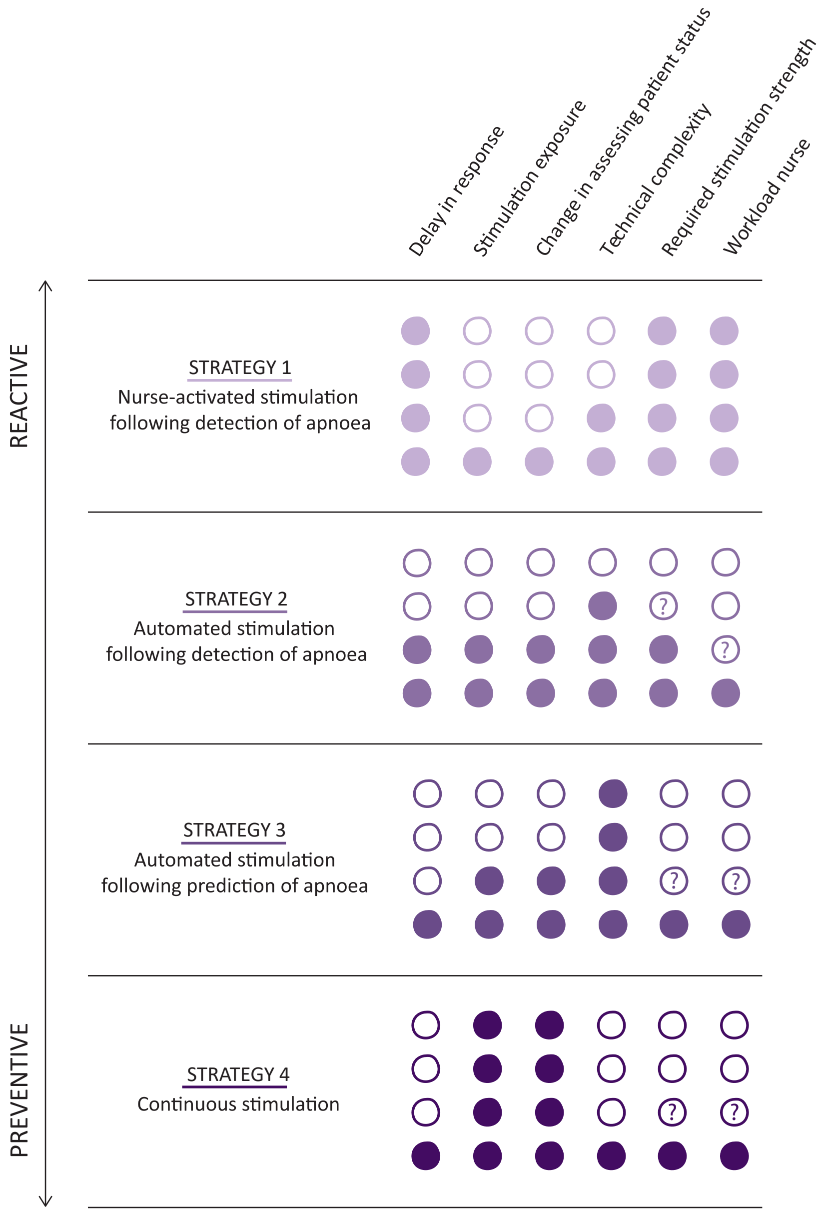



**Figure 1.** Different stimulation approaches with expected pro's and con's.

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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