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

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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 Two infants were withdrawn from the study prematurely: one infant required intubation for cyanotic spells and the other developed local non-blanching erythema consistent with a mild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

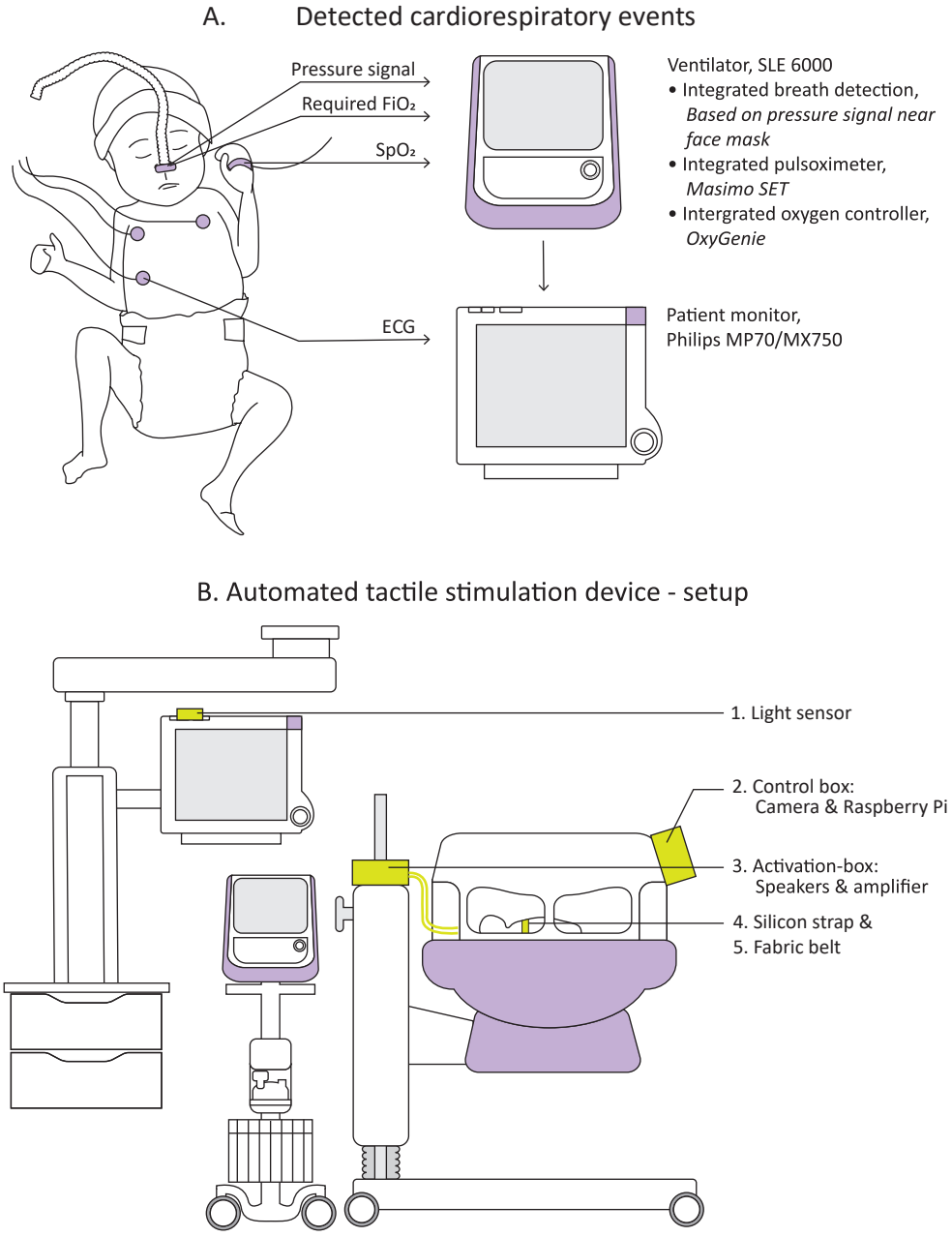

Figure 1. Overview of set-up (A, B) and embodiment (C) of the ATSD

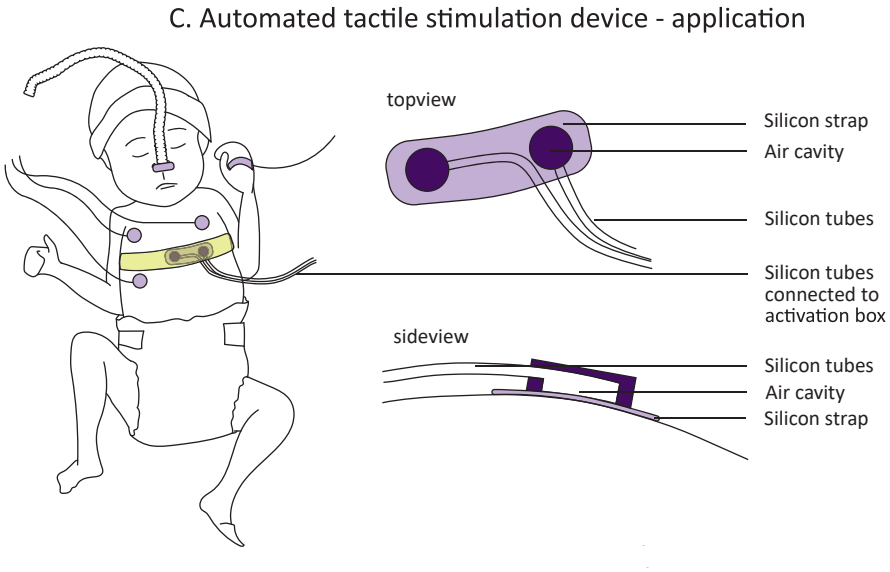

Figure 1. Overview of set-up (A, B) and embodiment (C) of the ATSD

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

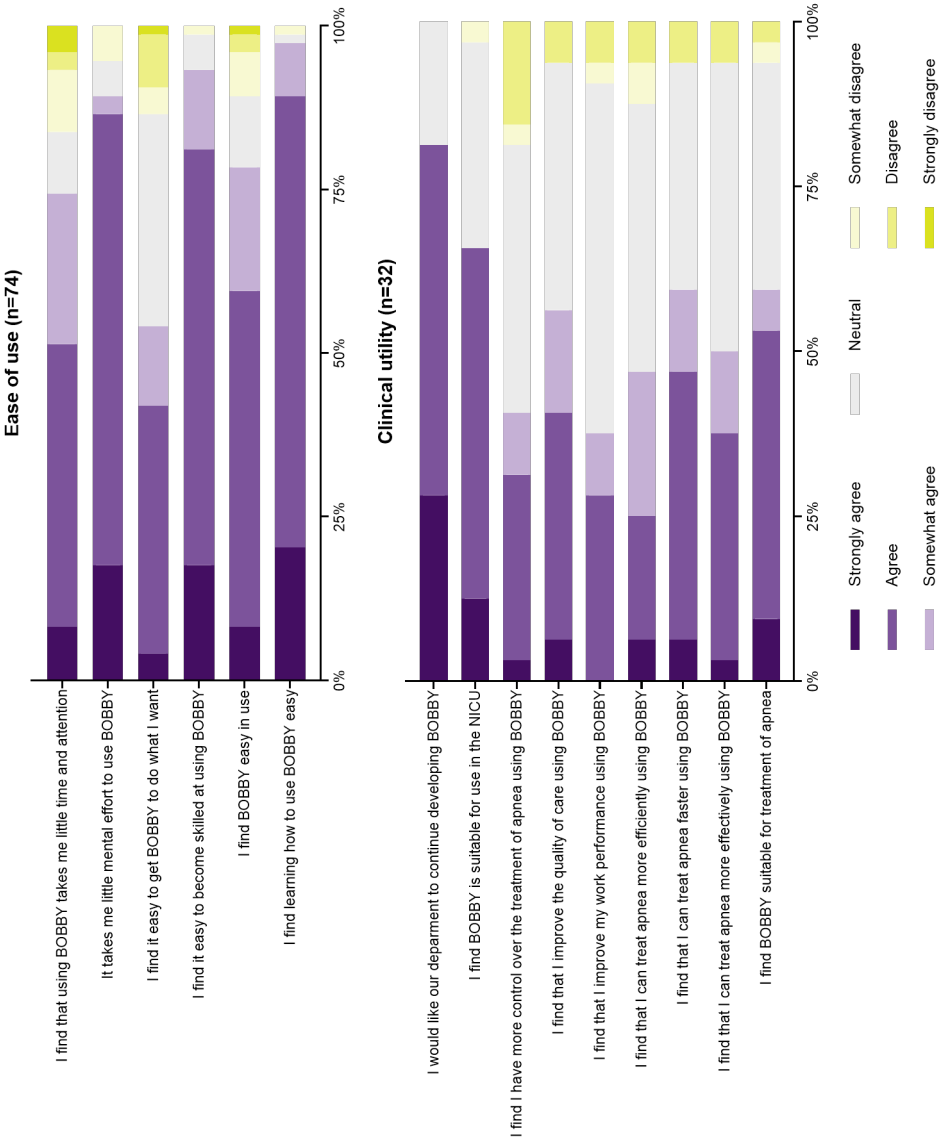

Table 3. Secondary outcomes

	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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