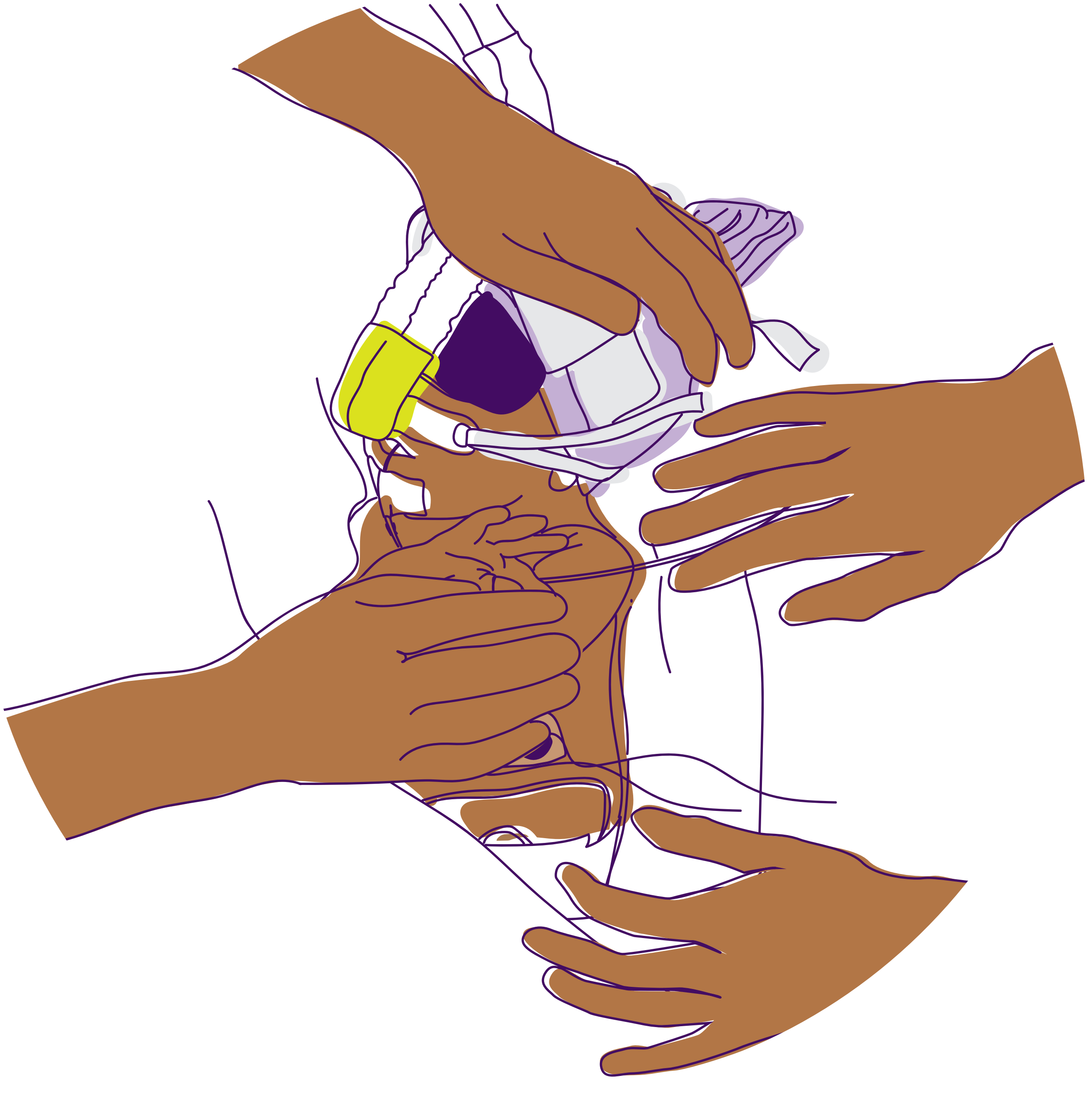
Touched by technology: automated tactile stimulation in the treatment of apnoea of prematurity

Cramer, S.J.E.



PART

3

CHAPTER 3

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

SJE Cramer, J Dekker, J Dankelman, SC Pauws, SB Hooper & AB te Pas

Frontiers in Pediatrics, 2018;6:45

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.

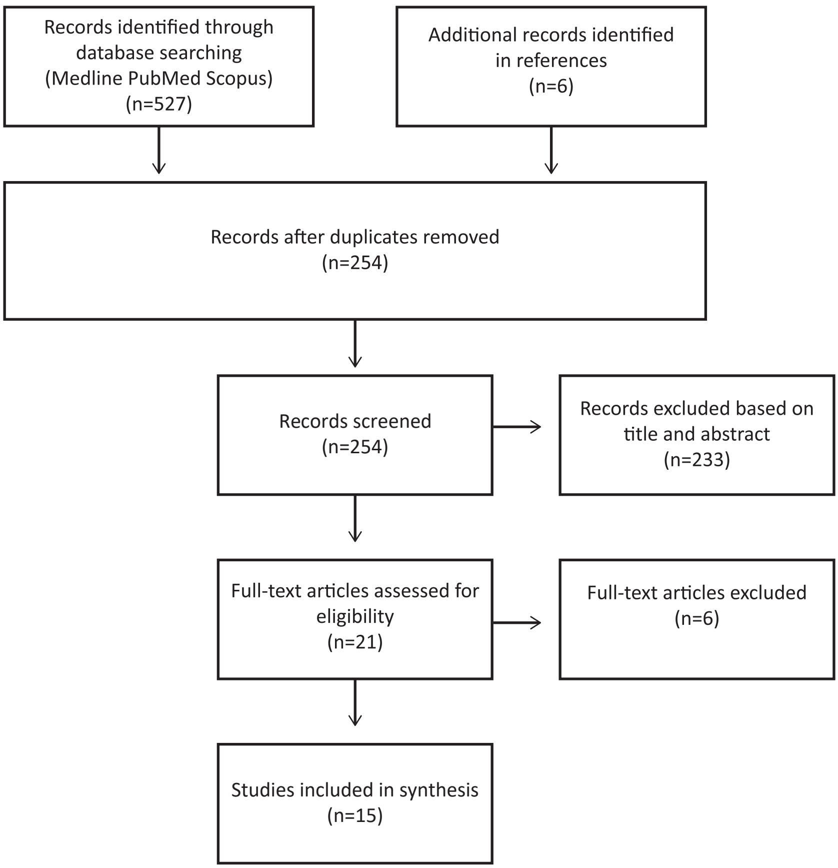


Figure 1. Flowchart of article selection

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 & CO_2 by thermistor or cannula PF by pulse oximeter SpO_2 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 O_2<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% O_2 + 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.

REFERENCES

1. Henderson-Smart, D.J., The effect of gestational age on the incidence and duration of recurrent apnoea in newborn babies. Aust Paediatr J, 1981. 17(4): p. 273-6.
2. Eichenwald, E.C., Apnea of Prematurity. Pediatrics, 2016. 137(1): p. e20153757.
3. Morton, S.U. and V.C. Smith, Treatment options for apnoea of prematurity. Arch Dis Child Fetal Neonatal Ed, 2016. 101(4): p. F352-6.
4. Martin, R.J., J.M. Abu-Shaweesh, and T.M. Baird, Apnoea of prematurity. Paediatric Respiratory Reviews, 2004. 5(suppl A): p. S377-382.
5. Atkinson, E. and A.C. Fenton, Management of apnoea and bradycardia in neonates. Paediatrics and Child Health, 2009. 19(12): p. 550-554.
6. Sale, S.M., Neonatal apnoea. Best Practice & Research Clinical Anaesthesiology, 2010. 24(3): p. 323-336.
7. Mathew, O.P., Apnea of prematurity: pathogenesis and management strategies. J Perinatol, 2011. 31(5): p. 302-10.
8. Abu-Shaweesh, J.M. and R.J. Martin, Neonatal apnea: what's new? Pediatr Pulmonol, 2008. 43(10): p. 937-44.
9. Baird, T.M., Clinical correlates, natural history and outcome of neonatal apnoea. Semin Neonatol, 2004. 9(3): p. 205-11.
10. Marayong, P. and M.S. Mostoufi, Foot Vibrotactile Device for Central Apnea Interruption in Premature Infants. Medicine Meets Virtual Reality, 2009. 17: p. 180-182.
11. Bhatia, J., Current options in the management of apnea of prematurity. Clin Pediatri (Phila), 2000. 39(6): p. 327-336.
12. Mohr, M.A., et al., Very long apnea events in preterm infants. J Appl Physiol (1985), 2015. 118(5): p. 558-68.
13. Poets, C.F., Apnea of prematurity: What can observational studies tell us about pathophysiology? Sleep Med, 2010. 11(7): p. 701-7.
14. Smith, V.C., et al., Stochastic resonance effects on apnea, bradycardia, and oxygenation: a randomized controlled trial. Pediatrics, 2015. 136(6): p. 1561-1568.
15. Zhao, J., F. Gonzalez, and D. Mu, Apnea of prematurity: from cause to treatment. Eur J Pediatr, 2011. 170(9): p. 1097-105.

16. Garcia, A.P. and R. White-Traut, Preterm infants responses to taste, smell and tactile stimulation. Journal of Pediatric Nursing, 1993. 8(4): p. 245-252.

17. Faille, E.O., A. Setya, and L. Eisenfeld, A Computerized System to Diagnose and Treat Neonatal Apnea Using Vibrotactile Stimulation. Connecticut Medicine, 2013. 77(9): p. 517-22.

18. Vergales, B.D., et al., Accurate automated apnea analysis in preterm infants. Am J Perinatol, 2014. 31(2): p. 157-62.

19. Pichardo, R., et al., Vibrotactile stimulation system to treat apnea of prematurity. Biomed Instrum Technol, 2003. 37(1): p. 34-40.

20. Gottfried, A.w., et al., Physical and social environment of newborn infants in special care units. Science, 1981. 214: p. 673-675.

21. Osborn, D.A. and D.J. Henderson-Smart, Kinesthetic stimulation for treating apnea in preterm infants. Cochrane Database Syst Rev, 2000(2): p. CD000499.

22. Camargo, V.C., et al., Instrumentation for the detection and interruption of apnea. Conf Proc IEEE Eng Med Biol Soc, 2014: p. 2127-2130.

23. Lovell, J.R., et al., Vibrotactile stimulation for treatment of neonatal apnea: a preliminary study. Connecticut Medicine, 1999. 63(6): p. 323-325.

24. Frank UA, et al., Treatment of apnea in neonates with an automated monitor-actuated apnea arrestor. Pediatrics, 1973. 51(5): p. 878-83.

25. Kesavan, K., et al., Neuromodulation of Limb Proprioceptive Afferents Decreases Apnea of Prematurity and Accompanying Intermittent Hypoxia and Bradycardia. PLoS One, 2016. 11(6): p. e0157349.

26. Bloch-Salisbury, E., et al., Stabilizing immature breathing patterns of preterm infants using stochastic mechanosensory stimulation. J Appl Physiol (1985), 2009. 107(4): p. 1017-27.

27. Jirapaet, K., The effect of a vertical pulsating stimulation on Apnea of Prematurity. J Med Assoc Thai, 1993. 76(6): p. 319-26.

28. Korner, A.F., E.M. Ruppel, and J.M. Rho, Effects of water beds on the sleep and motility of theophylline-treated preterm infants. Pediatrics, 1982. 70(6): p. 864-869.

29. Korner, A.F., et al., Reduction of sleep apnea and bradycardia in preterm infants on oscillating water beds: a controlled polygraphic study. Pediatrics, 1978. 61(4).

30. Jones, R.A.K., A controlled trial of a regularly cycled oscillating waterbed and a non-oscillating waterbed in the prevention of apnoea in the preterm infant. Arch Dis Child, 1981. 73: p. 889-891.

31. Kattwinkel, J., et al., Apnea of prematurity; comparative therapeutic effects of cutaneous stimulation and nasal continuous positive airway pressure. Journal of Pediatrics, 1975. 86(4): p. 588-594.

32. Svenningsen, N.W., C. Wittstorm, and H.-W. L., OSCILLO-oscillating air mattress in neonatal care of very preterm babies. Technol Health Care, 1995. 3(1): p. 43-46.

33. Saigal, S., J. Watts, and D. Campbell, Randomized clinical trial of an oscillating air mattress in preterm infants: Effect on apnea, growth, and development. J Pediatr, 1986. 109: p. 857-64.

34. Korner, A.F., et al., Effects of waterbed flotation on premature infants: a pilot study. Pediatrics, 1975. 56(3): p. 361-367.

35. Ronca, A.E. and J.R. Alberts, Cutaneous induction of breathing in perinatal rats. Psychobiology, 1995. 23(4): p. 261-269.

36. Scarpelli, E., S. Condorelli, and E. Cosmi, Cutaneous stimulation and generation of breathing in the fetus. Pediat Res, 1977. 11: p. 24-28.

37. Faridy, E.E., Instinctive resuscitation of the newborn rat. Respir Physiol, 1983. 51(1): p. 1-19.

38. Dekker, J., et al., Tactile Stimulation to Stimulate Spontaneous Breathing during Stabilization of Preterm Infants at Birth: A Retrospective Analysis. Front Pediatr, 2017. 5: p. 61.

39. Gaertner, V.D., et al., Physical stimulation of newborn infants in the delivery room. Arch Dis Child Fetal Neonatal Ed, 2018. 103(2): p. F132-F136.

40. Marcotte, A.L., et al., Development of Apnea Interruption System by Vibratory Stimulus. Proceedings of the IEEE 22nd Annual Northeast Bioengineering Conference, 1996: p. 28-29.

41. Trippenbach, T. and D. Flanders, Interaction between somatic and vagal afferent inputs in control of ventilation in 2-week-old rabbits. Respiration Physiology, 1999. 116: p. 25-33.

42. Ioffe, S., et al., Respiratory response to somatic stimulation in fetal lambs during sleep and wakefulness. Pflugers Arch, 1980. 388: p. 143-148.

43. McNamara, F., H. Wulbrand, and B.T. Thach, Characteristics of the infant arousal response. J Appl Physiol, 1998. 85: p. 2314-2321.

44. Lijowska, A.S., et al., Sequential arousal and airway-defensive behavior of infants in asphyxial sleep environments. J Appl Physiol, 1985. 83(1): p. 219-228.

45. Bolanowski, S.J., Jr., et al., Four channels mediate the mechanical aspects of touch. J Acoust Soc Am, 1988. 84(5): p. 1680-94.

46. Mortimer, B.J.P., G.A. Zets, and R.W. Cholewiakc, Vibrotactile transduction and transducers. Acoustical Society of America, 2007. 121(5): p. 2970-2977.

47. Fitzgerald, M., Cutaneous primary afferent properties in the hind limb of the neonatal rat. Journal of Physiology, 1987. 383: p. 79-92.

48. Ferrington, D.G., M.O.H. Hora, and M.J. Rowe, Functional maturation of tactile sensory fibers in the kitten. Journal of Neurophysiology, 1984. 52(1): p. 74-85.

49. Hagan, R., et al., Neonatal chest wall afferents and regulation of respiration. J Appl Physiol, 1977. 42(3): p. 362-367.

50. Homma, I., Inspiratory inhibitory reflex caused by the chest wall vibration in man. Respiration Physiology, 1980. 39: p. 345-353.

51. Ishida, K., Y. Yasuda, and M. Miyamura, Cardiorespiratory response at the onset of passive leg movements during sleep in humans. European Journal of Applied Physiology, 1993. 66(507-513).

52. Ethevenot, G., Response Ventilatoire du lapin nouveau-né la mobilisation passive des membres, in Medicine. 1973, University of Nancy: Nancy. p. 1-161.

53. Roll, J.P. and J.P. Vedel, Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. Exp Brain Res, 1982. 47(2): p. 177-90.

54. Paydarfar, D. and D.M. Buerkel, Dysrhythmias of the respiratory oscillator. Chaos, 1995. 5(1): p. 18-29.

55. Paydarfar, D. and D.M. Buerkel, Sporadic apnea: paradoxical transformation to eupnea by perturbations that inhibit inspiration. Med Hypotheses, 1997. 49: p. 19-26.

56. Remmers, J. and I. Marttila, Action of intercostal muscle afferents on the respiratory rhythm of anesthetized cats. Respiration Physiology, 1975. 24: p. 31-41.

57. Trippenbach, T., G. Kelly, and D. Marlot, Respiratory effects of stimulation of intercostal muscles and saphenous nerve in kittens. J Appl Physiol, 1983. 54: p. 1736-1744.

58. Binks, A.P., et al., Oscillation of the lung by chest-wall vibration. Respiration Physiology, 2001. 126(3): p. 245-249.

59. Monin, P., Modifications of ventilatory reflexes: an efficient therapy for apneas of prematurity? Biol Neonate, 1994. 65: p. 247-251.

60. Schelegle, E.S. and J.F. Green, An overview of the anatomy and physiology of slowly adapting pulmonary stretch receptors. Respir Physiol, 2011. 125: p. 17-31.

61. Arold, S., et al., Noise added to mechanical ventilation improves gas exchange in acute lung injury. Proceedings of the First Joint BMES/EMBS Conference. IEEE Engineering in Medicine and Biology 21st Annual Conference and the 1999 Annual Fall Meeting of the Biomedical Engineering Society, 1999. 1: p. 335.

62. Williamson, J.R., et al., Using physiological signals to predict apnea in peterm infants. Conference Record of the Forty Fifth Asilomar Conference on Signals, Systems and Computers, 2011: p. 1098–1102.

63. Williamson, J.R., D.W. Bliss, and D. Paydarfar, Forecasting respiratory collapse: theory and practice for averting life-threatening infant apneas. Respir Physiol Neurobiol, 2013. 189(2): p. 223-31.