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

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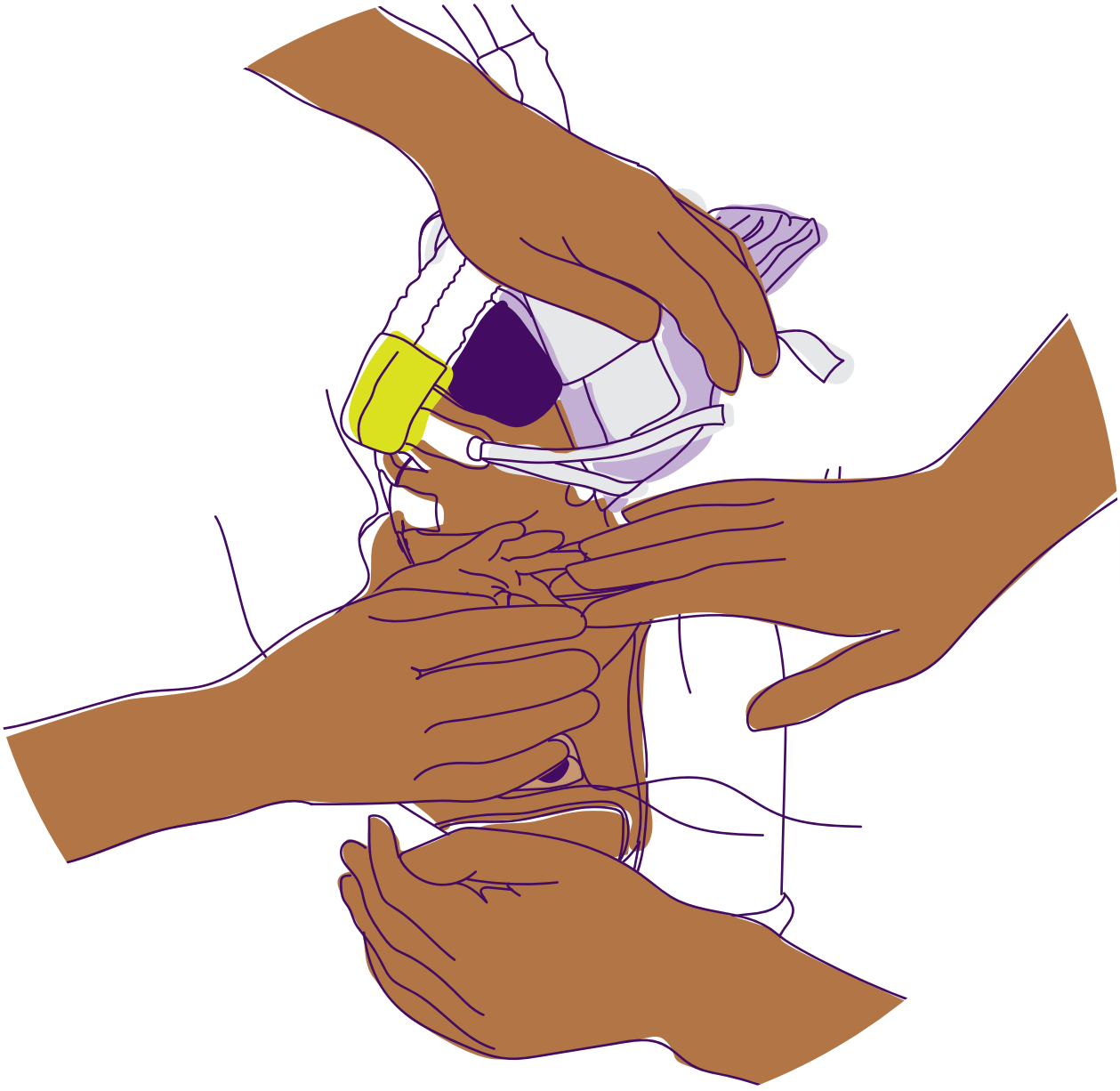

PART 1

GENERAL INTRODUCTION

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

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

APNOEA OF PREMATURITY

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

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

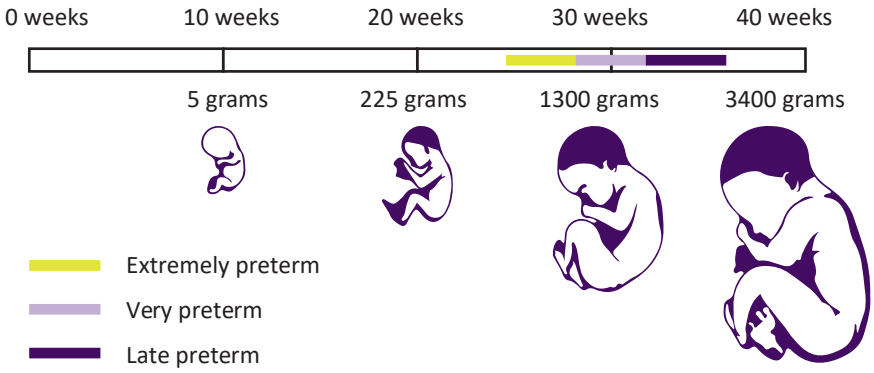

Figure 1. Categories of preterm birth

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

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

AETIOLOGY OF APNOEA

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

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

CONSEQUENCES OF APNOEA

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

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

CURRENT TREATMENT OF AOP

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

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

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

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

CHALLENGES IN TREATMENT OF AOP

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

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

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

AUTOMATION OF TACTILE STIMULATION

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

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

AIM AND OUTLINE OF THIS THESIS

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

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

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

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

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

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

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

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

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