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Multicentre paired non-inferiority study of the cardiorespiratory monitoring performance of the wireless and non-adhesive Bambi® belt measuring diaphragm activity in neonates: study protocol

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ABSTRACT

Introduction Cardiorespiratory monitoring is used in the neonatal intensive care unit (NICU) to assess the clinical status of newborn infants and detect critical deteriorations in cardiorespiratory function. Currently, heart rate (HR) is monitored by electrocardiography (ECG) and respiration by chest impedance (CI). Disadvantages of current monitoring techniques are usage of wired adhesive electrodes which may damage the skin and hinder care. The Bambi® belt is a wireless and non-adhesive alternative that enables cardiorespiratory monitoring by measuring electrical activity of the diaphragm via transcutaneous electromyography. A previous study showed feasibility of the Bambi® belt and this study compares the belt performance to ECG and CI.

Methods and analysis This multicentre non-inferiority paired study will be performed in the NICU of the Máxima Medical Center (MMC) in Veldhoven and the Emma Children's Hospital, Amsterdam University Medical Centre (AmsterdamUMC) in Amsterdam, The Netherlands. 39 infants in different postmenstrual age groups (minimally 10 infants<30 weeks, between 30–32 weeks and >32 weeks) will be recruited. These infants will be monitored with the Bambi® belt in addition to standard ECG and CI for 24 hours. The primary outcome is the HR, studied with three criteria: (1) the limits of agreement of the HR measurements in terms of the second-to-second difference in the HR between the belt and standard ECG, (2) the detection of cardiac events consisting of bradycardia and tachycardia and (3) the quality of HR-monitoring. The secondary outcome is the respiratory rate (RR), studied with the criteria (1) agreement in RR-trend monitoring, (2) apnoea and tachypnoea detection and (3) reliable registrations.

Ethics and dissemination This protocol was approved by the Medical Ethical Committee of the MMC and the Central Committee for Human Research. The MMC started patient recruitment in July and the AmsterdamUMC in August 2021. The results will be presented at conferences and published in peer-reviewed journals.

Trial registration number NL9480.

WHAT IS KNOWN ABOUT THE SUBJECT

⇒ Disadvantages of the cardiorespiratory monitoring technique in neonates are indirect measurements of respiration, usage of adhesive electrodes and hindering wires.
⇒ With transcutaneous electromyography of the diaphragm, respiratory activity is measured directly by recording the activity of the main respiratory muscle.
⇒ The Bambi® belt is a novel wireless and non-adhesive belt that enables cardiorespiratory monitoring by measuring diaphragm activity with dry electrodes.

WHAT THIS STUDY HOPES TO ADD

⇒ Demonstration of the non-inferiority of the Bambi® belt compared with the electrocardiography and chest impedance for cardiorespiratory monitoring in preterm and term infants.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ When non-inferiority of the Bambi® belt compared with the current cardiorespiratory monitor is confirmed, the belt could be used as a wireless and skin-friendly alternative.

INTRODUCTION

In the neonatal intensive care unit (NICU), cardiorespiratory monitoring is crucial to assess clinical condition and to timely detect and treat frequently occurring cardiorespiratory events to prevent morbidity and mortality.[1 2] To date, this is performed by measuring the electrocardiography (ECG) and chest impedance (CI) with three wired

adhesive electrodes. CI measures variation in electrical impedance across the chest during respiration caused by changes in lung aeration and chest wall movement. These techniques provide continuous monitoring of heart rate (HR), respiratory rate (RR) and breathing pattern. However, as CI measures respiration indirectly, adequate detection of breathing cycles and apnoea may not always be optimal.[3]

With transcutaneous electromyography of the diaphragm (dEMG) breathing effort can be recorded directly by measuring the electrical activity of this main respiratory muscle. To date, this technique also uses three adhesive electrodes and provides information on respiration and HR. Studies have shown its feasibility in the NICU setting.[4]

The use of adhesive electrodes is restricted in infants with a postmenstrual age <26 weeks in fear of skin damage.[5] Moreover, electrode removal may cause discomfort. Furthermore, the wires attached to the electrodes restrict movements of the infant and may hinder parent-infant interaction, nursing and kangaroo care. Restrictions in kangaroo care may impact patient outcome as it has been associated with beneficial effects such as decreased mortality, decreased risk of severe infection/sepsis and hypothermia, and increased likelihood of exclusive breast feeding.[6 7] All things considered, it is important to find alternatives for using wired adhesive electrodes.

In the past years, several wireless wearable sensors have been developed to measure various parameters in neonates such as ECG, HR, RR, peripheral oxygen saturation and (skin) temperature.[8–14] Recently, a novel wireless and non-adhesive sensor belt (Bambi® belt, Bambi B.V., Eindhoven, the Netherlands) was developed for neonatal use that measures ECG and respiration based on the dEMG technique. A recent pilot study showed that measuring HR and RR with this belt in preterm infants is feasible and that the measured HR and RR trend was similar to ECG and CI.[15] However, before replacing the current techniques using adhesive wired electrodes with the non-adhesive sensor belt, a larger study is required to demonstrate the non-inferiority of this belt as an alternative cardiorespiratory monitor. In this study, we compare the monitoring performance of the Bambi® belt to ECG and CI and hypothesise that the performance of the belt is non-inferior to the current monitoring techniques.

METHODS

Study design

This multicentre paired non-inferiority study will be performed in the NICU of Máxima Medical Center (MMC) in Veldhoven and the Emma Children's Hospital of the Amsterdam University Medical Centre (AmsterdamUMC), both located in the Netherlands. Each patient will be simultaneously measured with the belt and ECG/CI (paired design). To compare the devices, a non-inferiority/equivalence framework will be used.

Table 1 The non-inferiority/equivalence margins for the primary and secondary outcomes

Endpoints	Prespecified margins*
LOA of second-to-second HR differences	±8 bpm
LOA of RR-trend differences	±15 bpm
Sensitivity of brady-/tachycardia detection	90%†
PPV of brady-/tachycardia detection	90%†
Sensitivity of apnoea/tachypnoea detection	70%
PPV of apnoea/tachypnoea alarms	0%–100%‡
Data loss percentage	5%
Robust data percentage (HR)	90%
Robust data percentage (RR)	70%

Data loss is defined as the percentage of data with 'Leads off' or 'Bluetooth Loss Error' in the belt.
*The prespecified margins are compared to confidence intervals with corresponding confidence levels (see SAP for more details).
†Note: all missed bradycardias are checked for clinical relevance by two independent experts.
‡Since the reference devices for apnoea detection in the clinical practice are the peripheral oxygen saturation (SpO_2) and electrocardiogram instead of the respiration signal and the performance for chest impedance to detect tachypnoea is unsatisfactory due to the presence of cardiac interference, all values for PPV for apnoea/tachypnoea are acceptable. Interpretations will be made based on the results.
HR, heart rate; LOA, limits of agreement; PPV, positive predictive value; RR, respiratory rate; SAP, statistical analysis plan.

Here, equivalence is defined as the limit of agreement of the HR/RR between the belt and ECG/CI being within prespecified margins (see table 1 for the margins). Non-inferiority is defined as the performance of clinical event detection and quality criteria not being worse than prespecified margins.

Study population

Preterm and term infants being routinely monitored with the standard cardiorespiratory monitor (Intellivue MP90, Philips Healthcare, Eindhoven, The Netherlands) are included in the study. To ensure a representative sample of the target population, infants in different age groups will be included. Infants with chest skin lesions, congenital anomalies, and other scenario's preventing belt placement, such as (effects of) surgery or wrap for therapeutic hypothermia, will be excluded.

Primary outcome

As HR-monitoring is clinically most relied on and both ECG and dEMG provide the HR by measuring cardiac electrical activity, while CI and dEMG measure respiration with a different technique, the HR is considered the primary outcome.[3 16] This will be studied with three criteria, which will be compared with the prespecified margins in table 1: (1) Reliable monitoring performance through second-to-second HR measurement agreement in terms of differences in measured HR

between the belt and the ECG/CI monitoring; (2) The detection of a composite cardiac event consisting of bradycardia (HR <100 beats per minute for at least five seconds)[17] and tachycardia (HR >180 beats per minute for at least ten seconds)[18] between the belt and the ECG measured with adhesive electrodes. The minimal duration of a bradycardia or tachycardia will prevent the inclusion of technical errors (short drops or increases in the HR) in our analysis and is lower for bradycardia compared with tachycardia as bradycardias are shorter events.[1] The thresholds are empirically chosen to detect all low and high HR-values; (3) Non-inferior quality (percentage of time with HR recordings without data loss).

Moreover, we will perform subgroup analyses to investigate whether the HR measurement performance is consistent under different clinical activities (eg, kangaroo care, feeding) and in the different age groups.

Secondary outcomes

The secondary outcome is the measured RR. This will be studied using the following three criteria, which will be compared with the prespecified margins in table 1:

1. Comparing the trend in RR values provided by the belt and CI, based on the difference in the 10 min moving averages. The RR-trend is studied as this is used in the clinical practice to detect for example increases in RR over time as a marker of clinical deterioration of a patient.[3] Since CI is widely used for neonatal respiratory monitoring, it is used as the reference technique.
2. Next to comparing the RR-trend, the ability to detect apnoea and tachypnoea is studied as the detection of these critical respiratory events based on RR is another purpose of the respiratory monitoring. Clinically relevant apnoeas are considered when indicated by a RR <20 breaths per minute measured with CI for at least 10 s, associated with a desaturation (arterial oxygen saturation as measured by pulse oximetry (SpO_2) <80% for at least 10 s) and/or bradycardia (HR <100 beats per minute for at least five seconds) (objective apnoea measurement).[17] A RR <20 breaths per minute is chosen for the apnoea definition as we solely use the numerical RR-values, because despite the two different measurement techniques this endpoint is equal, and to capture all periods of low breathing frequency.

   Tachypnoea is defined as a prolonged period of the averaged (moving average with a window size of 10 min) RR >60 breaths per minute and >100 breaths per minute (approximately two times the average normal RR).[19] To cover short and long periods of tachypnoea, 3 different durations are studied (30 s, 60 s and 10 min).
3. Calculating the percentage of time with reliable respiratory monitoring (without data loss and with an acceptable signal-to-noise ratio).

Data collection

The following basic characteristics and demographic information will be collected at the baseline of the study: gestational age, birth weight, gender, age and weight at day of measurement, relevant medical status (respiratory support, medication and underlying illness during measurement), chest circumference, nipple distance, skin type at study start by visual inspection (normal, dry, flaky, oily, moist, other).

Sample size calculation

A power calculation is performed for the primary outcome using data collected in a previous study.[15] Among the three criteria, criteria 1 needs the largest sample size and is used for our study. This resulted in 39 required infants to achieve 80% power with an overall 5% type I error with a Bonferroni correction (details in the statistical analysis plan (SAP) in online supplemental file 1).

In addition, an interim analysis will be performed as the power calculation was based on the previous study and recruitment of infants without being able to answer research questions is unethical.[20] This will be performed after including one-third of the infants for sample size adaption using the method of Mehta and Pocock.[21] If the conditional power falls within the predefined 'promising zone', the sample size will be increased to an upper limit of 52 infants. Otherwise, the study will proceed with the original sample size. To ensure that a representative sample of the age distribution of infants at a NICU, infants in different postmenstrual age groups will be recruited with the same proportions as in the target population (minimally 10 infants <30 weeks, between 30–32 weeks and >32 weeks).

Study procedures

The Bambi® belt system is a non CE-certified medical device, designed for wireless cardiorespiratory monitoring of (pre)term infants in a hospital environment. All included infants will be monitored with the belt in addition to standard ECG/CI for 24 hours to obtain representative clinical scenarios throughout the entire day. The measurement setup is visualised in figure 1 and consists of (1) dEMG measurement with the belt and (2) the extraction of patient monitor data.

In the belt, three dry electrodes are incorporated (figure 2). When placing the belt at the height of the diaphragm, the outer two electrodes are in the nipple line and the middle electrode is in line with the sternum. The three ECG/CI electrodes are attached at the original location without hindering belt placement. The electrical signal of the diaphragm measured with the belt is wirelessly transmitted to the receiver module (REM) by the sensor module (SEM). The REM processes the dEMG signal to obtain the ECG and respiration signal (averaged diaphragmatic activity). An inbuilt algorithm provides the HR and RR out of the ECG and respiration signal respectively. This data is transported to a bedside computer. The data from the patient monitor (ECG, HR,

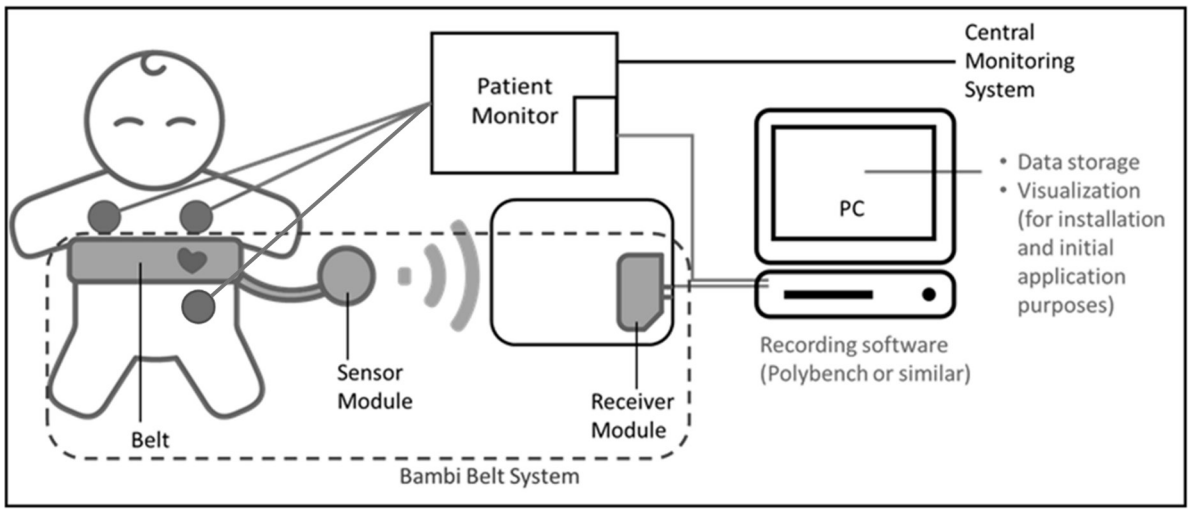

Figure 1 The measurement setup. The adhesive electrodes used for standard cardiorespiratory monitoring are attached at the original location, visualised by the three grey dots. The diaphragm activity measured with the Bambi® belt is wirelessly transmitted with the sensor module to the receiver module where the data is processed to obtain an electrocardiogram and respiration waveform (and heart rate and respiratory rate). These data and the data measured with the patient monitor are transported to a personal bedside computer with Polybench software to synchronise and record these signals.

RR and SpO_2) is extracted from the bedside monitor using an isolated cable and is also transported to the bedside computer.

The belt data from the REM and patient monitor are recorded and synchronised using a dedicated software package (Polybench, Applied Biosignals, Weener, Germany) on a personal bedside computer. Data is recorded at a sample rate of 1–500 Hz for rate and waveform data, respectively. The bedside software also provides the possibility to make measurements annotations by nurses and researchers during data recording, such as repositioning of the infant, nursing and kangaroo care.

During the study, daily routine care proceeds as usual. The location of the belt is regularly checked and if necessary repositioned (similar to the clinical practice). Notifications are visualised when contact between skin and the belt is lost (Leads off) or when there is no connection between the SEM and REM (Bluetooth Loss Error). In case of the first notification, the belt may be repositioned, while in case of Bluetooth loss the battery level of the SEM or blocking of this sensor (eg, by an arm) are checked.

Preferably, the belt stays in place during the study. However, the belt can be removed during diagnostic imaging, patient handling, or in case of skin irritation at the belt location. The reason for removal will be annotated. If the belt is removed, the medical staff, parents and one of the dedicated researchers will decide together if the belt can be reapplied.

Recruitment

Parents of all eligible infants are approached for consent to obtain a sample as heterogeneous and representative as possible. Preferably, infants are included as soon as possible after birth. During the 24 hours, the study can be terminated if requested by parents or the treating physicians. In case of withdrawal of a subject, an extra subject will be included.

Safety

Being a medical device study, this study was classified as a moderate risk.[22] A specified monitor plan for the study is made based on risk-classification.

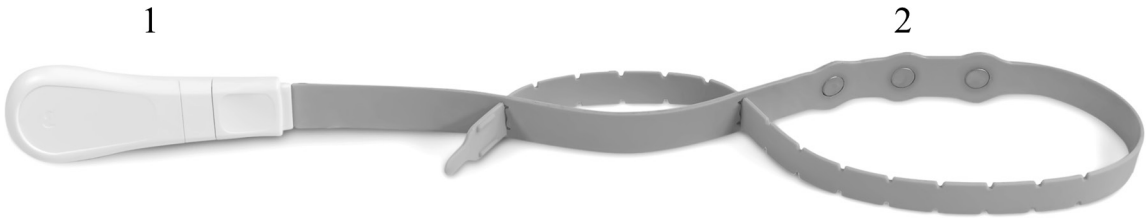

Figure 2 The Bambi® belt is a wireless non-adhesive belt designed for cardiorespiratory monitoring of (pre)term infants. The three dry electrodes[2] measure electrical activity of the diaphragm via transcutaneous electromyography. These data are wirelessly transmitted with the sensor module[1] to a receiver module that processes the diaphragm activity to obtain the electrocardiogram, respiration signal, heart rate and respiratory rate.

STATISTICAL ANALYSIS

A detailed SAP can be found in online supplemental file 1. Unless otherwise specified, all hypothesis tests are two sided with a significance level of 0.05. All statistical analyses will be performed using R V.4.0 (the R Foundation for Statistical Computing; Vienna, Austria) and SAS software V.9.4 (SAS Institute).

The non-inferiority/equivalence margins based on expert opinions (survey send to neonatologists of different NICU's in the Netherlands) and literature[4 23 24] are described in table 1. In the different subparagraphs, we refer to this table.

Summary and descriptive statistics

Categorical data will be summarised by numbers of counts and percentages. Continuous data will be summarised by mean, SD if data is normal and median, IQR if data are skewed. Minimum and maximum values will also be presented for continuous data when appropriate.

Statistical analysis of the primary outcome

Criteria 1: agreement in HR

To investigate the equivalence of HR measurement between the belt and ECG, we will fit a linear mixed model to the second-to-second HR difference between both. With this model, the 95% limits of agreement (Bland-Altman analysis) will be derived. The two-one-sided tests with a multiplicity corrected alpha of 0.0167 and the prespecified margin (±8 bpm) will test equivalence between the two devices. In addition, based on a bivariate heteroscedastic model fitted to HR segments of a prespecified length, additional performance measures will be calculated as sensitivity analyses (details in SAP).

Criteria 2: cardiac event detection

For HR monitoring, we also consider the detection of bradycardia and tachycardia. We will estimate the sensitivity and the positive predictive value (PPV) of the belt using the patient monitor data as the ground truth and perform a non-inferiority test with an alpha of 0.0167. The non-inferiority margin for the sensitivity and PPV are listed in table 1. In case of missed bradycardias, one independent expert per centre will qualify the safety and clinical consequences of each missing event by answering the same questions per figure containing the discrepancy in HR and the ECG-signals measured with CI and the belt. These figures will be blinded and thus it will be unknown which signal corresponds CI or the belt.

Criteria 3: signal quality

The quality of the investigational device will be quantified based on the percentage of time during the 24-hour period it produces any reading (percentage without data loss due to 'Leads off' or 'Bluetooth Loss Error') and the percentage in time it produces a good-quality reading (percentage of robust data) for the HR and RR, respectively. For the HR non-robust data can be caused by bad connection (suboptimal Bluetooth or skin-electrode connection). These criteria are built-in in the belt algorithm and therefore this data is automatically labelled. Hypothesis testing will be used to establish the non-inferiority of this 'uptime' percentage (percentage without data loss and percentage of robust data) of the belt.

For the RR, the uptime percentage is also categorised as (1) data readings without data loss and (2) robust data readings, being readings without unrealistic (eg, negative) values. Signal quality is only analysed for the belt. However, these results are compared with prespecified margins, described in table 1. As the HR monitored with CI is accurate and nearly continuous, while the RR is less relied on and may be unreliable, the prespecified margin for the RR is lower than for the HR.

Statistical analysis of secondary outcomes

Secondary analyses, based on the same statistical methods for the criteria of the primary outcome, include all secondary endpoints (apnoea and tachypnoea detection, RR-trend analysis (see SAP)) and evaluation during different scenarios.

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Contributors AWJS, HJN, MV, RWvL, FHdJ, AHvK, GJH conceptualised the study. ZZ and ERvdH made the statistical analysis plan, which was reviewed by all authors. AWJS wrote the first version of this manuscript. All authors contributed to the final draft of the manuscript.

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Competing interests Bambi Medical B.V. supports the study by a financial grant and use of equipment free of charge. Data collection, analysis, interpretation and reporting will be done independent of Bambi Medical B.V.

Patient and public involvement Patients were included in this study after obtaining parental informed consent. The patients could not be involved in the design, recruitment, conduction and dissemination of results of this study. Neither could we ask burden of the study. The outcome measures were developed by combining clinical and statistical knowledge to ensure a SAP that enables confirmation of non-inferiority of the belt compared with ECG/CI.

Patient consent for publication Not applicable.

Ethics approval The Medical Ethical Committee of the MMC (W21.042) and the Central Committee for Human Research in the Netherlands (CCMO, CCMO21/0167/PP) approved the study protocol (V.2, 19 May 2021). Local feasibility at the AmsterdamUMC was approved by the Medical Ethical Committee of the AMC (2021_146). Regarding patient safety, no belt related events were observed in the pilot study and are therefore unexpected. Moreover, as every patient is monitored with ECG/CI and the belt, safety is guaranteed in case of missing belt data. The MMC started patient recruitment in July and the AmsterdamUMC in August 2021. The duration of this study will be approximately seven months. The SAP will be used for the analyses. The results will be published in peer-reviewed journals and presented at future congresses.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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