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#### ORIGINAL ARTICLE



# Cardiorespiratory monitoring with a wireless and nonadhesive belt measuring diaphragm activity in preterm and term infants: A multicenter non-inferiority study

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#### Abstract

**Introduction:** We determined if the heart rate (HR) monitoring performance of a wireless and nonadhesive belt is non-inferior compared to standard electrocardiography (ECG). Secondary objective was to explore the belt's respiratory rate (RR) monitoring performance compared to chest impedance (CI).

**Method:** In this multicenter non-inferiority trial, preterm and term infants were simultaneously monitored with the belt and conventional ECG/CI for 24 h. HR monitoring performance was estimated with the HR difference and ability to detect cardiac events compared to the ECG, and the incidence of HR-data loss per second. These estimations were statistically compared to prespecified margins to confirm equivalence/non-inferiority. Exploratory RR analyses estimated the RR trend difference and ability to detect apnea/tachypnea compared to CI, and the incidence of RR-data loss per second.

**Results:** Thirty-nine infants were included. HR monitoring with the belt was noninferior to the ECG with a mean HR difference of 0.03 beats per minute (bpm) (standard error [SE] = 0.02) (95% limits of agreement [LoA]: [-5 to 5] bpm) (p < 0.001). Second, sensitivity and positive predictive value (PPV) for cardiac event detection were 94.0% (SE = 0.5%) and 92.6% (SE = 0.6%), respectively ( $p \le 0.001$ ). Third, the incidence of HR-data loss was 2.1% (SE = 0.4%) per second (p < 0.05). The exploratory analyses of RR showed moderate trend agreement with a mean RRdifference of 3.7 breaths/min (SE = 0.8) (LoA: [-12 to 19] breaths/min), but low sensitivities and PPV's for apnea/tachypnea detection. The incidence of RR-data loss was 2.2% (SE = 0.4%) per second.

Anouk W. J. Scholten and Zhuozhao Zhan contributed equally to this work and shared first authorship.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes. © 2023 The Authors. *Pediatric Pulmonology* published by Wiley Periodicals LLC. **Conclusion:** The nonadhesive, wireless belt showed non-inferior HR monitoring and a moderate agreement in RR trend compared to ECG/CI. Future research on apnea/ tachypnea detection is required.

KEYWORDS

newborn infants, preterm infants, transcutaneous electromyography

### 1 | INTRODUCTION

Preterm infants often experience apnea, intermittent hypoxemia, and cardiac events.<sup>1,2</sup> To prevent associated morbidity and mortality, timely detection and treatment of these events is crucial.<sup>3</sup> On the other hand, congenital anomalies and illnesses in term infants can also lead to respiratory instability, and thus require cardiorespiratory monitoring as well.<sup>4</sup> Monitoring is currently performed by measuring heart rate (HR) with electrocardiography (ECG) and respiratory rate (RR) with chest impedance (CI), using three wired adhesive electrodes. This conventional setup of cardiorespiratory monitoring has several disadvantages. First, the electrodes may cause skin damage and discomfort and the wires may hinder parent-infant interaction, including kangaroo and nursing care.<sup>5</sup> Furthermore, CI may not always measure RR accurately due to nonbreathing related changes in impedance and cardiac interference.<sup>2,6</sup> Therefore, there is a need for a skin-friendly and wireless alternative that improves the RRmonitoring accuracy compared to CI by measuring respiration directly.

Breathing effort can be measured directly by recording the electrical activity of the diaphragm with transcutaneous electromyography (dEMG). In addition to the registration of RR based on muscle contractions, it can also monitor heart rhythm and HR. A previous study showed feasibility of cardiorespiratory monitoring using this dEMG-technique in the neonatal intensive care unit (NICU).<sup>7</sup> However, up to now, dEMG recordings still require application of three wired adhesive electrodes as well.

Recently, a novel wireless and nonadhesive belt with three incorporated dry electrodes was developed (Bambi<sup>®</sup> Belt; Bambi Medical B. V.), which uses dEMG for cardiorespiratory monitoring in infants. Feasibility of monitoring with this belt was demonstrated in a pilot study.<sup>8</sup> However, before implementing the belt in clinical practice as an alternative for the current monitor techniques, it should be secured that the overall cardiorespiratory monitoring performance of the belt is non-inferior to ECG/CI.

In this study, we compared the monitoring performance of the Bambi<sup>®</sup> Belt to ECG/CI. Given the vital importance of HR monitoring in this population, the primary aim of this study was to determine whether the belt's performance is non-inferior to the standard ECG. Our secondary aim was to explore the belt's RR monitoring performance compared to CI. We hypothesized that the HR monitoring performance of the belt would be non-inferior to the ECG but that the RR-agreement between the belt and CI would be

modest considering the fact that CI has its inaccuracies and different techniques (impedance vs. electrical activity of the diaphragm) are used.

## 2 | METHODS

#### 2.1 | Study design

This multicenter paired non-inferiority trial was conducted in the NICUs of the Máxima Medical Centre (MMC) in Veldhoven and the Emma Children's Hospital of the Amsterdam University Medical Centre (Amsterdam UMC), both in The Netherlands. Approval was obtained from the institutional review boards (Medical Ethical Committee MMC, ABR registration: NL77436.015.21), the Central Committee for Human Research and was registered in The Netherlands Trial Register (NL9480). The study was monitored by independent bodies (Clinical Trial Centre Maastricht and Clinical Monitoring Centre of the Amsterdam UMC).

#### 2.2 | Study population

Infants on standard cardiorespiratory monitoring were eligible for inclusion. To ensure a representative age distribution of the NICU population, at least 10 infants were included in the following postmenstrual age (PMA) groups: <30, 30–32, and >32 weeks. Exclusion criteria were infants with chest lesions, congenital anomalies, and other scenarios preventing belt placement. Parental consent was asked when the inclusion criteria were met and no exclusion criteria were present.

#### 2.3 Study procedures

All included infants were simultaneously monitored with the Bambi<sup>®</sup> Belt (non CE-certified medical device, Bambi B. V.) and ECG/CI (Intellivue MP90; Philips Healthcare) for 24 h, while routine caregiving continued. The appropriate belt size was based on the infant's weight and inter-nipple distance (size 1: <1000 g and ±3.5 cm, size 2: 1000-2500 g and ±5.0 cm, size 3: 2500-3500 g and ±7.0 cm, size 4: >3500 g and ±9.0 cm). The belt was placed at the height of the diaphragm with the outer two electrodes in the nipple line. The three

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**FIGURE 1** The measurement setup. Simultaneous cardiorespiratory monitoring in an infant with the wireless and nonadhesive belt based on transcutaneous electromyography of the diaphragm, and with the three adhesive electrodes that measure chest impedance and the electrocardiogram. Parental consent (written and oral) was obtained to take and use this picture.

ECG/CI electrodes were placed on the standard location (see Figure 1). The study procedures are described in detail in the published study protocol.<sup>9</sup> In brief, the sensor module (attached to the belt) transmits the measured dEMG to the receiver module which processes the data and provides the ECG and respiration waveform from which the HR and RR were calculated. These data and the data from the patient monitor (ECG, HR, RR, and peripheral oxygen saturation [SpO<sub>2</sub>]) were transported to the bedside computer. A software package (Polybench; Applied Biosignals) enabled recording and synchronization of all data as well as annotating events (e.g., caregiving, feeding, kangaroo care, and medical procedures) during the measurement period. Notifications were visible when contact between skin and the belt was lost (leads off) or when there was no connection between the sensor and receiver (Bluetooth Loss Error, BLE) to allow correction for these events. In addition, patient baseline characteristics were collected at the start of the study.

#### 2.4 | Outcome measures

The primary outcome parameter was the HR measured with the belt and with the ECG electrodes (the gold standard in this study). We assessed the following HR-related criteria: (1) Second-to-second HRagreement between ECG and the belt. (2) Ability to detect a composite cardiac event, consisting of bradycardia (HR <100 bpm for  $\ge$ 5 s)<sup>10</sup> and tachycardia (HR >180 bpm for  $\ge$ 10 s),<sup>11</sup> with the ECG and the belt. (3) Non-inferiority of the incidence per second of measuring no HR data with the belt due to belt errors (HR-data loss) compared to what would be acceptable when using a wireless and nonadhesive device.

The secondary outcome parameter was the RR measured with the belt and with CI (the gold standard in this study). The following RR-related criteria were assessed: (1) The RR trend (10 min moving average) agreement between CI and the belt, as this is used in clinical practice to identify deterioration of a patient. (2) Ability to detect apnea and tachypnea with CI and the belt. For apnea we only focused on clinically relevant apnea, defined as a RR < 20 breaths/min for  $\geq$ 10 s, associated with a desaturation (SpO<sub>2</sub> < 80% for  $\geq$ 10 s) and/or a bradycardia (HR <100 bpm for  $\geq 5$  s).<sup>10</sup> For tachypnea different definitions were studied, being a RR > 60 breaths/min or >100 breaths/min, and both for three different durations, being 30 s, 60 s, and 10 min, to investigate both short and long periods of tachypnea.<sup>12</sup> (3) Non-inferiority of the incidence per second of measuring no RR data with the belt due to belt errors (RR-data loss), again compared to what would be acceptable when using a wireless and nonadhesive device.

#### 2.5 | Sample size

The power calculation was described in our published study protocol.<sup>9</sup> In short, this was based on previously collected data<sup>8</sup> and yielded 39 infants to achieve 80% power with an overall 5% type I error with a Bonferroni correction for multiplicity (see Supporting Information: 1). An interim analysis was performed at 13 included infants, which revealed that the sample size was adequate.<sup>13</sup>

#### 2.6 | Statistical analyses

All outcome measures were estimated using statistical models to quantify and test the belt performance compared to ECG/CI. For the primary outcome on HR related measures, equivalence and noninferiority with ECG/CI were assessed using prespecified acceptance margins that were based on expert opinion and literature (Table 1).<sup>7,14,15</sup> Equivalence on the HR was defined by prespecified equivalence margins (Table 1) on the 95% limits of agreement (LoA) for the second-to-second differences between the HR readings of the ECG and belt. The LoA was estimated using a linear mixed-effect model (Supporting Information: 2) and a two one-sided t-test (TOST) was used to demonstrate that the estimated LoA is within the prespecified equivalence margin. We also performed a sensitivity analysis to evaluate the correlation between the HR measured with the belt and with the ECG using the Spearman's correlation coefficient (Supporting Information: 2). Non-inferiority was defined on the (infant-specific) sensitivity and positive predicted value (PPV) of the detection of cardiac events (bradycardia, tachycardia, and combined) using an intersection-union test (Supporting Information: 3). The sensitivity and PPV of bradycardia were calculated after

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RR for the belt and CI. Second, mismatches in detected events were not reviewed by specialists and the sensitivity and PPV were only reported for apnea and tachypnea separately and not for the combined endpoint. As the secondary outcome was solely explorative, the RR measures were not tested against any predefined margins. The significance levels used in testing of the three criteria of the

The significance levels used in testing of the three criteria of the primary outcome were adjusted for the multiple comparison ( $\alpha = 0.0167$ ). The secondary, sensitivity, and subgroup analyses were tested without correcting for multiplicity.

All statistical analyses were performed using R (Version 4.2.0; The R Foundation for Statistical Computing) and SAS (Version 9.4; SAS Institute Inc.).

#### 3 | RESULTS

#### 3.1 | Measurements performed in this study

A total of 73 parents were approached of whom 41 provided consent for the study (Figure 2). Generally, the reason for parents to not give consent was related to them feeling overwhelmed by all occurring events, the clinical condition of their infant or their infant being transferred to another hospital within days. Of the 41 infants included in the study, 2 infants were withdrawn from the study by parental request after the clinical condition deteriorated, leaving 39 infants. The patient characteristics are presented in Table 2. A total of 13 infants had a PMA < 30 weeks, 12 between



**FIGURE 2** Flowchart for study enrollment. Seventy-three parents were approached for parental consent in both participating centers of whom 41 infants participated in the study. Two measurements were terminated prematurely yielding 39 full measurements.

reviewing all false positive and false negative bradycardias to assess if the HR did drop below 100/min in both the ECG and belt recording, but that some asynchrony between the signals prevented actual overlap. If this was the case, the event was corrected and marked as a true positive (Supporting Information: 5). Non-inferiority testing was also done on the estimated per-second incidences using (infantspecific) 1 min segments of HR-data loss (Table 1) and a randomeffects zero-inflated Poisson model. A one-sided t-test was used to compare the incidences with the prespecified margin (Supporting Information: 4).

The analyses of the secondary outcome RR were the same as for HR as described in Supporting Information: 2, 3, and 4, but with a few small modifications. First, we used the 10 min moving average of the

**TABLE 1** The equivalence/non-inferiority margins for the primary outcomes.

Endpoints	Acceptance margins
Equivalence	
LoA of second-to-second HR differences	±8 bpm
Non-inferiority	
Incidence per second of having HR- data loss	5%
Sensitivity of cardiac event detection	90%
PPV of cardiac event detection	90%

Abbreviations: HR, heart rate; LoA, limits of agreement; PPV, positive predictive value.

# TABLE 2 Patient characteristics.

	n = 39
Gestational age (weeks)	28.3 (26.9-32.1)
Birth weight (g)	1195 (880–1750)
Postmenstrual age at the start of the measurement (weeks)	30.9 (29.4-34.1)
Weight at the start of the measurement (g)	1245 (1020-2300)
Measurement duration (h)	24.2 (24.0-25.1)
Male gender, n (%)	22 (56.4)
Mode of respiratory support, $n$ (%)	
nIPPV	4 (10.3)
nCPAP	17 (43.6)
HFNC	5 (12.8)
LFNC	3 (7.7)
None	10 (25.6)
Belt size (weight, nipple distance), $n$ (%)	
1 (<1000 g, ±3.5 cm)	1 (2.6)
2 (1000-2500 g, ±5.0 cm)	26 (66.7)
3 (2500-3500 g, ±7.0 cm)	8 (20.5)
4 (>3500 g, ±9.0 cm)	4 (10.3)

Note: All continuous values are expressed as median (interquartile range). Categorical values are expressed as n (%).

Abbreviations: HFNC, high flow nasal cannula; LFNC, low flow nasal cannula; nCPAP, nasal continuous positive airway pressure; nIPPV, nasal intermittent positive pressure ventilation.

30 and 32 weeks, and 14 >32 weeks. One measurement did not contain belt data due to a software error on the bedside computer and another did not contain ECG/CI data due to an unknown technical error. These latter measurements were only used to estimate the risk of having HR-/RR-data loss in the belt. Generally, during 27.0% of the time clinical handling was performed, with kangaroo care being the most frequent one (10.2% of time).

#### 3.2 | Estimation of overall belt performance

#### 3.2.1 | HR

An estimated mean difference of 0.03 bpm (standard error [SE] = 0.02 bpm) with 95% LoA of [-5.0 to 5.0] 1 bpm (SE) = 0.4 bpm in second-to-second HR-agreement between the belt and ECG was observed. The LoAs were within the margins of -8 to 8 bpm (p < 0.001), demonstrating equivalent HR monitoring. The HR monitoring performance was similar in the different GA groups and during periods with clinical activities (p-values all <0.05) (see Tables 1 and 2 of Supporting Information: 2). The sensitivity analysis also

confirmed that the HR measurements of the two techniques were correlated (Spearman's  $\rho$  = 0.94, *p*-value < 0.0001).

In total, 4158 cardiac events, 306 bradycardias, and 3658 tachycardias were matched between both devices based on the automated detection algorithm. The algorithm detected 102 false positive bradycardias of which 95 were converted to true positives after visual inspection (see examples in Figure 2-5 of Supporting Information: 5). For bradycardia, the algorithm detected 92 false negatives of which only 9 events remained false negative (ECG HR < 100 bpm and belt HR > 100 bpm) after visual inspection. Overall after review, 500 true positive, 7 false positive, and 9 false negative bradycardia detections were observed by the belt. With respect to tachycardia, the algorithm detected 3658 true positive, 224 false negative, and 427 false positive tachycardias in the belt registration. Because of this high number, manual inspection and possible correction was not deemed feasible.

Based on these results, the sensitivity and PPV values for the detection of a cardiac event in general or bradycardia and tachycardia separately are presented in Table 3. All sensitivities and PPV's were non-inferior (p < 0.001) to the prespecified margin except for tachycardia (p = 0.15).

The estimated incidence of HR-data loss in a belt measurement was 2.1% (SE = 0.4%) per second, which was non-inferior to the margin of 5% (p < 0.05). The same was observed in infants with a GA < 30 and a GA > 32 weeks, during kangaroo care and during feeding (p < 0.05), but not in infants with a GA between 30 and 32 weeks, during nurse handling and medical procedures (p > 0.05) (see Table 5 and 6 of Supporting Information: 4).

### 3.2.2 | RR

An estimated mean difference of 3.7 (SE = 0.8), with 95% LoAs of [-11.5 to 18.8] breaths/min was observed between the RR trend of the belt and CI. Eventually, only the strictest definition for tachypnea detection, being a RR > 60 breaths/min for at least 30 s, was used as the RR was highly variable over time leading to only a few events

**TABLE 3**Sensitivity and positive predictive value of cardiac andrespiratory event detection.

	Sensitivity	PPV
HR		
Cardiac event detection	94.0% (SE = 0.5%)	92.6% (SE = 0.6%)
Bradycardia	98.0% (SE = 0.7%)	98.3% (SE = 0.6%)
Tachycardia	92.7% (SE = 0.6%)	90.8% (SE = 0.8%)
RR		
Apnea	32.1% (SE = 5.1%)	7.0% (SE = 1.1%)
Tachypnea	49.7% (SE = 1.9%)	53.3% (SE = 1.8%)

Abbreviations: HR, heart rate; PPV, positive predictive value; RR, respiratory rate; SE, standard error.

when using the duration of 10 min, and to also compare periods with higher breathing frequencies between both devices. In total, 231 versus 50 apneas and 4385 versus 4242 tachypneas were detected in the belt and Cl. The estimated number of true positives, false negatives, and false positives in apnea detection with the belt compared to CI were 34, 16, and 197, respectively. For tachypnea detection, these values were 2679, 1563, and 1644, respectively. The estimated sensitivities and PPVs for apnea and tachypnea detection were low (Table 3). The incidence of having RR-data loss in a belt measurement was 2.2% (SE = 0.4%) per second. Similar results were observed in infants born with a GA < 30 weeks and a GA > 32 weeks, during kangaroo care and during feeding (see Table 5 and 6 of Supporting Information: 4). In contrast, infants born with a GA between 30 and 32 weeks, nurse handling and medical procedure, showed a risk of 0.9% (SE = 0.8%), 8.6% (SE = 0.3%), and 9.0% (SE = 0.7%), respectively.

#### DISCUSSION 4

To our knowledge, this is the first study that investigated the overall performance of a wireless and nonadhesive electrode belt for cardiorespiratory monitoring based on diaphragmatic activity. HR monitoring with the belt was non-inferior to the ECG with highly similar second-to-second HR recordings and cardiac event detection ability, and with a low incidence of belt errors. Explorative analyses of the belt's respiratory monitoring performance showed a moderate RR-agreement, but considerable differences in apnea/tachypnea detection compared with CI.

For the belt to be used in daily clinical practice, especially HR monitoring should be continuous and accurate as this is one of the most sensitive variables to assess the infant's clinical status and the efficacy of an intervention.<sup>16</sup> Our study showed that close-toidentical HR readings were measured with the belt compared to the ECG. Similar findings were reported when comparing ECG with dEMG measured with adhesive electrodes or another wireless nonadhesive belt that solely measures HR.7,17 In accordance with the high HR-agreement between the belt and the ECG, the cardiac event detection (i.e., bradycardia and tachycardia) with the belt was non-inferior to the ECG. Almost all cardiac events were detected by our offline detection algorithm. In some events, both devices showed a HR < 100 bpm, but these failed to be matched by the algorithm because no overlap was reached or the duration of a HR < 100 bpm was shorter than 5s (used in our bradycardia definition for offline analysis) in one of the signals. As these were clearly the same event picked up slightly different by both techniques, we classified them as true positives. Remaining false negatives of the belt were mainly caused by signal noise or data loss (e.g., belt errors) in either device. The large amount of detected tachycardia was caused by the HR frequently fluctuating around the threshold for tachycardia, which were registered as multiple events. Nevertheless, similar to bradycardia, the sensitivity and the PPV of the belt was excellent. In terms of continuity of the measurements, our study showed that the belt,

connection and skin contact, resulting in HR-data loss. Fortunately, in line with our previously published feasibility study, the estimated incidence of data loss per second was very low, indicating that the belt enables continuous HR monitoring.<sup>8</sup> Data loss could be further minimized in the future by alerting the user in case a belt error emerges.

Respiratory monitoring is currently used to observe changes in RR trend over time and to detect apnea and tachypnea.<sup>18</sup> In contrast to HR monitoring, the estimated agreement in RR trend between the belt and CI was moderate with relative wide LoA. These findings are in line with studies measuring dEMG with adhesive electrodes, which also show that the agreement improves when solely using stable signal recordings.<sup>7,19</sup> Therefore, this moderate RR-agreement might be caused by differences in measurement technique (dEMG vs. impedance), as both could give a varying appearance of signal stability and both measure a different physiological aspect of respiration, which affects the agreement. In contrast to the moderate RR-agreement, apnea and tachypnea detection with the belt showed low sensitivities and PPVs. This discrepancy might be caused by not manually reviewing the false positives and false negatives, differences in algorithm and in the ability to detect central apnea. CI detected less central apnea compared to dEMG (50 vs. 231 apneas, respectively), which is in line with previous studies that showed cardiac interference and movement may (falsely) suggest breathing activity in CI measurements.<sup>10,20</sup> Similar to the HR measurements, our exploratory analyses showed a low incidence of RR-data loss caused by belt errors. This was again comparable to the feasibility study.<sup>8</sup>

#### **Study limitations** 4.1

There are several study limitations worth mentioning. First, the use of CI as gold standard might not be ideal, as the known disadvantages of this technique might have resulted in an underestimation of the belt's RR monitoring capabilities.<sup>18</sup> However, we aimed to compare the belt with the current clinical standard. In hindsight comparing both CI and the belt with a third, more reliable respiration measure, would have been more suitable. Second, extremely preterm infants with a GA < 26 weeks were not included as they are not routinely monitored with adhesive electrodes until a certain skin maturation has been reached. As a result, we could not simultaneously compare the belt to the gold standard in this population.

#### 4.2 **Clinical implications**

The belt enables continuous and reliable HR monitoring and has a moderate ability to monitor the RR trend compared to ECG/CI, with the advantage of providing additional knowledge of the infant's breathing effort. In addition, using the belt instead of wired adhesive electrodes has the aforementioned benefits of ease-of-use, reducing

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discomfort to the patient and improved parent-infant interaction. However, potential users should keep in mind that using the belt adds a new device to clinical practice, with additional costs. It is a different approach using a patient belt, compared to disposable ECG electrodes. The potential user can make its own evaluation whether the advantages of the belt outweigh the additional costs. When it comes to additional features of the belt, future studies (using a gold standard respiratory signal as a reference), need to determine the ability to detect central apnea and tachypnea with the belt compared to CI. In addition, whether the belt could be used in extremely preterm infants, who are currently not monitored with adhesive electrodes due to their skin immaturity, should be investigated. Note that the belt cannot be used in case of skin lesions, stoma, or drain at the belt location. Finally, the skin friendliness of the belt compared to adhesive electrodes should be studied objectively.

# 5 | CONCLUSION

This study shows that the Bambi<sup>®</sup> Belt enables wireless, nonadhesive and reliable HR monitoring compared to the ECG using adhesive electrodes. RR trend monitoring with the belt showed a moderate agreement with CI. Future studies using a third respiratory reference signal are required to assess the ability to detect respiratory events (i.e., central apnea and tachypnea) with the belt and CI.

#### AUTHOR CONTRIBUTIONS

Anouk W. J. Scholten, Hendrik J. Niemarkt, Marieke Vervoorn, Ruud W. van Leuteren, Frans H. de Jongh, Anton H. van Kaam, and Gerard. J. Hutten conceptualized the study. Zhuozhao Zhan and Edwin R. van den Heuvel made the statistical analysis plan, which was reviewed by all authors. Anouk W. J. Scholten, Hendrik J. Niemarkt, Marieke Vervoorn, Ruud W. van Leuteren, and Gerard. J. Hutten performed the measurements. Zhuozhao Zhan and Edwin R. van den Heuvel analyzed the results. Anouk W. J. Scholten wrote the first version of this manuscript. All authors contributed to the final draft of the manuscript.

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#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

#### DATA AVAILABILITY STATEMENT

Measurement data is available upon reasonable request. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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