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Adaptive bradycardia assessment in preterm infants

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Abstract

In preterm infants, bradycardias associate to critical health conditions. Standard algorithm for bradycardia identification assumes baseline heart rate (BHR) equal to 150bpm and identifies bradycardias when heart rate (HR) decreases below 100bpm. Since preterm infants show BHR varying from 120bpm to 160bpm, a new adaptive algorithm for real-time bradycardia identification was presented. The adaptive algorithm continuously adjusts BHR by averaging HR over the preceding 10-minute window after eliminating out-of-range HR values, and identifies bradycardias when HR decreases below 67% of BHR. Both standard and adaptive algorithms were evaluated using long-term (20.3-70.3h) electrocardiographic recordings of ten preterm infants (Preterm Infant Cardio-respiratory Signals database by Physionet). Bradycardias were characterized in terms of rate (BR, h^{-1}) and depth (BD, bpm). Being also indexes of infants' health conditions, gestational age at birth (GA), birth weight (BW) and HR were used to evaluate performances of the algorithms. Association between BR and BD vs GA, BW and HR was evaluated by computation of the correlation coefficient (ρ). Overall, standard and adaptive algorithms identified 516 and 546 bradycardias, respectively; median BR and BD values were comparable ($1.25h^{-1}$ and 76bpm vs $1.26h^{-1}$ and 70bpm, respectively). However, the adaptive algorithm provided higher BD for HR>150bpm, and vice versa. Significant (p value<0.05) correlations were found between BR and HR (ρ=0.69), BR and BW (ρ=-0.76), and BR and HR (ρ=0.76) only when using the adaptive algorithm. Thus, the adaptive algorithm is superior to the standard algorithm and represents a potentially clinically useful tool for real-time bradycardia assessment in preterm infants.

Keywords: Automatic heart-rate monitoring, Preterm infants, Heart rate, Bradycardia, Birth weight, Neonatal monitoring.

1. Introduction

A preterm infant is a newborn delivered before the 37th week of gestation. Despite its incidence remains under 11% of worldwide births, prematurity is increasing and passed from 9.6% in 2014 [1] to 10.2% in 2018 [2]; it increases mortality and morbidity rate [3,4]. Advanced innovations in preterm infants' treatment have significantly decreased mortality but, unfortunately, developmental disabilities have not declined accordingly [3,5]. Severe conditions of prematurity are usually associated with critical outcomes (such as chronic pulmonary diseases and neuromotor/sensory impairments) and disabling conditions (such as cognitive deficit and behavioural problems) [4].

A typical condition in preterm infants is represented by the immaturity of the cardiorespiratory system [6] that may cause apnoeic episodes [7,8]. In preterm infants, apnoea provokes hypoxemia and blood desaturation; the latter triggers the reaction of the parasympathetic autonomic nervous system that decreases preterm infant heart rate (HR), thus provoking bradycardia events [9]. Thus, similarly to what happens in foetuses [10] (whose conceptional age is like that of preterm infants), in preterm infants there is a link between blood desaturation/oxygen deficiency and episodes of HR deceleration and bradycardia. In foetal monitoring, occurrence of HR decelerations and bradycardia represents an index of risk for foetal hypoxia [10–12]; thus, their correct identification is fundamental for foetal well-being assessment [11]. In foetuses HR decelerations and bradycardia are evaluated in an adaptive way, by comparison with baseline HR (BHR) [10,11,13], which may change over time. Differently, in preterm infants evaluation of bradycardia usually relies on a rigid algorithm according to which bradycardia is defined as a HR decrement under an a priori experimentally determined HR value, typically ranging from 80bpm [14] to 100bpm

Abbreviations: BD: bradycardia depth; BHR: baseline heart rate; BR: bradycardia rate; BW: birth weight; GA: gestational age at birth; HR: heart rate; NB: number of bradycardias; t_{end}: end time of bradycardia; ton: onset time of bradycardia.

[15–17], lasting at least 1s. This algorithm assumes BHR to be 150bpm [18,19] in all preterm infants, assumption that represents a limit since BHR is subject to physiological intra and inter subject variabilities and can vary from 120bpm to 160bpm [20]. As a consequence, a HR decrement in healthy preterm infants with BHR lower than 150bpm may be wrongly identified as bradycardia (false positive detection); differently, a HR decrement in unhealthy or stressed preterm infants with BHR higher than 150bpm may be not identified as bradycardia (false negative detection). Thus, aim of the present work was to propose a new algorithm for bradycardia assessment in preterm infants based on an adaptive estimation of the BHR.

2. Materials and methods

2.1. Clinical data

This study used the "Preterm Infant Cardio-respiratory Signals" database by Physionet [15,21]. All Physionet data were fully de-identified and randomized, and can be used with no further independent ethics committee approval. The database consists of clinical data from ten preterm infants (identified as PTI1 to PTI10) admitted to the Neonatal Intensive Care Unit of the University of Massachusetts Memorial Healthcare. All preterm infants were spontaneously breathing and none of them was suffering from congenital or perinatal infection of the central nervous system, intraventricular haemorrhage of grade II or higher, or hypoxic-ischemic encephalopathy. Individual gestational age at birth (GA; in day) and birth weight (BW; in kg) of each preterm infant were annotated. BW was used to further classify preterm infants as: low BW, if birth weight was between 1.5kg and 2.5kg; very low BW, if birth weight was between 1.0kg and 1.5kg; and extremely low BW, if birth weight was less than 1.0kg [16]. Information about sex and neonatal clinical outcomes (i.e. blood pH, base excess, Apgar after 5 minutes from birth or similar) was not made available.

All preterm infants underwent long-term electrocardiographic monitoring. Acquired data were annotated [15] in terms of R-peak time occurrences, with t_i being the R-peak time occurrence of the i^{th} heartbeat in the electrocardiogram (i=1,2…N, where N is the total number of heartbeats in the electrocardiogram). Beat annotations were then used to obtain the RR-interval sequence ($RR_i=t_i-t_{i-1}$; in s) and, from it, the heart-rate sequence (HR_i=60/RR_i, in bpm). Eventually, BHR relating to the i^{th} heartbeat (BHR_i; in bpm) was computed from HR_i as described below.

2.2. Automatic bradycardia identification and characterization

The standard algorithm and the here proposed adaptive algorithm were applied to HR sequences of the preterm infants for automatic bradycardias identification. Specifically, a bradycardia was identified by determination of its onset time and end time (t_{on} and t_{end}, respectively; in s) and characterized in terms of its depth (BD; in bpm). BD was defined as the maximum HR decrement from BHR between t_{on} and t_{end}. Bradycardias shorter than 1 s (i.e. bradycardias for which $t_{end}-t_{on}<1$s) were rejected. Total number of bradycardias (NB) and bradycardia rate (BR, in h^{-1}; i.e. number of bradycardias per unit of time) characterizing each HR sequence were then determined.

2.2.1 Standard algorithm

According to the standard algorithm for automatic bradycardia identification [15,16,18,19,22] BHR_i is equal to 150bpm, independently from HR_i. Based on this assumption, t_i identifies a bradycardia onset (i.e. $t_{on}=t_i$) if $HR_{i-1}\geq$100bpm and $HR_i<$100bpm, respectively, where 100bpm is 67% of BHR_i. Instead, t_i identifies a bradycardia end (i.e. $t_{end}=t_i$) if $HR_{i-1}<$100bpm and $HR_i\geq$ 100bpm, respectively.

2.2.2 Adaptive algorithm

According to the here proposed adaptive algorithm for automatic bradycardia identification, BHR is characterized by both inter-subject and intra-subject variabilities; thus, its value has to be adapted to the subject and, within a subject, to the current HR. Specifically, BHR_i is computed over a 10-minute long window ending in t_i as the mean HR within an acceptability range identified as mean HR over the window ±10bpm. Based on this assumption, t_i identifies a bradycardia onset (i.e. $t_{on}=t_i$) if $HR_{i-1} \geq 0.67 \cdot BHR_{i-1}$ and $HR_i < 0.67 \cdot BHR_i$. Instead, t_i identifies a bradycardia end (i.e. $t_{end}=t_i$) if $HR_{i-1} < 0.67 \cdot BHR_{i-1}$ and $HR_i \geq 0.67 \cdot BHR_i$.

2.3. Clinical evaluation of the algorithms for automatic bradycardia identification

Reliability of automatic bradycardia identification by the standard and adaptive algorithms was evaluated in relation to GA and BW, which are indexes of infant development [16,23], and in relation to mean HR, which is an index of the cardiac-system development [24]. Eventually, results obtained using the two algorithms were compared to determine which one performed better.

2.4. Statistics

Given the long length (over 20h) of the electrocardiographic recordings (and thus of the HR sequences), distributions of individual HR and BD over time were described in terms of mean±standard deviation. Distributions of BD of a preterm infant obtained using the two algorithms were compared using the t-test for equal means. Given the small number of preterm infants (10 infants) involved in the study, distributions of GA, BW, HR and BD over the preterm infant population were described in terms of $50^{th}[25^{th};75^{th}]$ percentiles. Distributions of GA, BW, HR and BD obtained using the two algorithms were compared

using the Wilcoxon rank sum test for equal medians. Association between BR and BD vs GA, BW and HR was quantified by computation of the Pearson's correlation coefficient (ρ). Statistical significance (p value) was set at 0.05 in all cases.

3. Results

Table 1 reports clinical features (i.e. GA, BW, BW class and HR) for each preterm infant and for the entire population. Overall, preterm infant population counted 5 low BW infants (PTI2, PTI3, PTI5, PTI8 and PTI10), 4 very low BW infants (PTI1, PTI6, PTI7 and PTI9), and 1 extremely low BW infant (PTI4). Moreover, 4 preterm infants (PTI1, PTI4, PTI7 and PTI10) showed mean HR significantly higher than 150bpm (i.e. higher than BHR assumed by the standard algorithm), 5 preterm infants (PTI2, PTI3, PTI5, PTI6 and PTI8) showed mean HR significantly lower than 150bpm, and 1 preterm infant (PTI9) showed mean HR not significantly different from 150bpm. Median HR over population was 147bpm, not significantly different from 150bpm.

Fig. 1 shows HR sequences with relating BHR assumed by the standard algorithm and estimated by the adaptive algorithm of all preterm infants; BHR estimated by the adaptive algorithm is much more accurate than BHR assumed by the standard algorithm, even in the case (PTI9) for which HR has a mean value of 150bpm (Table 1) but also presents some physiological variability with time. Overall, the standard algorithm and the adaptive algorithm identified 516 and 546 bradycardias, respectively; as reported in Table 1, 411 were the bradycardias identified by both algorithms, 105 those identified by the standard algorithm only, and 135 those identified by the adaptive algorithm only. Table 1 also reports individual as well as population bradycardia characterization in terms of NB, BR and BD obtained using both algorithms. Difference between NB estimated by adaptive and standard algorithms was highly correlated to HR (ρ=0.85, p<0.0018) and tended to increase with seriousness of BW

class (Fig. 2); on average, the adaptive algorithm tended to provide higher NB than the standard algorithm for preterm infants characterized by mean HR higher than 150bpm, and vice versa; median value of such difference over the preterm infant population was +8 not significantly different from zero. Additionally, the adaptive algorithm provided higher BD than the standard algorithm for preterm infants characterized by mean HR higher than 150bpm, and vice versa; median values of BD estimated over the preterm infant population by the two algorithms were comparable.

Table 2 reports correlation values between BR and BD vs GA, BW and mean HR. Values of the correlation coefficient between bradycardia characteristics and GA were always negative, quite small in module ($0.26 \leq |\rho| \leq 0.54$) and never statistically significant, independently from the used algorithm. Values of the correlation coefficient between bradycardia characteristics and BW were always negative, with higher module when using the adaptive algorithm than when using the standard algorithm ($0.47 \leq |\rho| \leq 0.75$ and $0.32 \leq |\rho| \leq 0.45$, respectively), and statistically significant ($p<0.03$) only when indicating the association between BW and BD by the adaptive algorithm. Eventually, values of the correlation coefficient between bradycardia characteristics and mean HR were always positive, with higher module when using the adaptive algorithm than when using the standard algorithm ($0.69 \leq |\rho| \leq 0.76$ and $0.09 \leq |\rho| \leq 0.27$, respectively), and statistically significant ($p<0.01$) only when bradycardia characteristics were provided by the adaptive algorithm. Scatter plots of BR and BD in relation to GA, BW and mean HR are reported in Fig. 3; information relating to BW class is also represented. As general trend, seriousness of BW class increases with increasing BR and BD.

4. Discussion

This methodological work presented an adaptive algorithm for bradycardia assessment in preterm infants and tested it on the "Preterm Infant Cardio-respiratory Signals" database [15,21]. The algorithm adjusts baseline heart rate in correspondence of each heartbeat by averaging heart rate over the preceding 10-minute window, after eliminating very high or very low heart-rate values likely due to local arrhythmic events or noise. The window length was arbitrarily set at 10 minutes for clinical reasons: 10 minutes is the window length used in the clinical practise for foetal monitoring [11] and heart rate and heart-rate variability of fetuses and premature infants are comparable. In the absence of gold standards, it is impossible to mathematically demonstrate that this length is optimal. However, experimental preliminary evaluations indicated that use a 10-minute window represents a trade-off between the need of using a window sufficiently short to allow a correct tracking of significant heart-rate changes, and the need of using a window sufficiently long to allow neglection of local and temporary heart-rate changes around baseline level. Additionally, for window size ranging from 5 minutes to 20 minutes, number of identified bradycardias ranged from 523 to 567 (corresponding to an error, with respect to the 546 bradycardias identified when using the 10-minute window, between ±4%), and correlations between bradycardia rate and mean heart rate, bradycardia depth and body weight, and bradycardia depth and mean heart rate were statically significant (ranging from 0.61 to 0.77, from -0.75 to -0.73 and from 0.72 to 0.76, respectively). Small, statistically not relevant errors and confirmed significant correlations indicate that the adaptive algorithm is robust to window size variations. Eventually, in order to make the adaptive algorithm suitable for real-time monitoring of preterm infants, the preceding window was used for computation of baseline heart rate relating to a heartbeat; this property is fundamental to promptly send out bradycardia alerts during its clinical implementation. Once baseline heart rate has been determined, bradycardia is identified when

a heart-rate decrement of at least 67% of baseline value occurs. This is also an arbitrary setting that was selected because in analogy with the standard algorithm [15,16].

Despite its size being limited to 10 preterm infants, the population used in the present study included cases with mean heart rate over (40%), below (50%) and equal (10%) to 150bpm (Table 1), which are all the possible cases occurring in real scenarios. Additionally, lengths of the electrocardiographic recordings were quite long (from 20.3h to 70.3h; Table 1) so that over 500 bradycardias were automatically identified. This number is comparable to what reported in other studies [15,16,19,30] and sufficient for a reliable set up and a preliminary clinical evaluation of the adaptive algorithm (502 was the minimum number of bradycardias with a power of the test equal to 80%). Differences in the number of identified bradycardias and in their depth estimation by the standard and adaptive algorithms are due to more accurate estimations of baseline heart rate provided by the adaptive algorithm (Fig. 2). As graphically represented in Fig. 4, if baseline heart rate is below 150bpm, bradycardia may result identified by the standard algorithm only (Fig. 4A) or by both algorithms (Fig. 4B). In the former case, the standard algorithm may provide a false positive identification when baseline heart rate gets very low (thus close to 100bpm) since no significant heart-rate decrement occurs; in the latter case, bradycardia depth (i.e. difference between baseline and minimum heart rate) provided by the adaptive algorithm is smaller than that provided by the standard algorithm. If baseline heart rate is around 150bpm, bradycardia is identified by both algorithms and similarly characterized in terms of depth (Fig. 4C). Eventually, if baseline heart rate is over 150bpm, bradycardia may result identified by both algorithms (Fig. 4D) or by the adaptive algorithm only (Fig. 4E). In the former case, bradycardia depth provided by the adaptive algorithm is greater than that provided by the standard algorithm; in the latter case, the adaptive algorithm unlikely provides a false positive identification since a significant heart-rate decrement of at least 67% of baseline heart rate always occurs, while

the standard algorithm likely provides a false negative identification. Since in our population number of preterm infants with mean heart rate greater and lower than 150bpm is similar, such differences in the performance of the two algorithms cannot be appreciated by analysing population distributions of bradycardia depth (median bradycardia depths over population provided by the adaptive and standard algorithms are comparable; Table 1) but, rather, by comparing intrasubject distributions of bradycardia depth obtained using the two algorithms (statistically different mean values of bradycardia depth were observed in 6 out of 10 preterm infants; Table 1).

No commonly used neonatal clinical outcomes such as blood pH, base excess and Apgar after 5 minutes from birth, were available; thus, gestational age at birth, birth weight and heart rate were used to evaluate performances of standard and adaptive algorithms in bradycardia identification. If birth weight and gestational age at birth provide information about the clinical status of the infant at birth, heart rate provides information about the clinical status of preterm infant at the time of monitoring. In general, the smaller the gestational age at birth and the birth weight, the higher the heart rate, and the more critical the newborn's conditions [16,23,24]. Being our study population constituted by preterm infants only, gestational age at birth showed limited variability (from 206day to 240day, corresponding to 74% to 86% of ideal value; Table 1). Birth weight was more variable within studied population (from 0.80kg to 2.10kg; Table 1), which in fact included low birth weight infants (50%), very low birth infants (40%) and extremely low birth weight infants (10%; Table 1). Eventually, as previously discussed, heart rate was also significantly varying within the studied population (from 131bpm to 167bpm; Table 1). Since bradycardias occurrence also reflects newborn's health conditions (the lower the bradycardia rate and depth, the better the newborn's conditions) [14,26], bradycardia rate and depth were expected to inversely correlate with gestational age at birth and birth weight and to directly correlate with heart

rate. Results confirmed such expectations (Table 2). Still, associations were usually stronger when using the adaptive algorithm than when using the standard algorithm; additionally, statistical significance was obtained only computing bradycardia rate and depth with the adaptive algorithm. Specifically, when using the adaptive algorithm, association of bradycardia rate and depth with gestational age was weak, possibly because of the limited range of variability of this clinical feature within the preterm infant population; additionally, associations of bradycardia depth with birth weight and mean heart rate were stronger and more statistically significant than associations of bradycardia rate with birth weight and mean heart rate, respectively, suggesting that, in preterm infants, bradycardia depth indicates a critical health condition better than bradycardia rate.

Adaptive algorithms for neonatal bradycardia assessment have been previously proposed in the literature [25–27]; they are machine learning approaches showing high performance but low interpretability, feature that may limit their clinical applicability (interpretability is particular important in uncertain critical cases in which classification is supposed to drive an action). Indeed, bradycardia identification is performed independently from baseline heart rate and algorithm reasoning underlying classification remains unknown. Differently, the presented adaptive algorithm is data independent and identifies bradycardias based on an optimazed baseline computation, maximizing interpretability.

5. Conclusions

This methodological study presented a reliable adaptive algorithm for real-time bradycardia assessment that could have a practical application in neonatal intensive care units. When clinically evaluated, the proposed adaptive algorithm proved to perform better than the commonly used standard algorithm thanks to an adaptive estimation of baseline heart

rate. Future clinical studies are needed to confirm its clinical usefulness in automatic heart-rate monitoring of premature infants.

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References

[1] B.E. Hamilton, J.A. Martin, M.J.K. Osterman, S.C. Curtin, T.J. Matthews, Births: final data for 2014, Natl. Vital Stat. Rep. 64 (2015) 1–64.

[2] J.A. Martin, B.E. Hamilton, M.J.K. Osterman, Births in the united states, 2018, NCHS Data Brief. (2019) 1–8.

[3] J.P. Vogel, O.T. Oladapo, A. Manu, A.M. Gülmezoglu, R. Bahl, New WHO recommendations to improve the outcomes of preterm birth, Lancet Glob. Heal. 3 (2015) e589–e590. doi:10.1016/S2214-109X(15)00183-7.

[4] M. Meregaglia, I. Croci, C. Brusco, L.C. Herich, D. Di Lallo, G. Gargano, V. Carnielli, J. Zeitlin, G. Fattore, M. Cuttini, Low socio-economic conditions and prematurity-related morbidities explain healthcare use and costs for 2-year-old very preterm children, Acta Paediatr. 109 (2020) 1791–1800. doi:10.1111/apa.15183.

[5] J.L.Y. Cheong, P.J. Anderson, A.C. Burnett, G. Roberts, N. Davis, L. Hickey, E. Carse, L.W. Doyle, Changing neurodevelopment at 8 years in children born extremely preterm since the 1990s, Pediatrics. 139 (2017) e20164086. doi:10.1542/peds.2016-4086.

[6] C.F. Poets, Intermittent hypoxemia/bradycardia and the developing brain: How much is too much?, Neonatology 107 (2015) 147-149. doi:10.1159/000369775.

[7] L.M. Walter, B. Ahmed, A. Odoi, H. Cooney, R.S.C. Horne, F.Y. Wong, Bradycardias are associated with more severe effects on cerebral oxygenation in very preterm infants than in late preterm infants, Early Hum. Dev. 127 (2018) 33-41. doi:10.1016/j.earlhumdev.2018.08.008

[8] D.E. Elder, A.J. Campbell, D. Galletly, Current definitions for neonatal apnoea: Are they evidence based?, J. Paediatr. Child Health 49 (2013) E388-E396. doi:10.1111/jpc.12247

[9] K. Javorka, Z. Lehotska, M. Kozar, Z. Uhrikova, B. Kolarovszki, M. Javorka, M. Zibolen, Heart rate variability in newborns, Physiol. Res. 66 (2017) S203-S214. doi:10.33549/physiolres.933676

[10] G.A. Macones, ACOG practice bulletin no. 106: intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles, Obstet. Gynecol. 114 (2009) 192–202. doi:10.1097/AOG.0b013e3181aef106.

[11] D. Ayres-de-Campos, C.Y. Spong, E. Chandraharan, FIGO consensus guidelines on intrapartum fetal monitoring: cardiotocography, Int. J. Gynecol. Obstet. 131 (2015) 13–24. doi:10.1016/j.ijgo.2015.06.020.

[12] A. Agostinelli, F. Palmieri, A. Biagini, A. Sbrollini, L. Burattini, F. Di Nardo, S. Fioretti, L. Burattini, Relationship between deceleration areas in the second stage of labor and neonatal acidemia, in: Comput. Cardiol. (2016). doi:10.22489/CinC.2016.260-352.

[13] NICE, Interpretation of cardiotocograph traces, Intrapartum care nice guidel. CG190. (2014).

[14] C.F. Poets, R.S. Roberts, B. Schmidt, R.K. Whyte, E. V. Asztalos, D. Bader, A. Bairam, D. Moddemann, A. Peliowski, Y. Rabi, A. Solimano, H. Nelson, P. Shah, L. Brown, L. Wenger, S. Frye, F. Imbesi, E. Kelly, J. D'Ilario, M. Roy, J. Dix, B. Adams, J. Cairnie, P. Gillie, M. Hyndman, M. Lacy, D. Hohn, L.C. Kruk, S. Abbasi, T. Mancini, E. Sivieri, K. Finnegan, S. Bélanger, M. Deschenes, A. Fraser, J.A. Harrold, J. Frank, J. Barden, M. Vincer, S. Stone, R. Sauve, D. Cyr, H. Christianson, D. Anseeuw-Deeks, D. Creighton, L. Colby, A. Butt, A. Synnes, M. Peterson, A. Chaudhary, H. Hurt, D. Foy, K. Ziolkowski, M. Gerdes, J. Bernbaum, M. Kumar, L. Hendson, M. Athaide, J. Tomlinson, D. Bassler, J. Armbruster, N. Vain, C. Garcia, V. DiGruccio, F. Tamanaha, N. Jacobi, S. Garcia, N. Vivas, C. Osio, S. Sridhar, A.

Parekh, R. McGovern, S. Arnon, M. Meyer, R. Poller, N. Ali, M. Khairy, I. Paquet, L. Perepolkin, P. Grier, S. Wali, M. Seshia, J. Minski, V. Cook, K. Kwiatkowski, K.A.H. Penner, D. Williams, L. Givelichian, K. Sankaran, C. Thiel, B. Sandler, A. Chiu, D. Everatt, N. Granke, A. Golan, E. Goldstein, S. Dadoun, R. Vikevainen, H. Kallankari, T. Kaukola, M. Hallman, K. Barrington, J. Lavoie, W. Fraser, D.J. Davis, G. Wells, L. Costantini, W. Yacura, B. Gent, Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants, JAMA - J. Am. Med. Assoc. 314 (2015) 595-603. doi:10.1001/jama.2015.8841.

[15] A.H. Gee, R. Barbieri, D. Paydarfar, P. Indic, Predicting bradycardia in preterm infants using point process analysis of heart rate, IEEE Trans. Biomed. Eng. 64 (2017) 2300–2308. doi:10.1109/TBME.2016.2632746.

[16] A. Sbrollini, M. Mancinelli, I. Marcantoni, M. Morettini, L. Burattini, Bradycardia assessment in preterm infants, in: IFMBE Proc., 2020: pp. 100–107. doi:10.1007/978-3-030-31635-8_12.

[17] E.C. Eichenwald, Apnea of prematurity, Pediatrics. 137 (2016). doi:10.1542/peds.2015-3757.

[18] T.J.P. Huberts, E.E. Foglia, I.C. Narayen, J.J. van Vonderen, S.B. Hooper, A.B. te Pas, The breathing effort of very preterm infants at birth, J. Pediat. 194 (2018) 54-59. doi:10.1016/j.jpeds.2017.11.008.

[19] I. Marcantoni, A. Sbrollini, G. Agostinelli, F.C. Surace, M. Colaneri, M. Morettini, M. Pozzi, L. Burattini, T-Wave alternans in nonpathological preterm infants, Ann. Noninvasive Electrocardiol. 25 (2020). doi:10.1111/anec.12745.

[20] D. Roland, J. Madar, G. Connolly, The Newborn Early Warning (NEW) system: development of an at-risk infant intervention system, Infant. 6 (2010) 116–120. doi: 10.1007/s00431-019-03446-0

[21] A.L. Goldberger, L.A.N. Amaral, L. Glass, J.M. Hausdorff, P.C. Ivanov, R.G. Mark, J.E. Mietus, G.B. Moody, C.-K. Peng, H.E. Stanley, PhysioBank, PhysioToolkit, and PhysioNet, Circulation. 101 (2000) e215–e220. doi:10.1161/01.CIR.101.23.e215.

[22] A.P. Marshall, K. Lim, S.K: Ali, T.J. Gale, P.A. Dargaville. Physiological instability after respiratory pauses in preterm infants, Pediatr. Pulmonol. 54 (2019) 1712-1721. doi:10.1002/ppul.24451.

[23] S. Saigal, L.W. Doyle, An overview of mortality and sequelae of preterm birth from infancy to adulthood, Lancet. 371 (2008) 261–269. doi:10.1016/S0140-6736(08)60136-1.

[24] K. Javorka, Z. Lehotska, M. Kozar, Z. Uhrikova, B. Kolarovski, M. Javorka, M. Zibolen, Heart rate variability in newborns, Physiol. Res. 66 (2017) S203–S214. doi:10.33549/physiolres.933676.

[25] J. Cruz, A.I. Hernández, S. Wong, G. Carrault, A. Beuchee, Algorithm fusion for the early detection of apnea-bradycardia in preterm infants, in: Comput. Cardiol., 2006: pp. 473−476.

[26] F. Portet, F. Gao, J. Hunter, S. Sripada, Evaluation of on-line bradycardia boundary detectors from neonatal clinical data, in: Annu. Int. Conf. IEEE Eng. Med. Biol. - Proc., 2007: pp. 3288-91. doi:10.1109/IEMBS.2007.4353032.

[27] M. Altuve, G. Carrault, A. Beuchée, P. Pladys, A.I. Hernández, Online apnea–bradycardia detection based on hidden semi-Markov models, Med. Biol. Eng. Comput. 53 (2015) 1-13. doi:10.1007/s11517-014-1207-1.

[28] A. Agostinelli, E. Braccili, E. Marchegiani, R. Rosati, A. Sbrollini, L. Burattini, M. Morettini, F. Di Nardo, S. Fioretti, L. Burattini, Statistical baseline assessment in cardiotocography, in: 2017 39th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc., IEEE, 2017: pp. 3166–3169. doi:10.1109/EMBC.2017.8037529.

[29] A. Sbrollini, A. Agostinelli, L. Burattini, M. Morettini, F. Di Nardo, S. Fioretti, L. Burattini, CTG Analyzer: A graphical user interface for cardiotocography, in: 2017 39th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc., IEEE, 2017: pp. 2606–2609. doi:10.1109/EMBC.2017.8037391.

[30] V. Golder, M. Hepponstall, S.R. Yiallourou, A. Odoi, R.S.C. Horne, Autonomic cardiovascular control in hypotensive critically ill preterm infants is impaired during the first days of life, Early Hum. Dev. 89 (2013) 419–423. doi:10.1016/j.earlhumdev.2012.12.010.

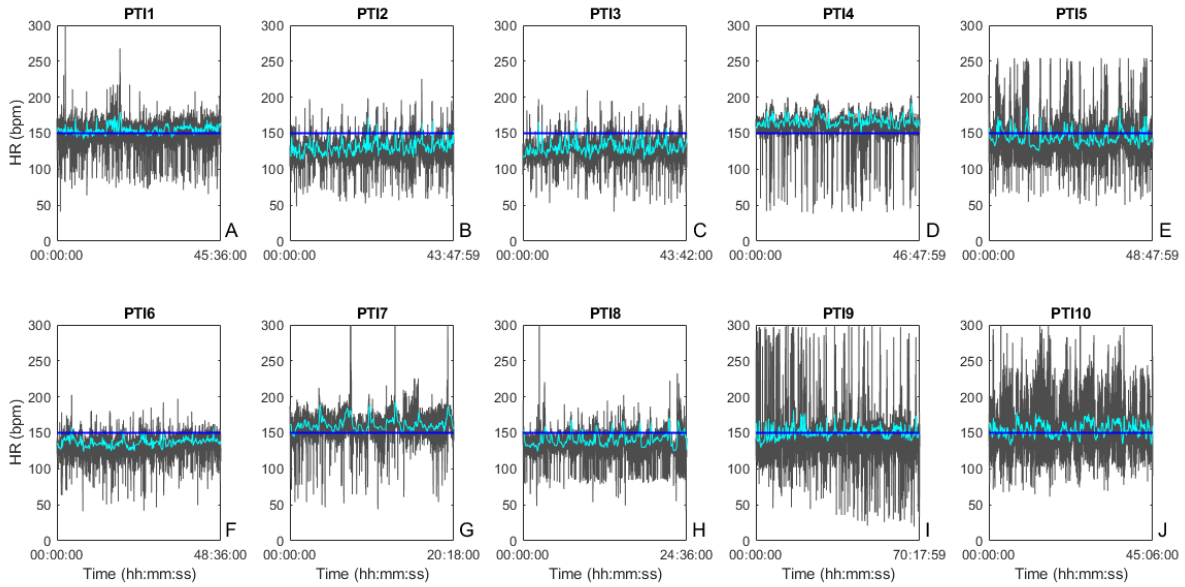

Figure 1. Heart rate (HR) sequences (in grey) with relating baseline heart rate as assumed by the standard algorithm (in blue) and as estimated by the adaptive algorithm (in cyan) of all preterm infants (PTI1 to PTI10).

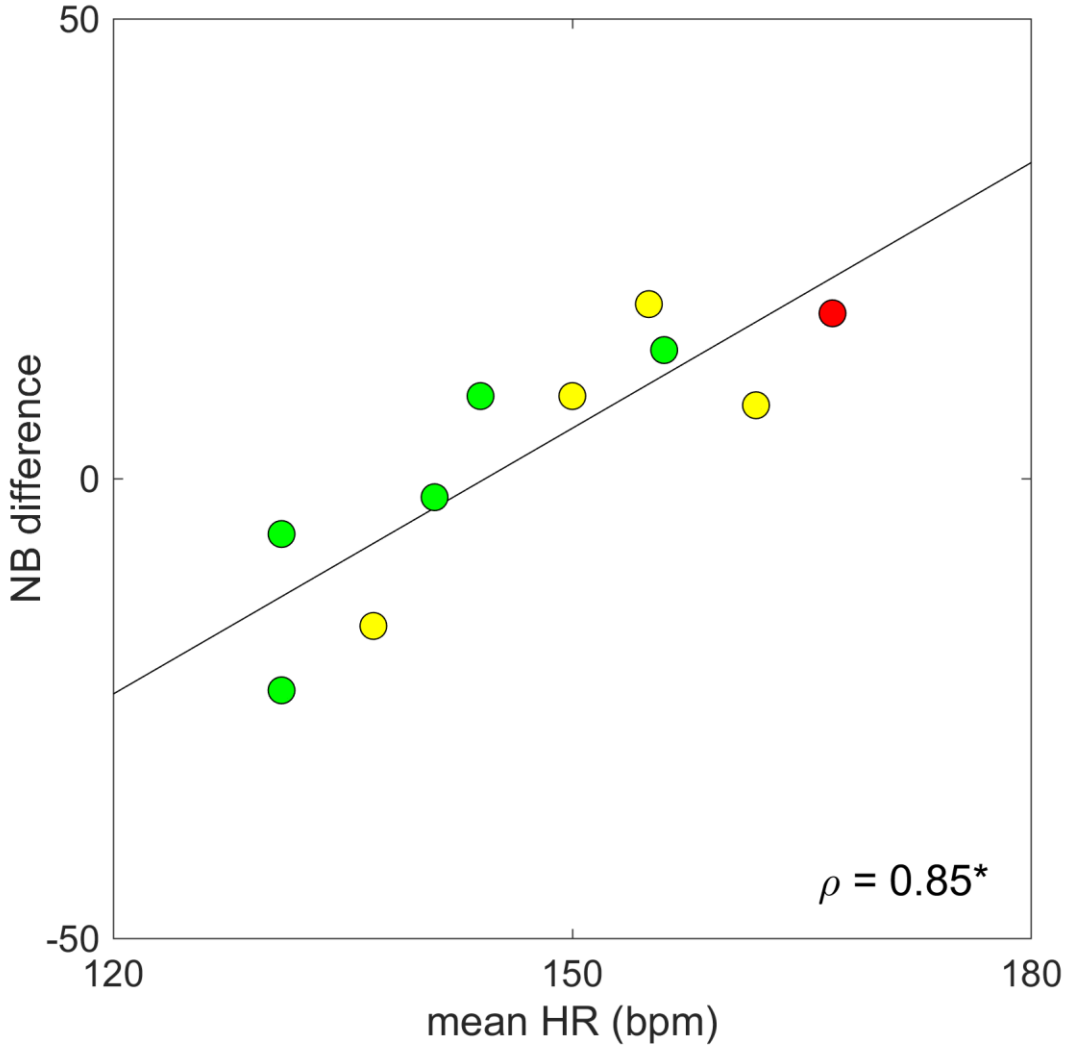

Figure 2. Scatter plot, regression line and correlation coefficient (ρ) of difference between number of bradycardias (NB difference) estimated by the adaptive and the standard algorithms vs mean heart rate (mean HR). Preterm infants are represented in green, yellow or red if classified as low birth weight, very low birth weight or extremely low birth weight, respectively.

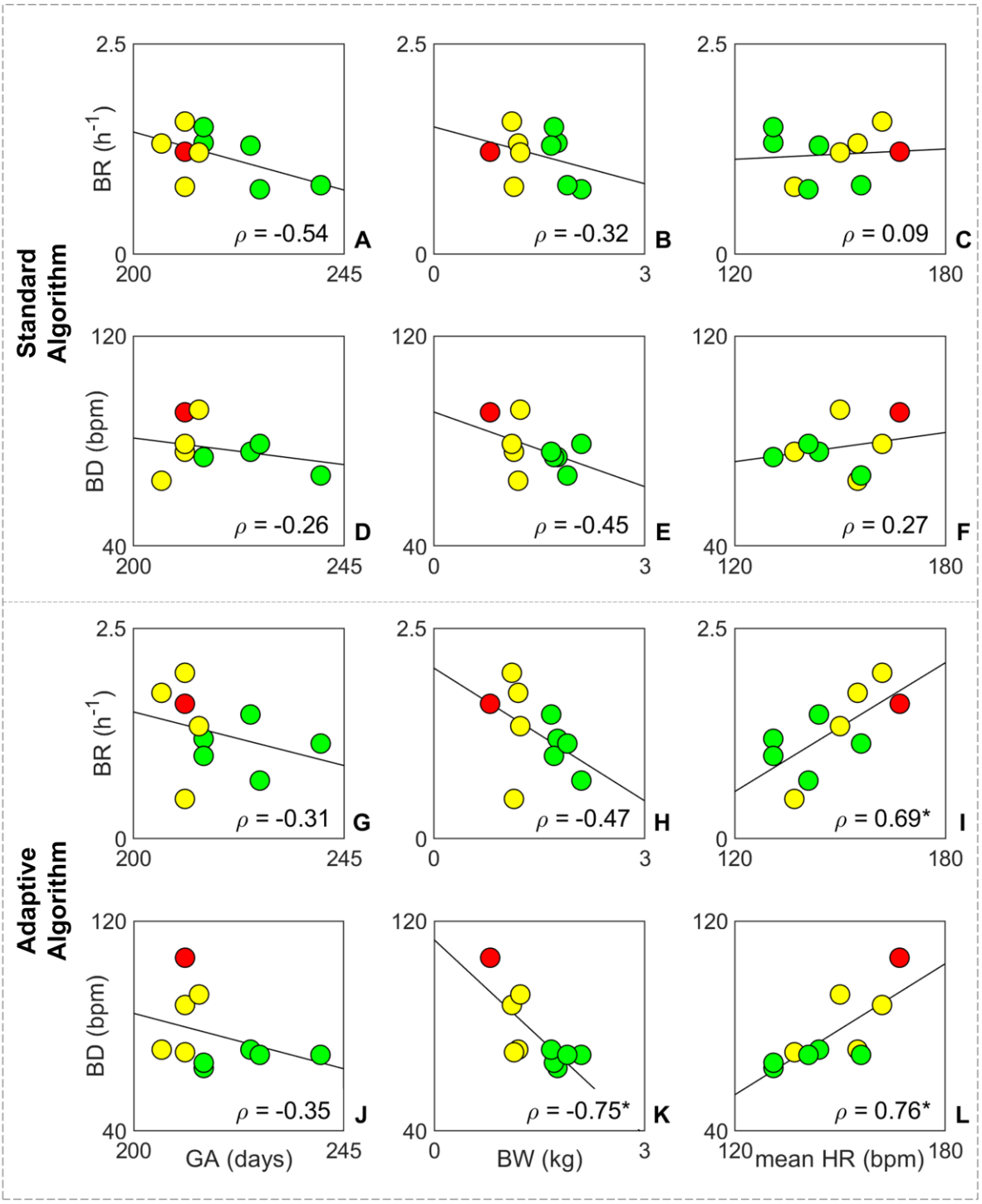

Figure 3. Scatter plots, regression lines and correlation coefficients (ρ) of bradycardia rate (BR) and depth (BD), as provided by the standard algorithm and the adaptive algorithm, in relation to gestational age at birth (GA), birth weight (BW) and mean heart rate (HR). Preterm infants are represented in green, yellow or red if classified as low birth weight, very low birth weight or extremely low birth weight, respectively.

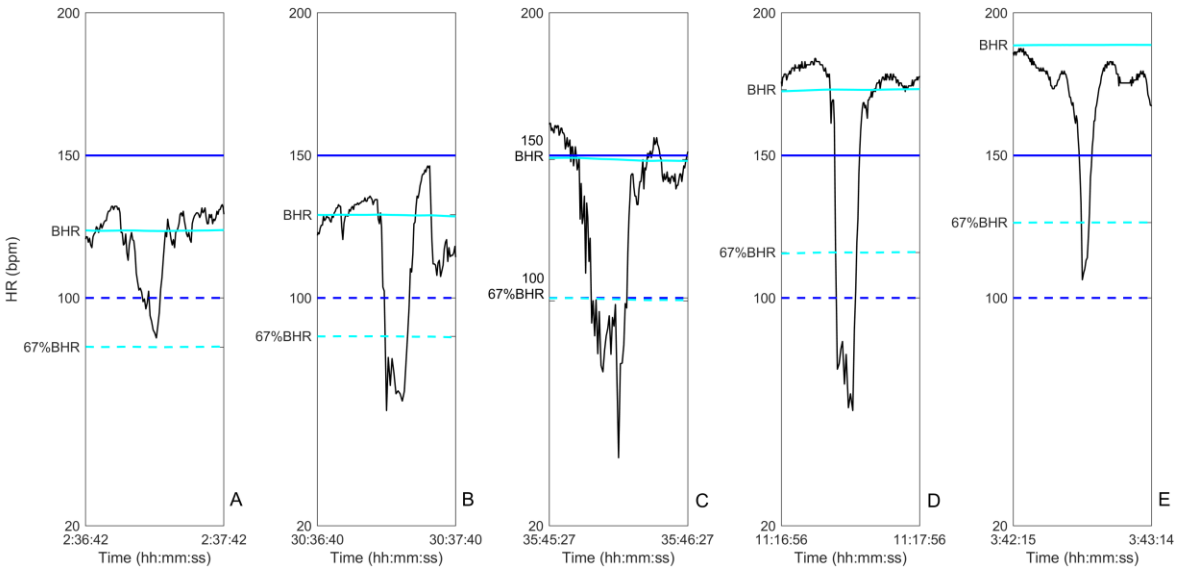

Figure 4. Effect of varying baseline heart rate (BHR) on bradycardia identification by the standard and adaptive algorithms. Solid and dashed lines indicate BHR and 67%·BHR, respectively, in blue for the standard algorithm and in cyan for the adaptive algorithm.

		Preterm Infants										Population
		PTI1	**PTI2**	**PTI3**	**PTI4**	**PTI5**	**PTI6**	**PTI7**	**PTI8**	**PTI9**	**PTI10**	
GA (day)		206	215	215	211	225	211	211	227	214	240	214 [211;225]
BW (kg)		1.20	1.76	1.71	0.80	1.67	1.14	1.11	2.10	1.23	1.90	1.45 [1.14;1.76]
BW class		Very low	Low	Low	Extremely low	Low	Very low	Very low	Low	Very low	Low	n.a
recording length (h)		45.6	43.8	43.7	46.8	48.8	48.6	20.3	24.6	70.3	45.10	45.3 [43.7;48.6]
HR (bpm)		155§ ±10	131§ ±14	131§ ±13	167§ ±9	144§ ±15	137§ ±8	162§ ±13	141§ ±13	150 ±12	156§ ±16	147 [137;156]
Standard algorithm	NB	60	58	66	57	63	39	32	19	85	37	57 [37;63]
	BR (h^{-1})	1.32	1.32	1.51	1.22	1.29	0.80	1.58	0.77	1.21	0.82	1.25 [0.82;1.32]
	BD (bpm)	65 ±9	74 ±14	74 ±14	91 ±14	76 ±11	76 ±17	79 ±13	79 ±16	92 ±22	67 ±8	76 [74;79]
Adaptive algorithm	NB	79	52	43	75	72	23	40	17	94	51	51 [40;75]
	BR (h^{-1})	1.73	1.19	0.98	1.60	1.48	0.47	1.97	0.69	1.34	1.13	1.26 [0.98;1.60]
	BD (bpm)	71* ±9	64* ±9	66* ±12	106* ±18	71* ±12	70 ±15	88* ±14	69 ±15	92 ±21	69 ±10	70 [69;88]
NB difference		+19	-6	-23	+18	+9	-16	+8	-2	+9	+14	+8 [-6;+14]
NB-both algorithms		58	35	33	57	51	21	32	15	76	33	411
NB-standard algorithm		2	23	33	0	12	18	0	4	9	4	105
NB-adaptive algorithm		21	17	10	18	21	2	8	2	18	18	135

Table 1: Individual and population clinical features (i.e. gestational age at birth, GA; body weight, BW; BW class; and heart rate, HR) and bradycardia characteristics (i.e. number of bradycardias, NB; bradycardia rate, BR; and bradycardia depth, BD) as identified by the standard vs adaptive algorithms.
n.a.: not available;
§: p value<0.05 when comparing HR vs 150bpm.
*: p value<0.05 when comparing bradycardia characteristics according to standard algorithm and adaptive algorithm.

		GA	BW	mean HR
Standard algorithm	BR	-0.54	-0.32	0.09
	BD	-0.26	-0.45	0.27
Adaptive algorithm	BR	-0.31	-0.47	0.69*
	BD	-0.35	-0.75*	0.76*

Table 2: Correlation coefficient between clinical features (i.e. gestational age at birth, GA; body weight, BW; and mean heart rate, HR) and bradycardia characteristics (i.e. bradycardia rate, BR; and bradycardia depth, BD) as provided by the standard and adaptive algorithms.
*: p value<0.05