Heart rate characteristics predict risk of mortality in preterm infants in low and high target oxygen saturation ranges

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The heart rate characteristics index (HRCi) up to 36 weeks post-menstrual age is highly predictive of mortality among preterm infants managed with both high and low target S_{pO_2} ranges. https://bit.ly/43wFj4l

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Abstract

Background The Neonatal Oxygenation Prospective Meta-analysis found that in infants <28 weeks gestational age, targeting an oxygen saturation (S_{pO_2}) range of 85–89% *versus* 91–95% resulted in lower rates of retinopathy of prematurity but increased mortality. We aimed to evaluate the accuracy of the heart rate characteristics index (HRCi) in assessing the dynamic risk of mortality among infants managed with low and high target S_{pO_2} ranges.

Methods We linked the SUPPORT and HRCi datasets from one centre in which the randomised controlled trials overlapped. We examined the maximum daily HRCi (MaxHRCi24) to predict mortality among patients randomised to the lower and higher target S_{pO_2} groups by generating predictiveness curves and calculating model performance metrics, including area under the receiver operating characteristics curve (AUROC) at prediction windows from 1–60 days. Cox proportional hazards models tested whether MaxHRCi24 was an independent predictor of mortality. We also conducted a moderation analysis.

Results There were 84 infants in the merged dataset. MaxHRCi24 predicted mortality in infants randomised to the lower target S_{pO_2} (AUROC of 0.79–0.89 depending upon the prediction window) and higher target S_{pO_2} (AUROC 0.82–0.91). MaxHRCi24 was an important additional predictor of mortality in multivariable modelling. In moderation analysis, in a model that also included demographic predictor variables, the individual terms and the interaction term between MaxHRCi24 and target S_{pO_2} range all predicted mortality.

Conclusions Associations between HRCi and mortality, at low and high S_{pO_2} target ranges, suggest that future research may find HRCi metrics helpful to individually optimise target oxygen saturation ranges for hospitalised preterm infants.

Introduction

While supplemental oxygen therapy is essential for survival in preterm infants, the resulting highly oxygenated environment may increase the risk of bronchopulmonary dysplasia [1], retinopathy of prematurity (ROP) [2] and other oxygen free radical-related diseases [3]. The Neonatal Oxygenation Prospective Meta-analysis (NeOProM) found that in infants <28 weeks gestational age, targeting a peripheral oxygen saturation (S_{pO_2}) range of 85–89% *versus* 91–95% resulted in lower rates of ROP but increased the risk of both mortality and necrotising enterocolitis [4]. There is limited evidence on the potential use of physiological parameters to optimise oxygen saturation targeting to reduce morbidity and mortality. As such, many neonatal care centres target a higher S_{pO_2} range of 91–95% for the care of extremely preterm infants. The choice of the 91–95% target range would be expected to increase survival by 2.8% (absolute), but also increase the rate of treated ROP by 4% (absolute) without an effect on

blindness [5]. A method to personalise this trade-off by safely limiting oxygen among patients at low risk of mortality could have benefits; in 2016, the American Academy of Pediatrics Committee on Fetus and Newborn concluded that the "ideal physiologic target range of infants of extremely low birth weight is likely patient-specific and dynamic and … remains unknown" [6]. This statement is consistent with the reasoning that identifying infants for whom the patient-specific risk of mortality is low might alter the risk/benefit calculus sufficiently for the low target oxygen range to become the better option for these patients. This work takes the first steps toward a strategy of personalising oxygen delivery among preterm infants to reduce morbidity without increasing mortality.

Successful environmental adaptation following extremely preterm birth may reflect pulmonary resilience, a homeostatic process driven by the autonomic nervous system that regulates physiological stress [7]. Previous studies have demonstrated that the heart rate characteristics index (HRCi), also known as the HeRO Score (Medical Predictive Science Corporation, Charlottesville, VA, USA), which measures autonomic nervous system-related changes in heart rate variability, predicts the risks for various adverse outcomes, including sepsis [8], urinary tract infection [9], necrotising enterocolitis [10, 11], meningitis [12], respiratory decompensation [13], extubation failure [14, 15] and mortality [16–20]. It is also associated with the presence of proinflammatory cytokines [21–23]. In a randomised controlled trial (RCT) that ran concurrently with the SUPPORT trial (one of the trials included in NeOProM), patients randomised to have HRCi displayed to clinicians had lower all-cause mortality [24], lower mortality after infection [25] and lower composite outcome of mortality or neurodevelopmental impairment [26] when compared with controls; the reduction in mortality may have been the result of earlier identification of infection [27]. A recent before-and-after implementation study was consistent with many of these findings [28].

It is unknown whether the predictiveness of HRCi for mortality is affected by target oxygen saturation range or whether measures of patient physiology, including autonomic nervous system function, could identify a subgroup of preterm infants for whom the risk of mortality is low, and may be outweighed by the reduced risk of bronchopulmonary dysplasia and ROP associated with a lower target oxygen saturation range.

In this secondary analysis of two concurrent RCTs, we aimed to assess whether the HRCi is associated with the dynamic risk of mortality among infants randomised to low and high target S_{pO_2} ranges. We hypothesised that the HRCi would identify infants at risk of mortality in both high and low S_{pO_2} target ranges.

Material and methods

Study subjects and design

The de-identified datasets of infants who participated in both the SUPPORT trial (NCT00233324) [29] and HRCi trial (NCT00307333) [24] from the University of Alabama at Birmingham were linked using the following shared demographic variables: birth weight, gestational age, sex, 1-min Apgar and 5-min Apgar, providing unique matches between the two datasets with no intended sample size. The HRCi RCT enrolled infants with birthweight <1500 g, while the SUPPORT trial included patients of <28 weeks gestational age. Further details, including ethics reviews and CONSORT reporting including flow diagrams, can be found in their previous publications [24, 29].

All infants in the HRCi RCT had continuous heart rate data collected and HRCi scores were generated hourly. However, only the patients randomised to display the HRCi score had it rendered to clinicians involved in their care; for control patients, the HRCi scores remained hidden until after the trial was completed [24].

In the SUPPORT trial, a two-by-two factorial designed RCT, pulse oximeters were modified to display an oxygen saturation reading that was either slightly higher or slightly lower than the actual reading to blind clinicians to determine whether the patient was randomised to the low or high target oxygen saturation range. As a second aspect to the RCT, patients were separately randomised to receive either continuous positive airway pressure (CPAP) or intubation and surfactant [28]. Clinical variables are defined in the SUPPORT trial data dictionary [30], including small for gestational age (based on the sex-specific Alexander growth curves [31]).

Statistical methods and analysis

We examined the utility of the maximum daily HRCi (MaxHRCi24) from each postnatal day up to 36 weeks post-menstrual age (PMA) to predict the risk of mortality within a range of prediction windows from 1 to 60 days among patients randomised to either the low or high target S_{pO_2} range. From each daily MaxHRCi24 for each patient and for each prediction time window, we generated predictiveness curves and calculated performance metrics. These included area under the receiver operating characteristics curve

(AUROC); and we calculated sensitivity, specificity, positive predictive value, negative predictive value and risk ratio using an HRCi threshold of 3.0 on each daily MaxHRCi24 (a value that we expected would achieve an appropriate balance between sensitivity and specificity from prior work [32]). To deal with the presence of repeated measurements of MaxHRCi24 from each patient during these calculations, 95% confidence intervals for AUROC and risk ratio were calculated *via* 200 iterations of bootstrapping with replacement at a patient level [33].

In multivariable analyses, we used Cox proportional hazards models, including demographics and target S_{pO_2} range, to test whether MaxHRCi24 was an independent predictor of mortality by 36 weeks PMA, and we conducted moderation analyses. Demographic predictor variables were chosen if they were both significant in univariable analysis and uncorrelated with other significant demographic predictor variables.

Missing HRCi scores were not included in the analyses. Differences among continuous variables were assessed using the t-test. Proportions were tested using Fisher's exact test. We assessed significance at $p<0.05$. During multivariable analysis, we considered two candidate predictor variables to be correlated when the absolute value of the coefficient of correlation between the two variables was >0.5, and removed one of the two in such cases. All calculations were performed in R (www.r-project.org). We used the STARD guidelines for reporting studies of diagnostic accuracy [34].

Results

There were 84 infants in the merged dataset (table 1). There were no significant differences in patient demographics between the low and high target S_{pO_2} range groups.

In the analysis of all days prior to 36 weeks PMA, the maximum daily HRCi score (MaxHRCi24) was available in 90% of patient days, and the presence of a high MaxHRCi24 (*i.e.* MaxHRCi24 ⩾3) was strongly predictive of mortality in all prediction time windows analysed in infants randomised to either target S_{pO_2} range (table 2). Figure 1 is a predictiveness curve for MaxHRCi24 at an example prediction window of 7 days, and supplementary table S1 shows metrics of model performance at MaxHRCi24 thresholds of 2.0 and 5.0. The three thresholds, 2.0, 3.0 and 5.0, correspond to roughly the 48th, 62nd and 76th percentile MaxHRCi24 scores, respectively. Figure 2 demonstrates the trends of MaxHRCi24 in the days prior to death, with the median, 25th and 75th percentile MaxHRCi24 scores of survivors plotted for reference.

In multivariable analyses, we evaluated candidate predictor variables in univariable Cox models to predict mortality by 36 weeks PMA. We found birth weight, gestational age, 1-min Apgar, 5-min Apgar, randomisation to CPAP, randomisation to HRC display, multiple birth status, full course of antenatal steroids and small for gestational age were significant, while sex, race and any course of antenatal steroids were not significant and were removed. We removed birth weight owing to collinearity with gestational

TABLE 1 Patient demographics

	Low target S_{pO2}	High target S_{pO2}
Patients (n)	45	39
Birth weight (g), mean±SD	861±204	781±200
Gestational age (week/day)	26/1 (25/3–27/3)	25/4 (24/6.5–26/6.5)
Small for gestational age	3 (7)	4 (10)
Male	23 (51)	25 (64)
Race		
Black	25 (56)	17 (44)
White	20 (44)	22 (56)
Hispanic ethnicity	0 (0)	0 (0)
1-min Apgar score	4 (2–6)	4 (2–6)
5-min Apgar score	7 (6–8)	7 (5.5–8)
Randomised to HRCi control	26 (58)	19 (49)
Randomised to SUPPORT CPAP	29 (64)	19 (49)
Died by 36 weeks PMA	7 (16)	8 (21)
After sepsis/meningitis	4 (57)	6 (75)

Data are presented as median (interquartile range) or n (%), unless otherwise stated. No differences were significant at $p<0.05$. S_{pO_2}: peripheral oxygen saturation; HRCi: heart rate characteristics index; CPAP: continuous positive airway pressure; PMA: post-menstrual age.

TABLE 2 Metrics of predictive performance of MaxHRCi24

Prediction window (days)	Target S_{pO2} range	AUROC (95% CI)	Risk ratio	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1	Low	0.89 (0.89–0.90)*	Inf (NA–NA)	100	63	1.2	100
	High	0.91 (0.90–0.91)*	Inf (NA–NA)	100	62	1.7	100
3	Low	0.88 (0.87–0.88)*	35 (31–40)	95	64	2.2	99.9
	High	0.86 (0.85–0.87)*	17 (15–18)	93	62	3.1	99.8
7	Low	0.86 (0.85–0.86)*	36 (28–38)	95	64	5.0	99.9
	High	0.84 (0.82–0.84)*	16 (12–17)	91	63	6.0	99.6
15	Low	0.84 (0.84–0.85)*	18 (16–19)	91	65	9.7	99.5
	High	0.82 (0.82–0.83)*	11 (10–13)	87	63	9.5	99.1
30	Low	0.80 (0.80–0.81)*	11 (10–11)	86	66	13.6	98.8
	High	0.85 (0.84–0.85)*	15 (14–15)	90	64	13.1	99.1
60	Low	0.80 (0.77–0.80)*	8 (6–9)	81	67	16.9	97.7
	High	0.85 (0.84–0.85)*	13 (12–13)	89	65	14.1	98.9

Metrics of MaxHRCi24 to predict mortality in the subsequent time window. MaxHRCi24 threshold set to 3 for calculating risk ratio, sensitivity, specificity, PPV and NPV. Confidence intervals were calculated *via* 200 iterations of bootstrapping with replacement at the patient level. MaxHRCi24: maximum daiy heart rate characteristics index; S_{pO_2}: peripheral oxygen saturation; AUROC: area under the receiver operating characteristics curve; PPV: positive predictive value; NPV: negative predictive value; Inf: infinite; NA: not applicable. *: p<0.05.

age, and 5-min Apgar owing to collinearity with 1-min Apgar. In a multivariable Cox model including the remaining candidate predictor variables, 1-min Apgar was not significant. Our final model of significant, uncorrelated predictor variables included gestational age, randomisation to CPAP, randomisation to HRC display, multiple birth status, a full course of antenatal steroids and small for gestational age. In a Cox model including these variables plus the target S_{pO_2} range, MaxHRCi24 from each postnatal day up to 36 weeks PMA was an important additional predictor of mortality by 36 weeks PMA (p<0.001).

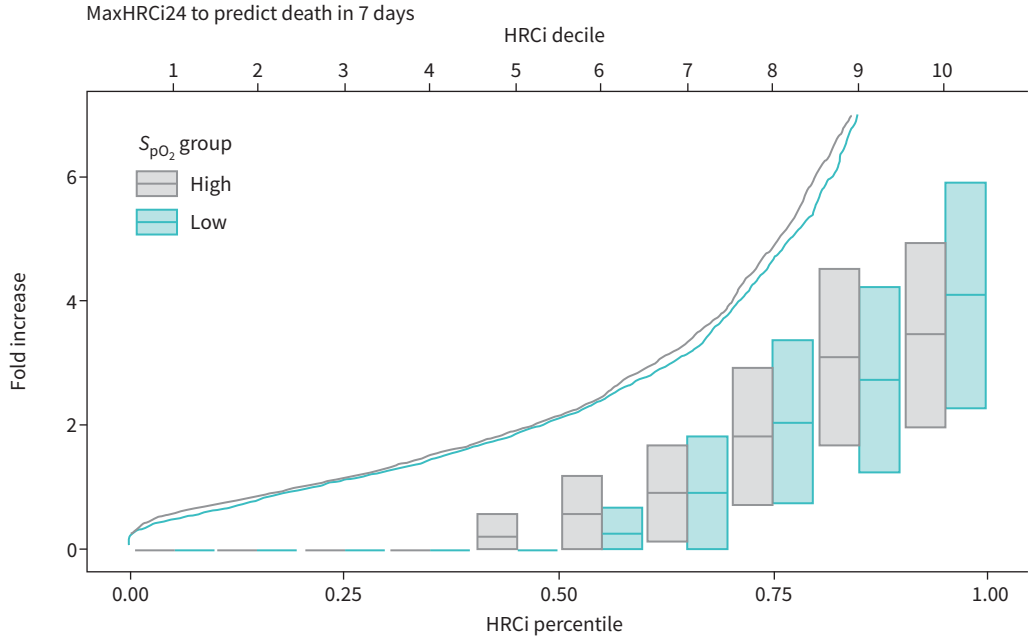

FIGURE 1 Predictiveness curve for maximum daily heart rate characteristics index (MaxHRCi24) to predict mortality within 7 days among low and high target peripheral oxygen saturation (S_{pO_2}) range patients. The lines are the MaxHRCi24 and represent the predicted risk of mortality. For example, the 50th percentile MaxHRCi24 for both groups was slightly over 2. The boxes represent the observed risk, with 95% confidence interval, for each decile of predicted risk. The y-axis is the fold-increase in risk over baseline (that is, the MaxHRCi24 for the smooth lines representing predicted risk, and the case rate of the decile divided by the overall case rate for the boxes representing observed risk). MaxHRCi24 was highly predictive of mortality within 7 days in both target S_{pO_2} ranges.

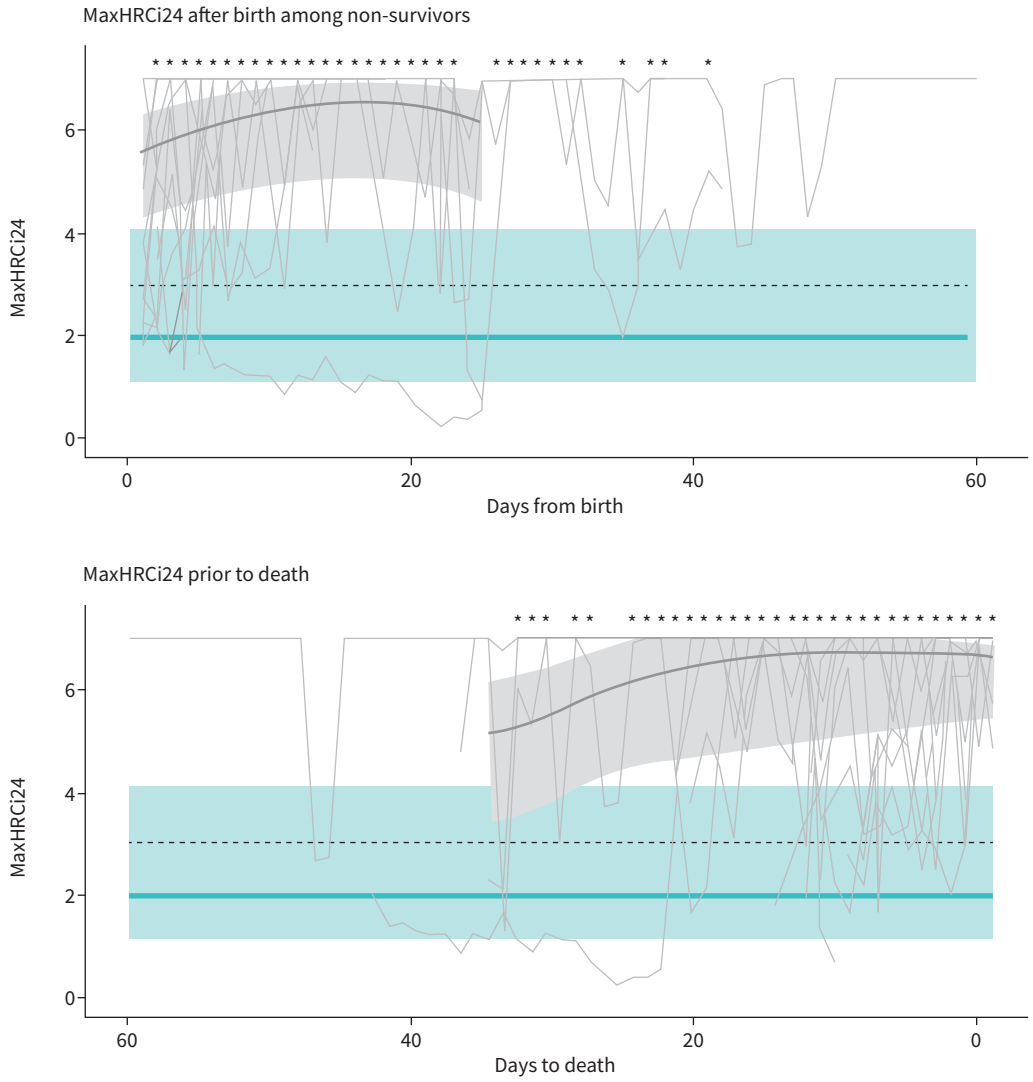

FIGURE 2 Maximum daily heart rate characteristics index (MaxHRCi24) in the days prior to death. Top panel registers time by birth, while the bottom panel registers time by mortality. The cyan line represents the median MaxHRCi24 for survivors, while the light cyan band represents the 25th to 75th percentiles. Each thin grey line represents the MaxHRCi24 from one patient in the days leading up to mortality, while the thick grey line and the grey band represent the LOESS-smoothed median and 25th to 75th percentile MaxHRCi24s among the patients who died. The black dashed line represents a MaxHRCi24 threshold of 3.0, which was used in calculating metrics of model performance. *: p<0.05 by t-test for the difference between the MaxHRCi24 for those who died *versus* those who survived.

In moderation analyses, in a Cox model that included the same group of significant, uncorrelated predictor variables, MaxHRCi24, target S_{pO_2} range and the interaction term between the two each predicted mortality by 36 weeks PMA (adjusted hazard ratio (aHR)±SE of 4.7±0.20, p<0.001; 2.6±0.41, p=0.02; and 0.38±0.23, p<0.001, respectively), indicating that the aHR of MaxHRCi24 was greater among patients in the high S_{pO_2} target range group than among those in the low S_{pO_2} target range group.

Discussion

We combined data from two RCTs with the aim of assessing the association between HRCi and mortality among preterm infants that were managed with a high or low target S_{pO_2} range. While the utility of HRCi in mortality prediction has been previously demonstrated, this has not been examined in the context of low or high S_{pO_2} targeting, and we found the HRCi up to 36 weeks PMA to be highly predictive of mortality among patients in both the low and high target S_{pO_2} groups. In multivariable analyses, HRCi was an

important independent predictor of mortality, and HRCi acted as a moderator of the association between the target S_{pO_2} range and mortality.

The results of the preplanned moderation analysis highlight an interaction effect between autonomic nervous system function and target S_{pO_2} range such that infants with low HRCi may be differentially resilient and protected against adverse clinical outcomes when exposed to a lower oxygen environment. It is possible that among infants with lower HRCi, oxygen exposure could be safely limited to a lower target S_{pO_2} range to reduce the risk of adverse clinical outcomes.

Our analysis of daily HRCi scores up to 36 weeks PMA for the prediction of mortality in a range of subsequent time periods demonstrates that a dynamic increase in a patient's risk of mortality would likely be preceded by rising HRCi scores. With sufficient early warning provided by the HRCi, adjusting S_{pO_2} into the high range may potentially still improve the outcome, as evidenced by the performance metrics at a 15-day prediction window, where the risk ratio for mortality in the next 15 days based on maximum HRCi in the previous 24 h was 11–18× with a sensitivity of 87–91%. The potential importance of a 15-day advanced warning is demonstrated by the survival curves of the NeOProM trials, which did not differ between the high and low oxygen saturation target groups during the first 15 days after birth but did differ by one month after birth [35].

This analysis provides evidence that a strategy of managing patients with low HRCi to a low target S_{pO_2} range and patients with high HRCi to a high target S_{pO_2} range has the potential to be safe from a mortality perspective while improving morbidity, and could be tested in a future interventional study.

In multivariable modelling, we were not surprised to find a high correlation between birth weight and gestational age, with both low birth weight and low gestational age well understood to be linked to poor outcomes. We elected to control for only one in multivariable modelling (including moderation analysis), selecting gestational age because it defined the more selective of the inclusion criteria (<1500 g from the HRCi RCT *versus* <28 weeks gestational age from SUPPORT). We have found in prior work [36] that models built using gestational age from a cohort of patients selected by birth weight are less robust, and we encourage other modellers to consider that small for gestational age infants that fall just within the cut-off for very low birth weight status comprise a decidedly different subgroup than patients of normal birth weight for gestational age who also fall just within the cut-off, skewing models including gestational age as a predictor among a cohort defined by birth weight. In addition to our preference for including the one that is used as an inclusion criterion, small for gestational age, birth weight Z-score and principal component analysis are example techniques that can help overcome this common pitfall of analysing neonatal datasets.

We noted that within our cohort of 84 infants, mortality was higher among patients randomised to the high target S_{pO_2} range, in contrast to the results of the larger SUPPORT and NeOProM datasets, although this difference was not statistically significant. We also noted trends towards lower birth weight, lower gestational age and proportionally more males among patients in the high target S_{pO_2} range, which, although not statistically significant, may explain the trend towards higher mortality in this group. These trends emphasise the importance of multivariable modelling, and in all of our analyses that included adjustment for *a priori* risk, the predictive performance of HRCi for mortality remained significant.

This work has strengths and limitations. Even though the data are from concurrent RCTs, the design was *post hoc* and the analysis was retrospective. Further, this dataset comprised only 84 infants from a single centre who were randomised to concurrent RCTs more than a decade ago when care practices may have been different. While there may be clear evidence from prior studies that 1) preterm infants who are targeted to low S_{pO_2} range have lower rates of ROP, 2) HRCi is predictive of mortality and 3) clinical action taken in response to elevations in HRCi can reduce mortality in the context of neonatal infection, we have not proven here that among patients managed with a low target S_{pO_2} range, increasing target S_{pO_2} range in response to elevations in HRCi can avert mortality. Despite these weaknesses, we found statistically and clinically significant results suggesting an association between autonomic function, as a marker of pulmonary resilience, and S_{pO_2} target ranges. The unexpected mortality difference in SUPPORT and NeOProM may make future RCTs of S_{pO_2} target ranges difficult; however, data from RCTs such as the SUPPORT trial can provide unbiased estimates of the effect of altering target S_{pO_2} ranges.

It is possible after further research that the HRCi or other measures of autonomic instability could be used to dynamically adjust the target S_{pO_2} range among preterm infants to individually balance the competing

risks of mortality and oxidative stress, achieving better patient outcomes. A future interventional study could test such a hypothesis.

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Data availability: A publicly available de-identified dataset of the SUPPORT trial may be requested from the National Institute of Child Health and Human Development Data and Specimen Hub (NICHD DASH). Academic researchers who provide a methodologically sound proposal may submit a request to the corresponding author for the de-identified individual participant data from the Heart Rate Characteristics trial that underlie the results reported in this article and the study protocol, up to 36 months following article publication.

Conflict of interest: W.E. King is a board member, shareholder and employee of Medical Predictive Science Corporation (MPSC), and is a co-inventor of pending patents owned by MPSC. U.J. Sanghvi has received consulting fees from MPSC and is a co-inventor of pending patents owned by MPSC. N. Ambalavanan is supported by grants from the National Institutes of Health (NIH), has participated on data safety monitoring boards by Shire and Oak Hill Bio, has received consulting fees from Radiometer and Provepharm, is an inventor of patents and pending patents owned by Airway Probiotics and Let-7b, respectively, and has stock options from ResBiotic and Alveolus Bio. V.V. Shukla is supported by a grant from the American Heart Association (23CDA1048106). C.P. Travers is supported a grant from the NIH (K23HL157618). R.L. Schelonka declares no conflicts. C. Wright is supported by grants from the NIH (R01HD107700 and R01HL13294), has received payment for expert testimony from the State of Texas, Sommers Schwartz and Dickie McCamey to his institution, and has received consulting fees from Chiesi. W.A. Carlo is supported by grants from the NIH. The funding agencies had no role in the study design; the collection, analysis and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication.

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