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Abnormal Heart Rate Characteristics Are Associated with Neonatal Mortality

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ABSTRACT

Estimating the risk of in-hospital mortality in the newborn intensive care unit can provide important information for health-care providers, and illness severity scores have been devised to provide mortality risk estimates. Calculation of illness severity scores is time-consuming, and the information used to predict mortality is collected only for the first 12 to 24 h of life. A noninvasive continuous measure that uses information collected throughout the hospitalization and that requires no data entry could be less costly and more informative. We have previously shown that the abnormal heart rate characteristics (HRC) of reduced variability and transient decelerations accompany neonatal illness such as late-onset sepsis. We hypothesized that more frequent and severe abnormal HRC are associated with an increased risk of death. We tested this hypothesis in two ways. Using data on infants older than 7 d of age, we first determined the association of the HRC index with death in the next week. Second, we devised a cumulative HRC score and determined its association with in-hospital death. There were 37 deaths in the 685 patients. The major findings were *1*) the HRC index showed highly significant association with death in the succeeding 7 d (receiver-operating characteristic area > 0.7, $p < 0.001$), and *2*) the cumulative HRC was highly significantly associated with neonatal in-hospital mortality (receiver-operating characteristic area > 0.80, $p < 0.001$). In both analyses, HRC added information to birth weight, gestational age, and postnatal age ($p < 0.01$). The HRC index provides independent information about the risk of neonatal death in the upcoming 7 d, and the cumulative HRC is an estimate of the risk of in-hospital neonatal mortality. **(*Pediatr Res* 55: 782–788, 2004)**

Abbreviations

NICU, newborn intensive care unit
HRC, heart rate characteristics
ROC, receiver-operating characteristic
HR, heart rate
SIRS, systemic inflammatory response syndrome
UVa, University of Virginia
WFU, Wake Forest University
BW, birth weight
GA, gestational age
cHRC, cumulative heart rate characteristics
SNAP, Score for Acute Neonatal Physiology
RR interval, interval between heartbeats

Estimations of the risk of mortality, the illness severity, and the burden of illness are important in planning patient care and providing health-care resources in clinical neonatology. Although standard neonatal illness severity scores correlate with neonatal mortality (1–5), their day-to-day use is limited by the large amount of data collection that is required. In addition, the accuracy of these standard scoring systems diminishes after the first few days (6). A simpler and more informative method for estimating in-hospital mortality in neonates is needed.

Early in the course of sepsis and SIRS, newborn infants have abnormal HRC, with reduced HR variability and transient decelerations similar to those of distressed fetuses (7). Predictive mathematical models based on logistic regression that use HRC are significantly associated with neonatal sepsis and SIRS in the subsequent 12 to 24 h (8). We have developed an HRC index using data from one tertiary care NICU and found that it

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was significantly associated with acute neonatal illness at another (8).

Although the physiology leading to the abnormal HRC is not known, we have speculated that it is related to circulating cytokines (7). Thus, the finding of abnormal HRC may not be limited to sepsis, and we have suggested that SIRS (9–13) may be a more appropriate diagnosis. In this way, abnormal HRC might reflect more than one etiology of subacute, potentially catastrophic neonatal illness and might be interpreted in a broader and more general way. Specifically, we hypothesized that HRC index measurements correlate with the illness severity of the infant, and that they become abnormal with many kinds of neonatal illness that lead to release of inflammatory cytokines, such as chronic lung disease (14, 15), along with early-onset and late-onset sepsis (16–22), meningitis (23), chorioamnionitis and brain injury (24, 25), and gastrointestinal disease such as necrotizing enterocolitis (26).

The burden of neonatal illness has intuitive meaning but no means for quantification. In this work, we have developed a measure based on HRC that is meant to be proportional to the burden of illness. The measurement, which we call cHRC, is based on the difference between the expected and observed HRC index. A relevant medical example is the glycosylated Hb and the blood glucose. The former is proportional to the cumulative difference between the expected normal blood glucose level and the measured level, and represents the burden of abnormal blood glucose levels. The HRC index and the blood glucose can change quickly whereas the cHRC and the glycosylated Hb levels change slowly. If our hypothesis (*i.e.* that the HRC index measurements correlate with illness severity) is correct, then we expect to find that both the HRC and the cHRC correlate with the mortality of infants in the NICU.

METHODS

Overview of study design. First, we tested the hypothesis that HRC are more abnormal in the week before death. We proceeded by estimating the strength of association between HRC and mortality, using multivariable logistic regression models for data prospectively collected at two university hospital–based tertiary care NICUs. We developed models at one center (UVa) and tested them at another (WFU).

Second, we tested the hypothesis that the total burden of neonatal illness was associated with neonatal mortality. To quantify this expected burden of illness, we made a multivariable logistic regression model relating the input variables of BW, GA, and days of age to the outcome of episodes of sepsis and SIRS (acute clinical deteriorations that prompted physicians to obtain blood cultures and start antibiotics after 7 d of age). When the output of this model is calculated, we call the result the "demographics index." It is the probability of an episode of sepsis and SIRS in the next 24 h as predicted only by demographic factors. Obviously, it has higher values in more premature infants. We reasoned that if we calculated the demographics index periodically and added the results, we would have a measure proportional to the total burden of illness expected as a result of the degree of prematurity and duration of hospitalization.

We estimated the observed burden of illness using a regression model relating input variables of HRC measures [SD, sample asymmetry (27), and sample entropy (28)] to the outcome of episodes of sepsis and SIRS. These are measures of variability (SD), asymmetry of histograms of RR intervals (sample asymmetry), and repeating patterns of RR intervals (sample entropy). This regression model was developed using data from infants at the UVa and validated using data from infants at WFU (8). When calculated for a set of HRC measurements for any infant, we call the output of this model the "HRC index." It is the probability of an episode of sepsis and SIRS in the next 24 h as predicted only by HRC analysis. It has higher values when reduced variability and transient decelerations are present. Although previously we derived this measure as an aid to early diagnosis of neonatal sepsis, we use it here as a measure of the degree of illness.

We reasoned that the arithmetic difference between the demographic and HRC indices at any point is proportional to the degree of illness at the time that is not accounted for by the degree of prematurity. We calculated the difference between the demographic and HRC indices at 6-h intervals, and added the differences together. We call this the cHRC. We reasoned that it is proportional to the total burden of illness that cannot be accounted for by the degree of prematurity. Thus, the cHRC is expected to be near 0 for infants whose demographic indices matched their HRC indices. Our interpretation is that the hospital course was no more complicated than would be expected based on BW, GA, and postnatal age. Conversely, HRC is expected to be greater than 0 for infants whose hospital course was more complicated than expected and less than 0 for those whose course was less complicated than expected.

Patient population. Between September 1999 and March 2001 we prospectively and continuously collected data on RR intervals for all infants admitted to the NICUs at UVa and WFU who survived longer than 7 d of age. Both NICUs are tertiary-care facilities with approximately 500 admissions per year. The UVa NICU admits both inborn infants as well as those transported from referral hospitals, whereas with rare exceptions, all infants admitted to the WFU NICU are born at other hospitals. The institutional review boards at both institutions approved this study. Because this was a noninterventional, minimal-risk, observational study, written informed consent was not required.

Data analysis. We used standard and previously described signal-processing methods to collect continuous ECG and HRC data (7, 8, 27, 29–31). We obtained the ECG signal from the defib/sync port that is a standard component of bedside monitors, and identified QRS complexes based on waveform pattern criteria. RR intervals were measured as the times between consecutive QRS complexes. Because the ECG signal was sampled at 4 kHz, RR intervals were measured to the nearest 0.25 ms. To reduce artifact, we excluded intervals that were more than 20% from the mean of the previous 15 intervals, or if the difference from one interval to the next was more than 5 SDs of the last 512 interval-to-interval differences. We obtained data 92% of the time, and the remaining 8% was explained by absent or poor-quality ECG signal, or by RR intervals that were excluded because of the possibility that they

were artifactual. HRC measures were calculated on data sets of 4096 beats, which ranged in duration from 20 min (mean HR, 200 beats/min) to 40 min (mean HR, 100 beats/min).

HRC data were grouped into 6-h epochs beginning each midnight, and HRC measures for the prior 12 h were summarized using median or 10th percentile values. For the purpose of logistic regression, the HRC results for the week (28 6-h epochs) before death were classified as outcome = 1, and all others were classified as outcome = 0.

Statistical analysis. The statistical significance of differences in demographic features and HRC at the two sites was tested using the Wilcoxon rank-sum test. As before (8), we developed regression models in a derivation cohort in the UVa NICU, and then tested the models on a validation cohort at WFU. Repeated-measures logistic regression models (32, 33) were built using death as a response with days of postnatal age (age), GA, BW, and repeated HRC measurements as independent predictors. Nonlinear terms for age were included using a cubic spline function with six knots. We used the Huber-White method to correct the covariance matrix of the model coefficients for correlated responses from the same infant (34). To compare models, we used Wald statistics and the area under the ROC curve. We obtained final models using Akaike's Information Criterion and penalized maximum likelihood techniques to shrink the regression coefficients to the level of complexity supported by the data (33).

The HRC index is derived from a regression model using HRC to predict sepsis and SIRS, and is proportional to the risk of the clinical diagnosis of sepsis and SIRS in the next 24 h. We also used regression analysis to test the hypothesis that the HRC index added predictive information to BW, GA, and age using a Wald test. Ninety-five percent confidence intervals for ROC area were generated using a cluster bootstrapping technique (8, 34).

To determine the cHRC, we calculated the HRC index and the risk of illness as predicted by demographic features at 6-h intervals (8). At each time point we determined their difference, and we summed the differences during the course of the hospitalization to determine the cHRC. If the infant had the degree of illness expected for the degree of prematurity, we expect the cHRC to be 0. A negative value connotes a less-than-expected burden of illness, and a positive number connotes a more-than-expected burden of illness.

We calculated the fold-increase in the probability of death in the next 7 d over and above that expected because of the BW, GA, and age as the exponent of the difference (HRC index minus demographic index).

Data display. In Figure 2, we plotted the HR, and decelerations are downward deflections. Previously, we have plotted RR intervals, and decelerations were upward. Although the display of HR is preferred because it is more intuitive, calculations were performed on RR intervals, which have closely related but nonidentical statistical properties (35).

RESULTS

Patient population. Six hundred eighty-five infants were enrolled in the study, and there were no significant differences in BW or GA at the two study sites. For the 341 infants at UVa, the median BW and GA with 25th and 75th percentiles were 1765 g (1104 g, 2866 g) and 32 wk (28 wk, 37 wk). For the 344 infants at WFU, the median BW and GA with 25th and 75 percentiles were 1855 g (897 g, 2792 g) and 33 wk (27 wk, 37 wk). Figure 1 shows the distribution of infants by BW, and the shaded portions of the bars represent infants who died.

Fourteen (4%) of the study infants at UVa and 23 (7%) of the infants at WFU died. There was a trend toward higher mortality at WFU, although the difference was not statistically significant for this sample size. We might expect higher mortality at WFU because of the difference in patient populations in the two NICUs. WFU has no obstetrical service and no in-born patients, and admits only infants referred for severe acute illness. UVa, on the other hand, admits approximately 50% of its patients as in-borns, and the severity of illness is expected to be less.

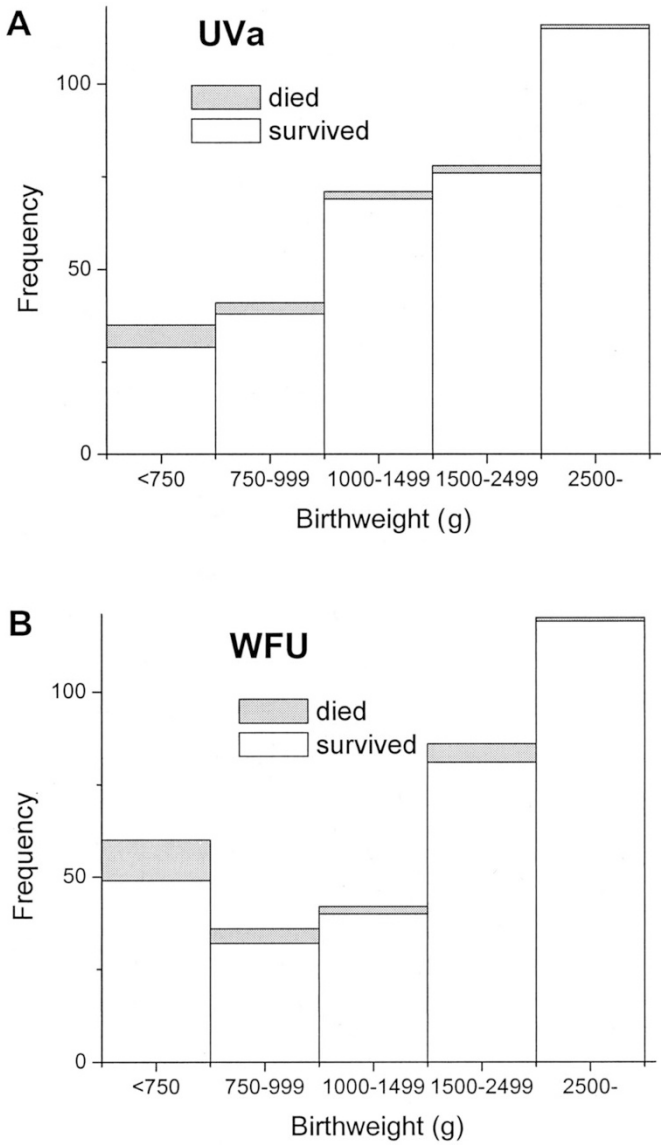

Figure 1. BW and mortality at the two NICUs. The *unshaded* portion represents the infants who lived, and the *shaded* portion those who died.

Many of the deaths were owing to infection. Proven sepsis (positive blood culture) was the cause of death in 11 infants, and clinical sepsis (sepsis-like illness with negative blood culture) was the cause of death in five infants. Another four died of necrotizing enterocolitis (two with a positive blood culture) and one with meningitis. In all, 21 of the 37 deaths were caused by catastrophic infectious illness. The remaining deaths were caused by respiratory failure ($n = 12$) or congenital heart disease ($n = 4$).

HRC abnormalities before death—reduced variability and transient decelerations. Figure 2 shows representative records of HR from the same infant delivered at 25 wk gestation with a BW of 827 g. He had a very complicated 7-wk hospital course ending in death. He was intubated and receiving mechanical ventilation for the whole course, and he underwent a surgical ligation of his patent ductus arteriosus. He had an episode of suspected necrotizing enterocolitis and pneumonia with *Serratia marcescens*. He died with SIRS and multiple-organ failure. Both traces show 30 min of recording, from 8 and 1 d before death, respectively. The top tracing shows a normal and varying HR pattern. The bottom one shows dramatically reduced variability and a single large transient deceleration, an extreme example of the HRC finding early in the course of neonatal sepsis and SIRS.

Use of the HRC index to predict mortality. We hypothesized that the HRC index would become abnormal before death, and we tested the hypothesis using multivariable regression analysis. The results are shown in Table 1. As expected, BW and GA were associated with death at both sites (models 1 and 2). We found that the HRC index derived at UVa was highly significantly associated with death at the test site as well as the training site (models 3 and 4), and added significantly to BW and GA (models 5 and 6).

Evaluation of the models. We evaluated the potential utility of the predictive models by calculating the increase in odds of death associated with a change in the model output. Figure 3 shows the fold-increase in odds of death for infants at the 25th and 75th, and 10th and 90th percentiles of the model values. An infant whose HRC index rises from the 25th percentile to the 75th percentile has a 3-fold increase in the risk of death in the next week: if the rise is from the 10th to the 90th percentile, the increase in risk is more than 5-fold. Models using HRC information were more useful in identifying infants at higher risk of death than models using demographic information alone.

Use of cHRC. The process of calculating the cHRC is demonstrated in Figure 4. Figure 4*A* shows an exemplary record from an infant born at 28 wk gestation with a BW of 867 g. She had a relatively uncomplicated 7-wk hospital course, which included extubation at 3 d of age, a normal cranial ultrasound, and no episodes of sepsis or SIRS. In the figure, the smooth dashed-dotted line is the demographics index, and the noisier dashed line is the HRC index. Note that the HRC index is often below the demographics index. This is reflected in the plot of cHRC, the solid line, which falls from the expected value of 0 (horizontal dotted line) to a value near −3. Our interpretation is that she had a lower burden of illness than predicted by BW and GA.

Figure 4*B* shows the results for the infant whose records are shown in Figure 2, and the times of those traces are marked

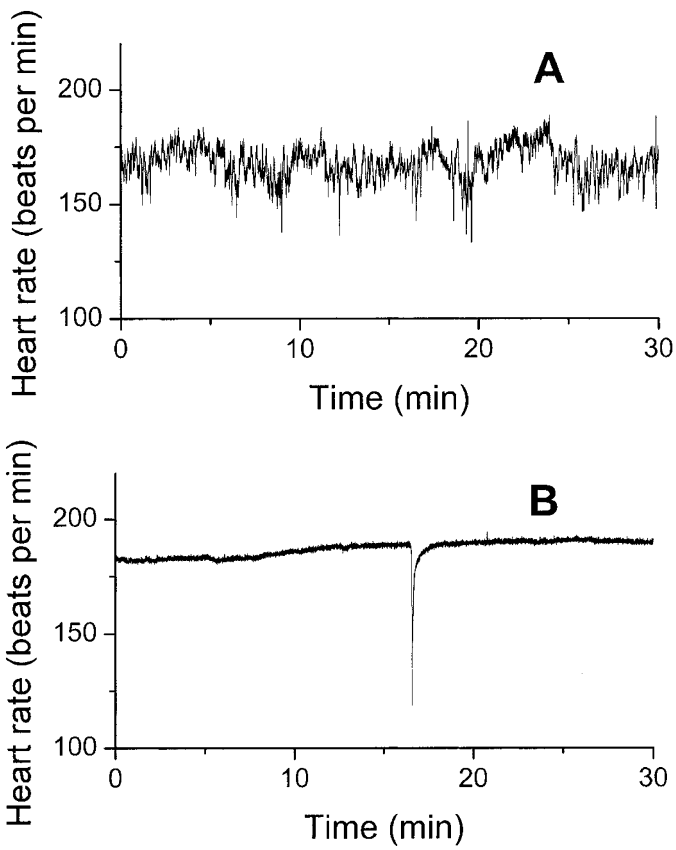

Figure 2. Exemplary records demonstrating the abnormality of reduced variability and transient decelerations in the HR record of an infant who died. *A,* 8 d before death caused by an episode SIRS that was manifest by renal and pulmonary failure. *B,* 1 d before death.

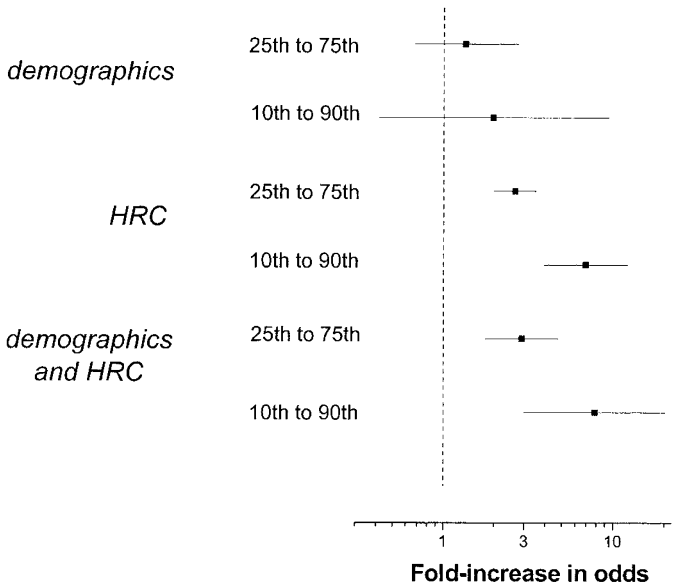

Figure 3. Fold-increase in odds of death with changes in predictive models. Bars are 95% confidence intervals. The demographics model corresponds to model 1 in Table 1; the HRC model is model 3, and the demographics and HRC model is model 5.

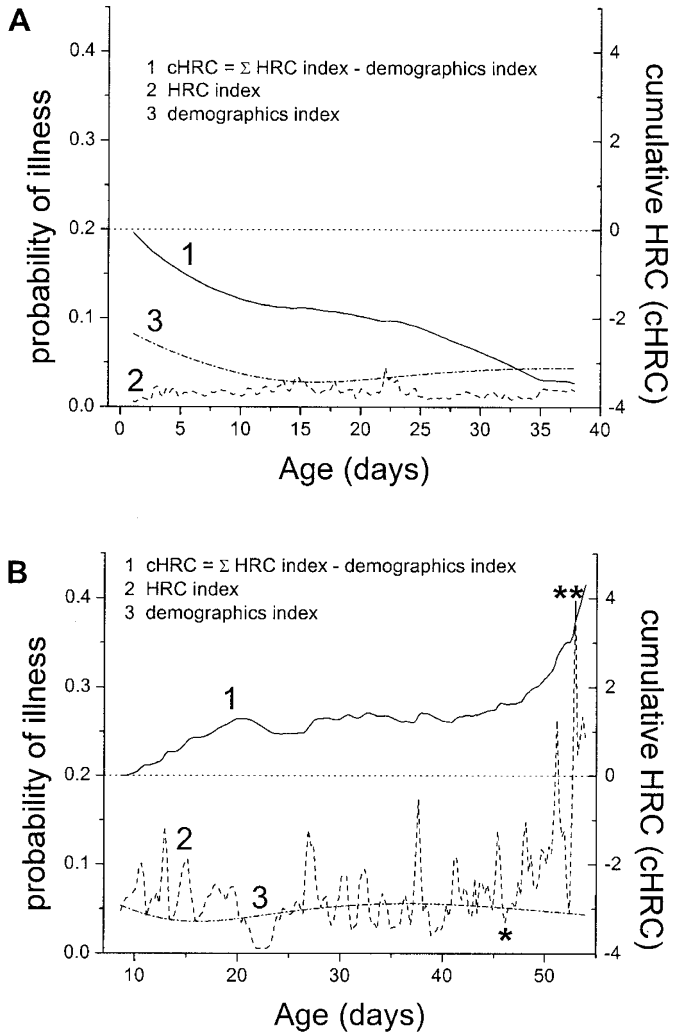

Figure 4. Exemplary records demonstrating the calculation of the cHRC in two premature infants. *A,* healthy infant who survived. *B,* infant with repeated episodes of illness who did not survive. * and ** mark the times of data traces shown in Figure 2, *A* and *B*, respectively. The *dashed line* labeled *2* is the dynamic predictive model using HRC; the *dotted-dashed line* labeled *3* is the more static model using BW, GA, and days of age. Their scale is given on the left *y* axis. The *solid line* labeled *1* is the cHRC and is calculated as the sum of the differences between the dynamic and static models. Its scale is given on the right *y* axis. The *dotted line* is cHRC = 0, the result when the infant has the expected burden of illness. Note that the cHRC is persistently negative in the infant who survived, suggesting a less-than-expected burden of illness, and persistently positive in the infant who died. In addition, note that the dynamic model increases dramatically in the days just before death.

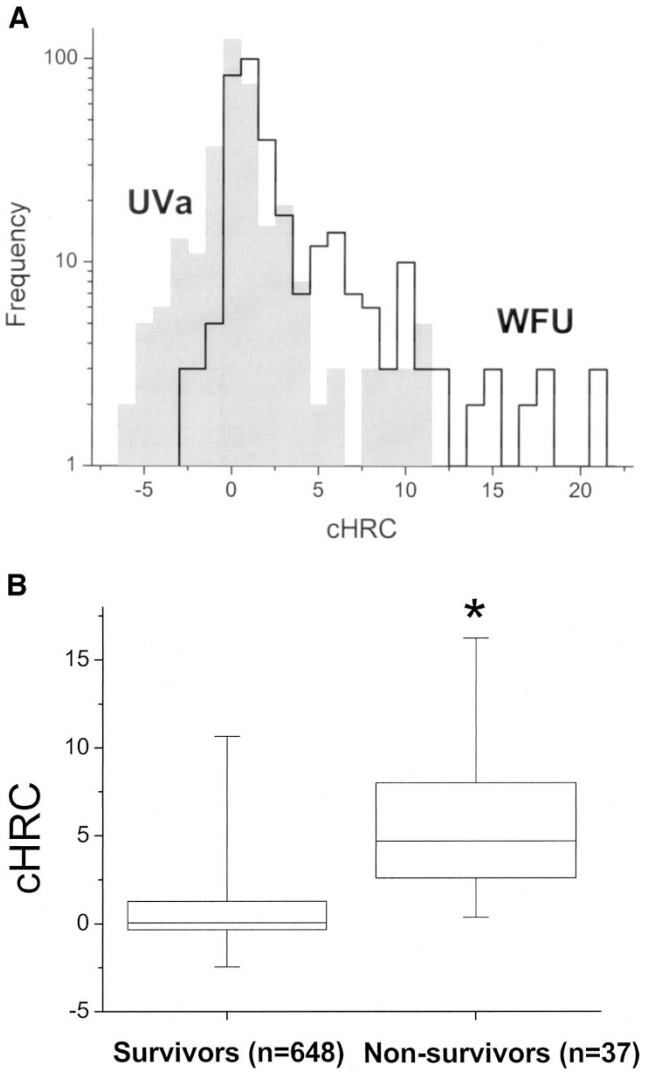

Figure 5. cHRC and neonatal mortality. *A,* frequency histograms of cHRC at UVa (*shaded*) and WFU (*unshaded*). *B,* box plots of cHRC for survivors and nonsurvivors. In the box plot symbol, 50% of the data points are within the box and 80% within the hatches. The horizontal line marks the median values of 0.05 for the survivors and 4.68 for the nonsurvivors. *$p < 0.001$.

with asterisks. The HRC index had several epochs of elevated values, especially during the few days before death. The cHRC is increased to a value near 4 at the time of death.

Distributions of cHRC at the study sites. Figure 5*A* shows frequency histograms of cHRC at the two centers. As expected, cHRC was centered near 0 for the UVa data. At WFU, values were higher. The difference is in keeping with the differences in patient attributes at the two NICUs, with a higher population of infants referred to WFU for severe acute illness.

The cHRC is not expected to correlate with BW and GA, as the illness-predicting information of these variables is subtracted during the calculation. We confirmed this by calculating the Spearman rank correlation coefficient. Indeed, it was very low (<0.1), affirming the efficacy of the cHRC in adjusting for BW and GA.

Association of the cHRC with mortality. Figure 5*B* shows box plots of cHRC for survivors and nonsurvivors at both sites. The large increase in median cHRC in nonsurvivors was highly significant ($p < 0.001$, rank sum test).

We tested the hypothesis that cHRC added information to BW and GA in predicting death in the hospital, and the results are shown in Table 1. Although BW and GA were significantly associated with in-hospital death, as expected (model 7, ROC area 0.76), cHRC was also highly associated and added new information (model 8, ROC area 0.83 and model 9, ROC area 0.79).

DISCUSSION

We tested the hypothesis that measurement of HRC, a measure of reduced variability and transient decelerations of

Table 1. *Regression analyses of demographic features and HRC before death*

Model	Training site	Test site	Predictor	Predictor	Outcome	ROC area	*p*1	*p*2
1	UVa		demographics		death next week	0.70	0.020	
2	WFU		demographics		death next week	0.67	0.052	
3	UVa			HRC index	death next week	0.74	<0.01	
4	UVa	WFU		HRC index	death next week	0.73	<0.01	
5	UVa		demographics	HRC index	death next week	0.85	<0.01	<0.01
6	WFU/UVa	WFU	demographics	HRC index	death next week	0.79	<0.01	<0.01
7	UVa	WFU/UVa	BW, GA		death in-hospital	0.76	<0.01	
8	UVa	WFU/UVa		cHRC	death in-hospital	0.83	<0.01	
9	UVa	WFU/UVa	BW, GA	cHRC	death in-hospital	0.79	<0.01	<0.01

Abbreviations used: demographics, GA, BW, and days of postnatal age; *p*1, *p* value for overall model; *p*2, *p* value for HRC index or cHRC adding information to demographics; WFU/UVa as training site, models generated with demographic features from WFU and the single HRC index developed at UVa as predictor variables; WFU/UVa as test site, combined database used for model.

HR, would add information to demographic factors in estimating the risk of mortality in infants in a tertiary care NICU who survived beyond 7 d of life. The major findings are that *1*) HRC are highly significantly associated with death in the next 7 d, and *2*) cHRC is highly significantly associated with in-hospital death.

The major strength of our approach is that multivariable regression models were developed using data from one center and found to be associated with clinical outcome at another center. The major limitation of our approach is that we used an imprecise outcome in developing the models. That is, the original outcome of interest was an acute clinical deterioration defined to be present when a physician obtained blood cultures and initiated antibiotic therapy. This conforms to the U.S. Centers for Disease Control and Prevention definition of "clinical sepsis" in newborn infants (36) and to an accepted disease entity of sepsis and SIRS. As this outcome does not require a positive blood culture, however, and because the personal threshold for such an action varies among physicians, it is fair to question what exactly the models are predicting. We justify this approach on the basis of the wide variation in manifestations of acute infectious and noninfectious neonatal illness expected under the heading of SIRS (9–13).

We hypothesized that a larger total burden of risk would be associated with higher mortality rates. To estimate the total burden of risk for the entire hospitalization, we devised a cHRC score that we liken to the glycosylated Hb level for estimation of the burden of abnormal blood glucose. It is the sum of the differences between the values of a model based on demographics and the model based only on HRC that is used to give the HRC index, calculated during all 6-h epochs. A result greater than 0 suggests that more risk than expected was present on the basis of BW, GA, and days of age.

Note that the cHRC is increased at the time of the normal data record shown in Figure 2*A* and marked by an asterisk in Figure 4*B*. At that time, 8 d before death, the HR pattern was normal in appearance, and the HRC index was close to the demographics index. We would interpret this to mean that the infant was no more ill than expected at that time, but that he had a history of past illness.

Cytokines modulate signal transduction in myocardial cells (37–40). We hypothesize that the alterations in HRC are related to the cellular effects of circulating cytokines. Future research needs to test this hypothesis directly, by correlating cytokine levels with HRC in patients, and by testing the effects of cytokines on sinus node membrane excitability.

Like illness severity scores, the HRC index has been developed at one NICU and validated at another and correlates with mortality. The major differences are that HRC monitoring is a noninvasive, continuous measurement that incorporates information about the clinical course from d 1 of life throughout the hospitalization, and does not require any laboratory tests or data entry. In addition, HRC has been shown to become abnormal before the clinical diagnosis of sepsis and SIRS (7, 8).

BW is a good predictor of mortality, with ROC areas of 0.87 (3) and 0.91 (2) in other studies and 0.77 at our two NICUs. Neonatal illness severity scores add information to BW in predicting mortality (3). For example, the SNAP and SNAP–Perinatal Extension developed by Richardson and coworkers assign points for hemodynamic and laboratory abnormalities on the first hospital day (1, 2). SNAP-Perinatal Extension additionally takes into consideration perinatal factors such as BW, and improves the estimate of mortality risk. In our study, we found that HRC added independent information to BW in estimating the risk of mortality. This suggests that knowledge of both HRC and BW might be profitably added in estimating neonatal mortality risk. Indeed, we found that predictive models incorporating HRC data with demographic data had the best predictive performance.

Because the outcome was death in the next 7 d, our analysis included HRC measurements from throughout the hospital course and averaged the predictive information. This approach differs from that previously used to determine that the SNAP very early in the hospital course was more predictive of eventual death than later scores (6). For example, the ROC area for SNAP as a predictor of NICU death was 0.84 on d 1 and fell to 0.64 on d 10. The ROC areas for models using HRC, on the other hand, were consistently 0.8 or greater, suggesting improved predictive information over SNAP, especially if determined after the first few days of life.

An important adjunctive use for SNAP is in determining resource allocation and effectiveness of NICU care (41). It will be interesting to see whether HRC measures obtained throughout the hospitalization add to these scores obtained only at the time of admission.

CONCLUSIONS

In summary, we demonstrated that HRC adds significant information to BW in predicting mortality in infants who survive beyond 7 d of life. Unlike illness severity scores such as SNAP (6), HRC measurements require no data entry and preserve predictive accuracy throughout the hospital course. The findings in this study suggest that, regardless of mechanism, HRC measurements may be of clinical utility in estimating the risk of neonatal mortality in the NICU. We speculate that HRC might prove useful as an index to adjust for confounding owing to illness severity in research studies. For clinicians, cHRC might prove to be useful as an integrated measure of the illness severity experienced by an infant.

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