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Heart Rate Characteristics Monitoring and Viral Infection in the Neonatal Intensive Care Unit

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Background

There is a growing appreciation of the prevalence, morbidity, and mortality of viral infections in neonatal intensive care units (NICUs). Studies have found that 7-55% of premature infants tested positive for viruses (1-5). Outbreaks of viruses in NICUs have been described, including adenovirus (6-8), coronavirus (9), echovirus (10), herpes simplex virus (HSV, 11), influenza (12), parainfluenza (13,14), respiratory syncytial virus (RSV, 15), rhinovirus/enterovirus (16-20), and rotavirus (21), while cytomegalovirus (CMV, 22) and respiratory viruses (23) have been detected among NICU patients undergoing sepsis evaluation. A viral infection is associated with a longer duration of mechanical ventilation (1) and length of stay (1,5,24), prolonged antibiotic exposure (5), as well as a greater risk of bronchopulmonary dysplasia (1,5) and mortality (24-26). Viral infections can be difficult to differentiate from bacterial infections without appropriate testing, which may contribute to unnecessary exposure to antibiotics (10).

Heart Rate Characteristics monitoring (HRC; aka HeRO monitoring, Medical Predictive Science Corporation, Charlottesville, Virginia) has been proven to decrease all-cause NICU mortality (27), mortality after infection (28), mortality at 18-22 months (29), mortality-or-severe-cerebral-palsy at 18-22 months (29), and NICU length of stay (30). The probable mechanism was earlier detection of infection, leading to earlier and more effective intervention (28). Indeed, the Heart Rate Characteristics index (HRCi; aka HeRO Score) has been shown to predict sepsis (31-41), UTI (42), NEC (43,44), meningitis (42), respiratory decompensation (45), extubation readiness (46,47) and death (48-52), and is associated with cytokines (53-55).

No previous attempts have been made to characterize the predictive ability of HRC monitoring to assess viral infection apart from other infections.

Methods

We analyzed 2989 Very Low Birth Weight (VLBW) patients enrolled in the HeRO randomized controlled trial (27). Briefly, patients at nine NICUs were randomized shortly after birth or transfer to one of two arms: either standard of care or standard of care plus HRC monitoring. There were no mandated interventions other than displaying the hourly HRC index to clinicians for those patients randomized to the HRC-display arm. Demographic and clinical variables were tracked for each patient, including all blood, urine, CSF, respiratory, peritoneal, and other cultures with their results.

Among all HRC index scores in the RCT database, cases were defined as HRC index scores in the 24-hour period immediately preceding culture of any type (blood, urine, CSF, respiratory, peritoneal, or other) with a result coded as CMV, HSV, RSV, or Other Viral. For each Other Viral code, the Comments field was examined manually, and an automated script was developed. Other Viral results containing the string "herpes" were re-coded as HSV. Other Viral results containing the strings "para," "flu," or "rota" were coded accordingly, whereas those where the Comments text entered by the research nurse included "urea," "myco," "hemophilus," or "haemophilus" were discarded from the analysis. All strings were converted to uppercase prior to matching, and the match for "para" was performed and coded prior to matching/coding for "flu."

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We defined control (well patient) data as those scores, not within ±10 days of any blood, urine, CSF, respiratory, peritoneal, and other cultures, regardless of the result. HRC index scores within ±10 days of culture were ignored from this analysis unless they were defined as cases.

Analyses were performed with cases defined as a specific virus (CMV, HSV, Rotavirus, RSV, Parainfluenza, or Influenza) and as grouped by Order, then Class where the number of cases was small.

For both cases and controls, we analyzed the highest HRC index score in each 24-hour period (HeROMax24). We compared the distributions of HeRO scores between cases and controls using a two-tailed student t-test, setting significance at $p<0.05$. We also calculated the area under the curve of the receiver operating characteristics curve (AUC ROC) with 95% confidence intervals. For the assessment of Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Risk Ratio, we defined a threshold of HeROMax24 > 2.0. All calculations were performed in R (R Core Team) (56).

Results

"For both cases and controls, we analyzed the highest HRC index score in each 24-hour period (HeROMax24). We compared the distributions of HeRO scores between cases and controls using a two-tailed student t-test, setting significance at p<0.05. "

Baseline demographics of the patient population were described elsewhere and were not different between the two arms (27).

Cases	n	ROC (CI)	Sens	Spec	PPV	NPV	Risk Rat	p
HSV	4	.910 (.822-.999)	50%	92%	.07%	99.99%	11.7x	.10
CMV	7	.708 (.479-.936)	43%	92%	.10%	99.99%	8.8x	.16
Order Herpesvirales	**11**	**.781 (.625-.938)**	**45%**	**92%**	**.17%**	**99.98%**	**9.7x**	**.035**
Rotavirus	2	.846 (.544-1.00)	50%	85%	.02%	99.997%	11.7x	.49
Class incertae sedis	**13**	**.791 (.655-.928)**	**46%**	**92%**	**.20%**	**99.98%**	**10.0x**	**.034**
RSV	6	.755 (.552-.959)	50%	92%	.10%	99.99%	11.7x	.13
Parainfluenza	4	.795 (.633-.956)	25%	92%	.03%	99.99%	3.90x	.18
Class Monjiviricetes	**10**	**.771 (.639-.903)**	**40%**	**92%**	**.13%**	**99.98%**	**7.79x**	**.045**
Influenza	**7**	**.884 (.778-.989)**	**71%**	**92%**	**.17%**	**99.99%**	**29.2x**	**.016**
All Viral	30	.806 (.729-.883)	50%	92%	.50%	99.96%	11.6x	.0011

Table 1. Predictive statistics comparing the maximum HeRO Score in the 24 hours prior to positive viral culture against maximum HeRO Score in 24 hours periods for controls. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Risk Ratio were all calculated at a threshold of HeRO > 2.0. Rows with significant results are bold.

Controls included a total of 37,768 days of HRC index scores. Table 1 details the results of these analyses. Positive viral cultures were rare in this population, with 30 positive results among 2989 patients. In each of the analyses, there was a trend toward higher HeRO Scores among the viral-positive cases when compared to controls. The trend was statistically significant whenever the number of cases was greater than seven, and non-significant whenever there were fewer. HeRO scores were statistically significantly higher for All Viruses, Influenza, Class Monjiviricetes, Class incertae sedis, and Order Herpesvirales. HSV, CMV, RSV, Parainfluenza showed non-significant trends toward higher HeRO Scores. The AUC ROC was .806 (.729-.883) for All Viral infections, Sensitivity was 50%, Specificity 92%, Positive Predictive Value .50%, Negative Predictive Value 99.96%, Risk Ratio 11.6x, p=0.0011. The boxplot in Figure 1 shows the range across all cases of each individual's maximum HeRO Score in the 24 hours prior to culture, with Controls for comparison. Figure 2 shows the trend in the range of each individual's maximum HeRO Score for the ten days before and after a positive viral culture compared with ranges of individual maximum HeRO Score in 24-hour periods for controls. HeRO Score rose dramatically, beginning four days prior to culture.

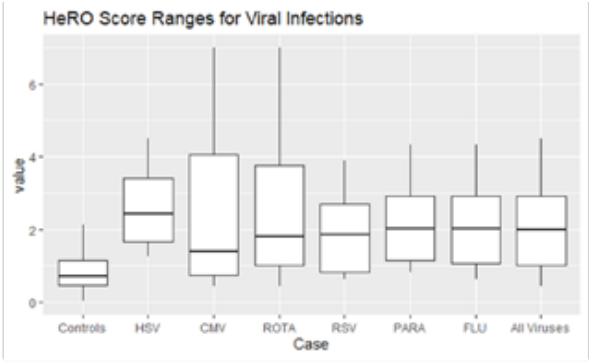

Figure 1. Boxplot of HeRO Score Ranges for Viral Infections. The box represents the 25th and 75th percentiles, the bold line represents the median. The whiskers represent 1.5x the IQR.

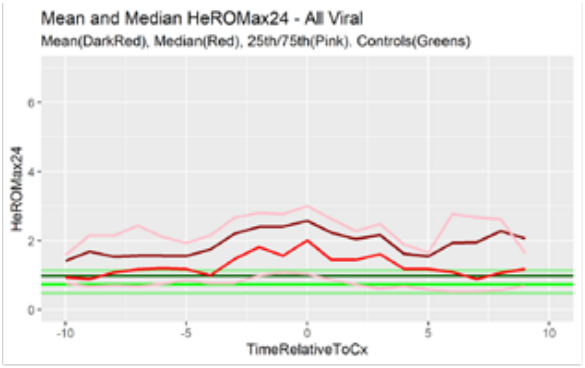

Figure 2. HeRO Scores for 10 days before and after positive viral infections (red) versus controls (green).

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Discussion

We found the HRC index to have excellent predictive characteristics for viral infections, similar to other previously described forms of infection. There are several important implications of this result. First, clinicians ordering a sepsis workup subsequent to an elevated HeRO score should consider including viral testing. A positive viral result could be used to initiate appropriate therapy and reduce unnecessary antimicrobial exposure in cases that might otherwise be considered clinical sepsis.

Second, given the nature of viral outbreaks within NICUs, HeRO monitoring acting as a NICU-wide surveillance system may improve the timing of diagnoses on an individual basis and earlier recognition of a viral outbreak within the NICU itself, leading to greater containment and reduced morbidity and mortality.

Third, in an era of increased global trade, supply chains, and travel, viral epidemics may become increasingly prevalent. Worldwide surveillance systems are challenged by variations in resources, availability, consistency of testing, terminology, and patient populations' heterogeneity. A worldwide network of HeRO-monitored NICUs would offer a unique signal among a cohort of relatively homogeneous patients where unexpected deviations from expected patterns in HeRO Score distributions may indicate increased incidence and transmission among the local community, perhaps prior to this signal manifesting through traditional means of surveillance.

Weaknesses of the current study include the retrospective nature of the analysis and the small number of positive viral cultures limiting our ability to provide statistically significant results for many individual types of viruses. Strengths of this analysis include a large number of patients at a geographically disperse set of NICUs conducted over a six-year period, as well as the consistency of results—both between types of viruses as well as comparing viruses to other forms of infection.

Conclusion

Heart Rate Characteristics monitoring has clinical utility in the assessment of viral infections in the NICU. Clinicians may be able to reduce unnecessary antibiotic exposure and improve therapy for symptomatic patients.

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