PEDIAPOD MAY 2023 TRANSCRIPT

Geoff Marsh
Hello and welcome to Pediapod for May 2023. This month we hear how predictive models using both heart rate and respiratory data may improve neonatal sepsis detection.
Early detection of late-onset sepsis reduces mortality and improves outcomes for survivors. However, the signs and symptoms of infection can be subtle and overlapping with other abnormalities associated with prematurity, and can occur late in the course of illness.
Heart rate characteristics and demographic factors have long been used to aid early detection of late-onset sepsis. However, respiratory data may contain additional signatures of infection. In this episode, we meet this month's highlighted Early Career Investigator, Brynne Sullivan from the University of Virginia. She and her team developed machine learning models to predict late-onset sepsis that were trained on heart rate and respiratory data to provide a cardiorespiratory early warning system, which outperformed models using heart rate or demographics alone.

Brynne Sullivan
So I was born and raised in Virginia. I started out in Richmond, then went to college in Lexington, Virginia, Washington and Lee University. From there, I went to medical school at the University of Virginia and I have been here ever since I did my residency fellowship. And now I've been on faculty for five years at UVA. In residency, I discovered this interesting field of research involving predictive analytics for preterm infants. I stayed for fellowship and that interest and research has sort of built into my career and this paper that's highlighted using heart rate and SPO^2 data to predict sepsis in premature infants.

Geoff Marsh
How common is late-onset sepsis in very low birth weight neonates?

Brynne Sullivan
Late onset sepsis, as defined by a positive blood culture treated with antibiotics, which is not a perfect definition, but it's sort of the best one we have right now, that happens in about 15% of very low birth weight infants.

Geoff Marsh
What makes the detection of it difficult?

Brynne Sullivan
Well, the signs and symptoms of sepsis overlap with common conditions and physiologic changes in premature infants based on immature organ systems. Things like apnea of prematurity are very common and healthy preterm infants. But apnea also increases near the onset of sepsis. Apnea when it occurs near sepsis, or anytime causes changes in heart rate and oxygenation. And we're monitoring those vital signs continuously in these infants who are in the NICU for months, but only threshold-based alarms alert the clinical team to one of these vital signs going outside of this generic threshold. And a lot of times in the NICU, the infants have scheduled assessments and the rest of the time are covered

in an incubator by a blanket. There's a lot of alarm fatigue, alarms are ignored sometimes until the signs of symptoms of sepsis are really obvious and at that point the care is reactive and not necessarily proactive. So the idea with predictive monitoring is to sort of tell you a little bit earlier that there's abnormal patterns that we can't see on the monitor but that happen to correlate with sepsis and inflammation, and to go look at the infant maybe a little bit sooner than you would have otherwise.

Geoff Marsh
There's a couple of new components to the techniques that you're talking about in this study. One is that you've got this continuous monitoring of physiological measurements, but also you're incorporating not just the heart rate data, but also respiratory data as well.

Brynne Sullivan
Correct. My research group has done a lot of work on heart rate analytics and my mentor's developed a heart rate characteristics algorithm that is in use in some NICUs. The piece that this adds is oxygenation and in my work over the years we've discovered that there's some important patterns in combining heart rate and oxygenation. One of those is the cross-correlation of the two. And that cross-correlation captures periods when the heart rate and SPO^2 co-trend together often in the setting of apnea with bradycardia and desaturation. So it's in a way quantifying changes in apnea frequency and severity but also detecting subtle changes in heart rate and SPO^2 in the form of desaturations and heart rate variability, all really a downstream effect of systemic inflammatory response to infection that affects the autonomic nervous system and the control of heart rate and breathing.

Geoff Marsh
So it sounds like that would be too much for a clinician to monitor all those things at the same time and so that's why your team used machine learning methods for this?

Brynne Sullivan
Right. The bedside monitors only display a few seconds or minutes and even with monitors that can look at trends, it's hard to detect all of these patterns at once and to translate it into something useful. And so the machine learning model takes all of these variables into account at once and translates it into a risk of sepsis and the next 24 hours. So we calculated these features continuously in the streaming data and then said, is there a sepsis diagnosis in the next 24 hours of this window of data, and trained the models that way. And we used multiple different machine learning methods to try and get at the best way to detect these patterns.

Geoff Marsh
So you retrospectively went back through all this data on very low birth weight infants' vital signs, and whether they went on to develop sepsis. And you basically wanted to know whether your machine learning methods that incorporated the heart rate data and the respiratory data, if that combined was more predictive than the heart rate data alone?

Brynne Sullivan
Correct. We wanted to know if these features captured by the oxygenation, the SPO^2 data added to heart rate characteristics. And also whether baseline risk factors like gestational age, sex, and

postnatal age also improved the risk prediction of sepsis. But understanding these are static risk factors, while the heart rate and SPO^2 features are dynamic and can tell you that an infant is changing or getting sick.

Geoff Marsh
Let's get onto your findings. Firstly, from that pulse oximetry data, was there a clear cardiorespiratory signature of neonatal sepsis?

Brynne Sullivan
Well, the features that we chose and the modeling methods that we used did predict sepsis very well. And a strength of this study is that we had three collaborating NICUs with infants from each center and we were able to externally validate. And that showed that the model could be useful at many NICUs with infants with slightly different demographics and clinical management.

Geoff Marsh
And so across all those three different NICUs was the predictive power of your model using the heart rate and the oxygen saturation better than just the heart rate alone?

Brynne Sullivan
Yes. The combined model with heart rate and SPO^2 did perform better than heart rate alone. And we also tested whether we could use pulse rate from the pulse oximetry recording in place of heart rate from the ECG leads and found that the performance using pulse rate was very similar and so we termed the combined model of heart rate and SPO^2 data 'POWS', or Pulse Oximetry Warning Score.

Geoff Marsh
And how much warning did your pulse oximetry warning system give you? How long before the onset of sepsis did the alarm bells ring?

Brynne Sullivan
We plotted the predicted risk over time and while we didn't in this study set thresholds, we saw an increase from baseline as early as 24 hours before the blood culture was drawn to diagnose sepsis.

Geoff Marsh
And how did your machine learning method compare against those static demographic factors that we talked about?

Brynne Sullivan
We found that the static demographic factors alone perform fairly well to predict sepsis but they give you just a point in time and don't change over time. So combining all this information with the dynamic risk factors - heart rate and SPO^2 patterns - seems to be the best approach.

Geoff Marsh
So some really impressive results from this pulse oximetry warning system. What needs to happen next, in your opinion, to really validate its predictive power?

Brynne Sullivan
The next step is prospective monitoring and figuring out how best to display the information at the bedside, human factors and protocols that might go along with implementing something like this, but also how it would perform at the prospective episodic level and for events other than sepsis, since our definition of sepsis is not perfect, how does it predict events without a positive blood culture but that also results in significant cardio respiratory deterioration? Ultimately, the plan would be to do a clinical trial to test the impact at the bedside.

Geoff Marsh
So you're a clinician. Did you get heavily into coding in the development of these machine learning algorithms? Or was this the result of a fruitful collaboration with some coders?

Brynne Sullivan
A little bit of both! I began working with this group in my pediatric residency and as I got more involved with the work I realized that I needed to learn more about modeling, predictive analytics and machine learning. And so I've taken several courses but also learned a lot from my mentors. I know just enough coding to be dangerous and speak the language of the data scientists on the team to understand what they're doing and to help direct the data analytics in a way that applies to clinical care and gets at the clinical scenario that we think will be useful for babies.

Geoff Marsh
And I wonder, generally do you see machine learning becoming more of a feature in pediatrics?

Brynne Sullivan
Definitely. I think that there's so much that we can learn from the data at hand that we can't see, and computers and machine learning algorithms can help to uncover those relationships and patterns and present them in a way that we can use in our decisions. The combination of artificial and human intelligence is the way of the future.