PEDIAPOD NOVEMBER 2021 TRANSCRIPT

Geoff Marsh
Welcome to Pediapod for November 2021. This month how caffeine affects renal tissue oxygenation in preterm neonates.
Acute kidney injury is common in preterm neonates and is associated with increased morbidity and mortality. Caffeine administration has been associated with reduced rates of acute kidney injury in preterm neonates, but the effects of caffeine on renal tissue oxygenation is unknown. In this episode, we meet this month's highlighted EarlyCareer Investigator, Dr. Matthew Harer from the University of Wisconsin School of Medicine and Public Health. He's been investigating the potential use of near infrared spectroscopy, a non-invasive means of continuously measuring tissue oxygenation, to assess the effects of caffeine on renal oxygenation, in the hope that caffeine might one day be used to prevent and even treat acute kidney injury. Here's Matthew.

Matthew Harer
I was born and raised in Wisconsin and did most of my training here at the University of Wisconsin, all the way through my pediatric residency. I then finally escaped Wisconsin and went to the University of Virginia to do my NICU fellowship training and that's really where I became interested in studying and researching neonatal kidney issues. I had a great mentor there at the University of Virginia, Dr. Charlton, who really taught me about how important acute kidney injury is in neonates and particularly in preterm babies. So after I finished my fellowship, I came back here to the University of Wisconsin and within the first couple of years, I started studying this non-invasive continuous monitor called Near Infrared Spectroscopy, which can detect oxygen levels in tissues, and ultimately, trying to figure out using this NIRS monitor to see if we can monitor oxygen levels in the kidney as an early way to detect acute kidney injury.

Geoff Marsh
And preterm neonates, I read in your paper, are at risk of decreased renal perfusion. What do we mean by that?

Matthew Harer
Every baby when they're born, whether it's preterm or term, really, in the first few days, the blood flow to the kidney is slowly increasing and it actually increases significantly over the first few weeks of life. In preterm babies, that process is slower, so they initially get a very small amount of blood flow from the heart to the kidneys. And then preterm babies also have patent ductus arteriosus, where they can actually get blood steal away from the kidneys. And so that low amount of cardiac output to the kidneys actually gets even smaller when you have a hemodynamically significant PDA.

Geoff Marsh
Is low renal tissue oxygenation a feature of AKI?

Matthew Harer
Yeah, that's a great question. That's something that we're currently trying to prove. So those markers of acute kidney injury, the increase in serum creatinine and the decrease in urine output typically don't happen or develop until either 24 to 48 hours after the injury has already happened. So they're very delayed. The nice thing about NIRS monitoring and looking at oxygen levels is that it's occurring in real time. So currently, myself and a few other groups are looking at whether oxygen levels decrease a day or two before those changes in serum creatinine and urine output. And now we have a couple of published papers that show babies who have low renal tissue oxygenation, typically below 50, have a higher risk of developing acute kidney injury during the first week of life.

Geoff Marsh
The paper we're here to talk about today is another arm of that work isn't it, about the role of caffeine, which is quite commonly administered in the NICU?

Matthew Harer
Yes exactly. So caffeine is used first and foremost for apnea of prematurity in the NICU, so to keep babies breathing. But there's been several studies, particularly by Dr. Barbara Schmidt's group, that have shown that caffeine really has a lot of significant benefits even outside of the respiratory system, both as far as related to the brain and long term neurodevelopment. I was fortunate enough a few years ago to look at how caffeine might impact the kidneys in the NICU. And what we found is that babies who were exposed to caffeine had significantly less acute kidney injury than babies who were not exposed to caffeine early in life.

Geoff Marsh
So there are previous studies that have correlated caffeine administration with clinical outcomes like AKI, and people have been thinking about renal tissue oxygenation as a factor perhaps in AKI. So you're linking those ideas with NIRS monitoring in this paper, right?

Matthew Harer
Yeah, exactly. My hope is that ultimately in the future, we'll be able to diagnose acute kidney injury, using NIRS monitoring of renal tissue oxygenation by itself. And that because we may then be detecting acute kidney injury as it's actually happening, then we might be able to develop therapeutics or use things that have shown previous promise for preventing kidney injury in that moment, and ultimately then save some kidney tissue for these premature babies.

Geoff Marsh
And this was a retrospective study, wasn't it? Could you tell us what the original study was and how that ended up giving rise to useful data for this question?

Matthew Harer
Our original study was just a pilot study doing both renal and cerebral NIRS monitoring in preterm neonates born less than 32 weeks and over the course of 12 to 18 months, we enrolled 35 babies. Ultimately, we found that three of the 35 had acute kidney injury in the first seven days that we were

doing the nearest monitoring. So we developed this robust database on those 35 babies that had the continuous renal and cerebral monitoring. And ultimately, one of the factors that we really wanted to collect and look at then was caffeine dosing.

Geoff Marsh
So moving on to the results of this study, what happened to the level of renal oxygenation in relation to the caffeine being administered?

Matthew Harer
So what we found is that the babies who had renal tissue oxygenation, less than 40%, had the highest increases in renal oxygenation after they got their caffeine. And really, the timeframe that we saw those increases was primarily between one and three hours after the dose of caffeine.

Geoff Marsh
I know this is perhaps beyond the scope of this study but do you have any idea of the mechanism behind how caffeine has this effect on renal oxygenation?

Matthew Harer
The way that caffeine works is on adenosine receptors, which there are several of them in the kidney. So we know that babies who have acute kidney injury likely have high circulating levels of adenosine that result in decreased oxygenation in the kidney. So we think that babies who have renal oxygen values below 40 likely have high circulating adenosine levels. And then when you give a dose of caffeine, the caffeine actually will block those adenosine receptors. So that's why we think after caffeine, when those receptors are blocked, you actually see an increase in the renal oxygenation.

Geoff Marsh
And does that also explain why you didn't see this effect in neonates that had a normal baseline?

Matthew Harer
Yeah, that's what we believe, because we think the babies who had normal levels likely have low circulating levels of adenosine, so there really aren't any receptors to block that are gonna then change the kidney oxygenation.

Geoff Marsh
And from this study, were you able to correlate those findings with acute kidney injury outcomes?

Matthew Harer
We were not in this paper because we looked at just individual doses of caffeine, not individual patients, so that's something in the future that we would like to do. When we have more babies in a sample that have had acute kidney injury, we'll actually have the power to look at that but since we only had three babies that had acute kidney injury, we weren't able to specifically evaluate that.

Geoff Marsh

But even if we aren't able to say that directly, do you think that this study supports the idea of caffeine being used as a protective therapeutic against AKI?

Matthew Harer
Yeah, I think so. What I would really like to do is study some higher doses. Frequently, babies in the NICU will receive a miniature load of caffeine if they have more pauses in their breathing. So a dose like 10 milligrams per kilogram. So I would like to, at some point, evaluate how the kidney oxygenation changes in response to higher doses of caffeine, because I think that might even result in more increases in oxygenation. I am hopeful though, that in five to 10 years, we'll be utilizing caffeine as a therapy.

Geoff Marsh
As we know the pathophysiology of AKI is multifactorial, isn't it? Is there a limit to how much caffeine could do? Are there forms of AKI that you think this just wouldn't help with?

Matthew Harer
Yeah, I think that is a really important point, because I think some babies who have acute kidney injury, it's likely primarily related to either anemia or hemodynamically significant PDA. So while caffeine may result in some transient increases in oxygenation, it's likely that the acute kidney injury is not going to be totally resolved until you address the underlying issue - whether it's giving a blood transfusion or treating the hemodynamically significant PDA with either medication or surgery, so this might be one small piece in that complicated AKI picture.

Geoff Marsh
And you said that you'd maybe want to do this again with larger doses. Is there anything else you'd like to ask if you had funding for further research?

Matthew Harer
I think really to establish the underlying mechanism we would really need to collect caffeine levels to know and get a sense of if there's a certain threshold or level that's important to cause an increase in oxygenation. And I think ultimately, to prove our theory as it relates to adenosine, it would be great to also be able to evaluate adenosine levels in these babies to really show that the babies who have low baseline oxygenation have high adenosine levels and the babies who have normal oxygenation actually have low baseline circulating adenosine levels.