PEDIAPOD JUNE 2021 TRANSCRIPT

Geoff Marsh
Hello and welcome back to Pediapod for June 2021. This month we're looking at the protective effects of CPAP against hyperoxia-induced airway reactivity in a mouse model.

Respiratory support plays a crucial role in the care of preterm infants in the NICU, ensuring that they get enough oxygen during this critical period of their development. But it's becoming increasingly clear that former preterm infants who've been exposed to ventilatory support are more likely to go on to develop asthma and other respiratory disorders. In this episode, I speak to Peter McFarlane, an associate professor in the Department of Pediatrics at Rainbow Babies and Children's Hospital, Cleveland, Ohio. He and his team have developed a mouse model to study the effects of CPAP in combination with supplemental oxygen on lung function.

Peter Macfarlane
One of the biggest challenges for preterm infants is that their lungs have really not developed sufficiently so they're not able to extract the oxygen that they need and expel the co^2 that they produce. And so having really immature lungs, they often need various forms of respiratory support and that can come in different flavors - quite commonly, it's supplemental oxygen and some form of positive pressure support as well. A really severe, extremely preterm infant might require intubation and mechanical ventilation.

Geoff Marsh
Right. But over the past decade or so, there's been a shift from those more invasive methods like intubation to more noninvasive ventilation techniques?

Peter Macfarlane
Yeah, that's right. And I think one of the concerns that is associated with the clinical care of preterm infants is that these various forms of respiratory support can have unintended consequences to lung development. So more aggressive forms, like higher oxygen levels or mechanical ventilation, can impose significant adverse effects on lung development. So in the last ten or twenty or so years, there's been a push towards minimizing the severity of those interventions to minimize the effects that they have on lung development.

Geoff Marsh
Can you elaborate a little bit on some of those adverse effects that we see with these noninvasive techniques?

Peter Macfarlane
Yeah, so it basically contributes to the pathophysiology of bronchopulmonary dysplasia, or chronic lung

disease is another way of describing it. And so severe cases can lead to oxidative stress and inflammation. Supplemental oxygen has long been known to be a major contributor to that sort of pathophysiology. But not a lot has really been known about the effects of continuous positive airway pressure or CPAP, which is the second component of this particular study. Delivering CPAP in animal models, especially very young or immature neonatal animal models has been a major challenge. So we developed a model of CPAP, using this mouse model and tried to mimic the clinical setting of combining both CPAP and supplemental oxygen.

Geoff Marsh

Am I right in thinking that using this model you were able to ask questions about what CPAP and supplemental oxygen do individually and in combination?

Peter Macfarlane

Yeah, that's right. As scientists we try to tease apart the individual components of a particular disease state or therapy, as in this case, but very rarely do we think to combine the individual components. And that's important in this setting, too, because a lot of preterm infants require some combination of both oxygen and CPAP. So we were really trying to mimic the clinical setting that a lot of these preterm infants are experiencing,

Geoff Marsh

And your end goal with your animal experiment was to look at the function and the morphology of their lung tissue?

Peter Macfarlane

Right. And that was especially the case with the effects that these treatments would have on airway function. And that's really the nuts and bolts of this particular model. We're trying to evaluate the effects that these treatments have on the airways. A lot of these preterm infants who have been predisposed to bronchopulmonary dysplasia go on to develop wheezing disorders later in life.

Geoff Marsh

What effect did the CPAP on its own have compared to the control mice?

Peter Macfarlane

Yeah, one of the surprising results that we revealed was that CPAP alone is sufficient to cause an increase in airway reactivity. And this mimics the wheezing disorders of preterm infants, or former preterm infants is really what I should say. And that was surprising, in part because a lot of the wheezing disorders in former preterm infants has been attributed to not just being born with immature lungs, but also as a consequence of being exposed to the supplemental oxygen. So for decades, the oxygen has always received the finger of blame for contributing to the long term airway hyperreactivity associated with wheezing disorders in preterm infants. So for us to reveal that CPAP can have a similar effect on the airways was really quite a surprising finding.

Geoff Marsh
And what did that actually look like in terms of the morphology of the cells?

Peter Macfarlane
Similar to oxygen. They are different insults, or different challenges, but they contribute to changes in lung morphology or airway morphology in a similar sort of a way. And that relates to the changes in smooth muscle expression around the airways. So the idea is that if you have a more reactive airway, it can, at least, in part be explained by an increased smooth muscle mass.

Geoff Marsh
Why is that?

Peter Macfarlane
Well think about it as though you've gone to the gym. You know - bigger weights - more muscle - more contractility. So both oxygen and CPAP contribute to a smooth muscle expression or smoother muscle proliferation, leading to more mass around the airways and they become more contractile.

Peter Macfarlane
I suppose the key result was that in combination, supplemental oxygen with the CPAP *did not* lead to any of the adverse effects...

Peter Macfarlane
That was one of the more surprising effects. You know, you could argue that if oxygen alone could cause an increase in smooth muscle, leading to an increase in airway reactivity, and CPAP alone could also have a similar effect, then when you combine them...

Geoff Marsh
Yeah, double trouble...

Peter Macfarlane
Right - one plus one should equal two, right?

Geoff Marsh
Have you got any kind of hypotheses as to why they seem to cancel each other out?

Peter Macfarlane
It's a challenging one, to be honest. We hesitated about making too bold a statement. I'll take the easy way out and let's just say that they are different challenges, they're different insults to the lung. You have

mechanical forces imposed by the CPAP and you have an oxygen toxicity insult from the oxygen. So even though the phenotype of airway reactivity and smooth muscle expression is similar between those two different types of insults, they impose a different effect on the lung. And so it is possible that, for example, if I was to make a bold statement, I could maybe say that the mechanical stretch sort of removes some of the oxygen toxicity effects through sort of proliferation and maybe improving lung development. It's just a little too early to say at this point, I think.

Geoff Marsh

It sounds like your next experiment should be some sort of *in vitro* cell culture- lung muscle cells being stretched with oxygen on them...

Peter Macfarlane

I think you've been reading our grant applications! Our collaborators on this manuscript actually, at the Mayo Clinic do have human fetal smooth muscle cells, where they are exposing them to both oxygen and mechanical stretch. So in that sense, we are taking the animal model *in vivo* and applying it to specifically human-related tissue. In fact, in this sense the smooth muscle is completely relevant.

Geoff Marsh

Well you'll have to come back to *Pediatric Research* with that. So what's your next step? Do you stick with the animal models or are these results in any way translational?

Peter Macfarlane

Yeah, very much they're translatable. I'm very fortunate to work with some very intelligent physician-scientists who help us with the translational aspect, taking the animal results to the clinical setting to try to make it translatable to infants. So some of the next steps that we're looking at are especially focused on CPAP and looking at the effects that it has on lung development and airway development in the context of mechanical stretch. So the ultimate goal would be to either come up with alternative treatments that don't have unintended side effects, or minimize the effects that these treatments have by, for example, titrating the severity of the different methods of respiratory support, or even just coming up with a combination therapy. These are necessary modes of respiratory support for these preterm infants, at least currently so the idea would be to come up with alternative, or combinational therapies that can be administered to these infants to minimize the adverse effects while maximizing the benefits. So a lot of preterm infants, for example, receive caffeine therapy as another form of support to minimize respiratory distress. Caffeine is an interesting story and another piece of the puzzle that we focused on. It can have benefits, both from an anti-inflammatory perspective, but it has other benefits, too - it promotes respiratory drive so it can minimize the severity of apnea of prematurity that these infants have. And so that's just one combinatorial method of treatment for these preterm infants. But again, the ultimate goal would really be to either come up with some alternative methods of respiratory support or titrate the severity of the ones that they're receiving right now to minimize the adverse effects and maximize the benefits. Maybe even further down the road we can come up with some sort of therapy that we could use to reverse the effects these treatments have had on airway function later in life. So if you're in your teens, for example, and you're starting to wheeze because you'd

received oxygen or CPAP in your NICU setting, it might not be too late. We might be able to come up with some sort of treatment to reverse the effects of treatment that you'd had previously.