[MUSIC PLAYING]

JUSTIN C. YEH: I have no disclosures. What I'm hoping to do today is talk a little bit about neural developmental outcomes. What we'll start with is a little bit of background and try to help you understand the scope of how congenital heart disease ultimately impacts neurodevelopment in our patient population. I hope that I'll help you understand that it's a multi-factorial process, which extends beyond the factors that are happening intraoperatively And then because I work in the cardiac ICU, I hope to talk to you a little bit about interventions that we can make in the cardiac ICU, which may ultimately benefit the neural developmental outcomes in our patients.

So since I'm new here, I thought I'd talk a little bit about my journey to Pittsburgh. And as I've only been here a month, it's not unusual for me to run into people and they ask me, so, Justin, why did you come from the coastline of beautiful San Diego to the four season world of Pittsburgh? Is it the emerging Pittsburgh food scene? Perhaps. Is it the great athletic teams here? I'm, of course, a big sports fan. But I'll be honest, I don't think I'm going to get rid of my allegiance to the Dodgers and the LA Lakers. But I could be convinced to follow the black and gold of the Steelers maybe.

And it sounds corny, but really the honest truth is that there is an extremely talented group of people here at Children's Hospital of Pittsburgh. I'm very excited to be here, to be leading the cardiac intensive care team. And what I hope to do is show you that really Children's Hospital of Pittsburgh, particularly in congenital heart care, is positioned to really deal with some of the problematic issues that I'm going to discuss today in neurodevelopmental care. And what I'd like to do is, at different points during the lecture, try to highlight what some people are already doing here at Pittsburgh. And hopefully, I'll be able to collaborate with those people on some new work.

So really, this slide shows how much progress we've made in the last 40 to 50 years in congenital heart care. And it's really a testament to the great fathers of our field, with advances in medical therapy, including the development and use of prostaglandins, catheterization care, of course, advancements in surgical care, and then refinements of our care in the cardiac ICU.

This is a nice diagram which comes from historical data in Norway, but it really parallels what we've seen worldwide in terms of improvements in the care of patients with congenital heart disease. In particular, you can see that there are certain lesions, like tetralogy of Fallot and transposition of the great arteries.

Although we've made refinements in the care of those patients, we started to develop improved surgical techniques even in the 70s, particularly with tetralogy of Fallot, with that being one of the first lesions where we discussed doing early primary repair with Dr. Barratt-Boyes and Aldo Castaneda leading the forefront in that area. And then you can see over time even lesions such as single ventricles, truncus arteriosus, complex arch lesions, and total anomalous pulmonary venous return, with the line in green being the most current era, have shown excellent surgical outcomes.

So with that progress, there's been a lead to a shift in focus. So instead of just focusing on mortality, we've been focused more on morbidity in our patient population. And clearly, one of the greatest focuses and one of our greatest concerns are what are the potential neurologic complications that can be associated with not just congenital heart disease, but the multiple exposures to critical illness that these patients have.

Our primary focus in the initial part of this investigation has clearly been on focusing on intraoperative events and things that we can do from a surgical standpoint and aesthetic standpoint to try to optimize care. This was one of the first efforts to do this. For the folks in the audience that are in the field of congenital heart care, they'll recognize this study, which was in the *New England Journal of Medicine.* It wasn't called this at the time, but this ultimately was called the Boston Circulatory Arrest Trial.

And what they looked at in this study was comparing patients with transposition of the great arteries and an intraoperative surgical strategy of randomizing them to either hypothermic circulatory arrest or a low-flow bypass. What they ultimately found was that there wasn't a significant difference in neurologic outcomes between these two groups. The early parts of the study show that there was an increased incidence of seizures. And in the group that did have seizures, they did have worse neurologic outcomes.

The real testament to this study that they've been able to have excellent follow-up in this group. They've followed this group now into their late teens. This is a follow-up in this group from 2011. They were actually able to follow-up on greater than 80% of the children in that group. And what they found was very important.

It didn't really matter whether they were exposed to deep hypothermic circulatory arrest or a low-flow bypass, all the patients in this group-- or I should say the mean-- showed issues with executive function. They had issues with memory. It's not included in this slide, but many of these patients required special education support. Up to 30% of these patients require increased educational services to help them. And so this started to ring the bell a bit that patients with congenital heart disease may be at risk for worse and neurodevelopmental outcomes.

Over time, I think we've been able to appreciate that there is cognitive impairment in our patient population. And subsequent analysis and other patient cohorts has supported these findings from the Boston Circulatory Arrest Trial. But there's been important new findings that have extended beyond this trial, which is really that all patients with congenital heart disease are at risk, in particular, patients who undergo surgical repair in early infancy. And those who have prolonged ICU stays appear to be the most vulnerable patient group. Key areas of deficit appear to be in reasoning, executive function, visual spatial skills, and language. And behavioral problems such as inattention, ADHD, and impulsive behavior are more common.

But is it really all related to what's happening in the OR? The surgeons frequently get blamed for things that they aren't always responsible for. Victor's shaking his head over there. What we've really learned is that this is a much larger scope than just the intraoperative process for these patients.

And as more sophisticated neuroimaging has become available, it's now clear that patients with congenital heart disease may have structural brain abnormalities that precede their operative repair. In particular, we found that patients with transposition of the great arteries, and then patients also with left-sided obstructive heart lesions, the most extreme of which is hypoplastic left heart syndrome, appear to have decreased brain volume and signs of impaired development in brain maturity, like you would see in premature infants. And most important for us in the OR as well as in the ICU, we know that these patients are at increased risk for white matter brain injury, particularly with episodes of low-flow and hypoxemia.

This is just an example of an MRI, which is from a recent review looking at this same discussion. It's focusing on neonatal brains. The first one is from a patient with hypoplastic left heart syndrome, which shows some areas of white matter lesions. The second is from a patient whose status post-Norwood, who shows some injury in the MCA distribution. And the last is from a patient with transposition, who has a white matter lesion as well.

Interestingly, the transposition group became a focus a couple of years ago, particularly with these white matter injuries. And a lot of discussion was generated around the risk of performing balloon atrioseptostomies and whether that increased the risk for patients to develop stroke. While that's still a bit controversial, I think we're starting to understand that while that is a risk, it may not be the exact smoking gun that's causing these white matter injuries in this patient population.

As we've developed more sophisticated genetic tools, we've also understood that there's a relationship between genetics and neural development. For a long time, we've known that patients who have trisomy 21 and DiGeorge syndrome clearly have both congenital heart disease and may have impaired cognitive performance. With improved laboratory techniques that allow for more rapid whole genome sequencing, we're starting to identify scores and novel gene variants in patients with congenital heart disease. And this technology is rapidly improving. Actually, one of the leading centers for this happens to be my old institution at Rady, where they've now been able to sequence the whole genome in just over 24 hours.

Understanding of the genetic underpinnings of congenital heart disease is going to be critical, not only for elucidating the mechanisms of specific cardiac malformations, but it may also help us to identify certain factors which contribute to neural development. In fact, the group here with Dr. Lo's focus on ciliary dysfunction-- and that was related a bit to my work with her when I worked with her at the NIH-- has noted that ciliary dysfunction is related to congenital heart disease, in particular in patients who develop heterotaxy syndrome. And that, in fact, there may be extra cardiac lesions in these patients, including brain dysplasia associated with a ciliary dysfunction. In addition to Dr. Lo, you can see that there are many members of the Heart Center team here as well as Dr. Panigrahy, who's one of the eminent radiologists here.

What you'll notice here are some of the brain lesions, which they found in this patient population, including thinning of the corpus callosum, hypoplasia in the olfactory bulb, and abnormalities in the hippocampus. Not included here was that this patient group also seemed to have increased extra axial space, and there's the suggestion that there is increased CSF volume, which I don't think is surprising in the setting of having ciliary dysfunction.

So really putting these together, you can start to imagine that there is a multi-hit hypothesis, where it's not just the intraoperative of events which are affecting these patients' neurodevelopmental outcomes, but really it's a sequence of events which leaves these patients at risk. Starting at conception, there could be genetic factors. And that's part of what Dr. Lo's lab is looking at.

There can be intrauterine events. These can be several-fold. There may be inadequate oxygen delivery, which is inherent to the patient's circulation, in particular, that may be why we see these abnormal brain developmental lesions in the patients with hypoplastic left heart syndrome and transposition of the great arteries. You can imagine that at some of the extreme forms of hypoplastic left heart syndrome, those patients are dependent on retrograde blood flow in the arch to supply the brain. And so then it would not be surprising to see decreased brain volume and brain immaturity. For the transposition patients, with their essential parallel circulation, those patients are going to be also at risk for decreased oxygen delivery secondary to the way their circulation is comprised.

In addition, there may also be maternal events. There's starting to be an increasing awareness of potentially the importance of placental health on fetal development. And Dr. Panigrahy and the perinatology groups here at Pittsburgh are looking into that. And in addition, there are some future studies that people are doing in the cardiac fetal world considering maternal hyperoxygenation to both discriminate the sickest patients in our patient cohort as well as to see if that could be a potential rescue therapy for some of these brain abnormalities.

We know that there can be perinatal events. Certainly historically, this was a major issue for our patient population in that fetal echo either did not exist or was early in its development, and so there were patients that we did not catch who had critical heart disease and would come in in shock or extreme hypoxemia, who would then suffer secondary hypoxic-ischemic brain injury. That happens to be less the case now, but there's still some patients who are extremely critically ill in the delivery room who could benefit from skilled multi-disciplinary care.

There is, of course, important things that are happening in the operating room, which includes not just what the surgeons are doing, but a thoughtful approach from our anesthesia colleagues in terms of choice of anesthetic and how they support the hemodynamics in the OR. And what I hope to talk about is what we can do in the perioperative, of course, and, of course, the postoperative time so that we can optimize not just our ICU outcomes, but how patients do on into adulthood.

So what are some of the things that we're going to be talking about with the rest of the lecture? We'll spend a little bit of time looking at the impact of neurosedative agents and how they can potentially affect brain development, and what may be strategies that we can do in the cardiac ICU to be cognizant of the current data in this area, and whether it should change our practice.

Consider the development of early warning systems to try to decrease periods of low-flow or low cardiac output and try to reduce the incidence of cardiac arrest. Better recognize our at-risk populations and enroll them early in services that will address their areas of deficit. And then as a last thing-- a little bit of a lark-- I'll talk a little bit about some interesting animal work that was discussed both at the last year before ACC meeting and Pediatric Intensive Care Society, which may be a novel therapy for helping to reduce the brain injury that occurs during low-flow periods.

So I'm sure our anesthesia colleagues are aware, but many of you may be aware that in 2016, the FDA released a communication in which they said that they were approving label changes for the use of general anesthetic and sedatives in young children. Essentially, this came from work that suggests that in animal models, there is evidence that brain injury can occur with exposure to common general anesthetic agents and certain sedative drugs. That has not been proven to be the case for the most part in clinical studies, but at least raises a concern.

And so the FDA did release a statement suggesting that elective procedures in children should be delayed if possible to later in childhood, that repeated exposures to anesthesia may be necessary, but that those patients are at risk and should be monitored closely, and that perhaps as we start to study these drugs more, maybe we're going to have to be making some very careful decisions about which anesthetics we use.

And are there certain agents? And what is their mechanism of action? That's still being studied. But this is a proposed potential mechanism of injury, which is that there's two particular groups which are of concern. Those are the GABA agonists, which would include the large category of inhaled anesthetics as well as benzodiazepines, and NMDA antagonists, which included in that group would be a common drug that's used in pediatrics, which is ketamine. The thought is that both of these agents are going to decrease synaptic signaling, and then through a complex cascade are ultimately going to lead to apoptosis.

So we know that this is seen in animal models, particularly in animal models which would be potential correlates to young patients. There is some suggestion-- although it's not totally clear-- that opioids and alpha-2 agonists like dexmedetomidine maybe at least have a neutral effect or potentially could be neuroprotective. As I said, the clinical studies are really fraught with confounding variables. And that makes sense based on that schematic I showed you, where it's really a multi-hit hypothesis which affects neural development in children. So it's really hard to tease out the effects of these anesthetics when we know that there's genetic factors, prenatal insults, things that happen in the operating room as well as in the ICU afterward.

But people are making the effort to initiate prospective trials to better understand the effects of neurosedatives on the developing brain. And in particular, these studies are focusing on randomizing patients into different arms using these different agents that I've just described and really taking a kind of approach of observing the patients and seeing if there is any true neurodevelopmental effects on their ultimate outcome.

The results from these trials are going to take time. And clearly, it's going to be several years before we really know what kind of impact we're seeing from anesthesia and neurosedatives. So it's still too early to draw definitive conclusions, but there may be a time in the near future where we're trying to minimize exposure and avoid NMDA antagonists and GABA agonists, move towards maybe a primary use of opioids and dexmedetomidine as well as local agents to try to decrease our opioid use.

I know that in our ICU at San Diego, we had a very collaborative approach with our neonatal group and our anesthesiologist. And both of those groups were very concerned about the use in particular of benzodiazepines in the neonatal population and developing brain. And so we came up with a primarily fentanyl and dexmedetomidine based strategy for support of our neonatal patients. And in the last year I was there, we were making significantly increased use of local anesthetic agents to try to minimize our total opioid use. And of course, we should always be trying to encourage non-pharmacologic measures to try to decrease agitation. That's why those volunteers who are baby holders are very important, so we can try to minimize our use of opioids and sedatives.

So what about prevention of cardiac arrest? Without question, episodes of cardiac arrest lead to hypoxic-ischemic injury in subsequent neurodevelopmental ways. And in our population, particularly in the cardiac ICU, we know that they are very likely to get exposure to mechanical circulatory support with ECPR, mini-ECMO, which is going to carry additional neurologic risks, including potential for intracranial bleeds and thromboembolic stroke.

So there's a new quality initiative, which I'd like to talk to you about a little bit, to try to reduce the incidence of cardiac arrest in cardiac ICUs nationwide, and it's called the Cardiac Arrest Prevention, or CAP, initiative. So the CAP initiative is being brought out of the pediatric cardiac critical care consortium, or PC4, which is a developing national collaborative of now 39 centers.

The goal of PC4 is to try to create purposeful collection of specific clinical data on outcomes and practices. So one element of the collaborative is to try to bank data on how our patients are doing in the intensive care unit. The goal is to get timely performance feedback to clinicians. So the idea is that we have these databases. Unlike some of the other databases that we interact with, there's a local server which keeps this information. And you can access your own patient's information at any time from any terminal as long as you have the appropriate digital access. And then the idea is that there's a continuous improvement based on empirical analysis and collaborative learning.

So the idea is that the collaborative is supposed to be transparent. Centers who are within the collaborative identify themselves that you can share information with each other. And high performers in certain areas can be sought out to try to improve your own practice. Or if you are a high performer, people will seek you out to try to learn what you have in terms of performance improvement.

So based on evaluation of cardiac arrest in this PC4 database, there were high risk groups which were identified. I don't think these are surprising at all, but we'll go through them. They include the post-op surgical patients, and in particular, all neonates, after cardiac surgery which requires cardiopulmonary bypass, all neonate or small infant single ventricle palliation, any premature neonate, and in our medical patients, any medical patient who on a mission requires mechanical ventilation within the first four hours after being admitted.

So we've come up with a bundle, which is included in this quality initiative. There's five elements to the bundle. Really, I think the first two ones are what are going to end up being the most important for this quality initiative. And the concept is really kind of increasing situational awareness and doing just-in-time teaching to improve provider performance at the bedside.

So the first element is what's called a CAP safety huddle. So this is a multi-disciplinary discussion of cardiac arrest prevention twice a day. So this should include the providers at the bedside, the nurse, that patient's respiratory therapist, as well as nursing leadership, in particular the charge nurse for the day so that they get a best sense for who are the sickest patients in the unit. That should occur on both the AM and the PM shift. The idea is that you review the physiology of the patient. You discuss potential mechanisms in which the patient could decompensate. And then you talk about mitigation strategies for each of those decompensation mechanisms.

Those goals and plans are posted at the bedside. I know this is the digital age, but the initiative asks that we have paper sheets that are visual documentation of what we're trying to do for the patient as a reminder to providers of the goals for the day. Just as important, there are patient-specific vital sign goals, which are established, and alarm parameters are adjusted so that communication is very clear between the different providers, so that the nursing and respiratory staff know exactly what the physicians and advanced practice providers are concerned about for those patients.

In addition, there is encouraged to be discussion about pre-sedation before noxious stimuli. I know that at least the surgical colleagues at my institution were a little concerned that when they first promoted this study that it was going to be automatic sedation for patients with any noxious stimuli, and that those could have deleterious effects on hemodynamics. It was ultimately adjusted to make this more of a discussion about whether that's appropriate to have sedation during mainly procedures.

We're encouraging emergency medications at the bedside, essentially epinephrine, to be available and pre-drawn. This is probably going to leave the bundle because essentially, if there's a pharmacist in the audience-- I don't know if Don's here-- know we frequently go through medication shortages. And many of you may be surprised, but there are occasionally epinephrine shortages. And so after looking at the early results from this, most centers were not using these pre-drawn epinephrine syringes, and so we're probably going to be backing away from this in later iterations of the bundle.

And then, of course, there should be formal review of all cardiac arrest events so that not only do you get this just-in-time learning, but there can be a retrospective review of events after they occur so we can get a better understanding of how we can do better in the future.

So what are the ALCA measures that we're going to be looking at? We're going to try to shoot for a 25% reduction in the overall cardiac arrest rate across the entire collaborative after one-year of bundle implementation. The average rate across the PC4 collaborative is 4.1, so we want to get that down. We want to try to increase the days between cardiac arrest and decrease the cardiac arrest rate by 33% in bundle patients.

So our process measures are going to include making sure that we're compliant with the bundle. All centers are having individuals who are not participating in the study audit to make sure that parameters are appropriately discussed during these huddles. And then of course, as in any quality initiative, you want to have balancing measures. So we want to ensure that the cardiac arrest rates in the non-bundle cohorts do not significantly increase. We want to try to make sure that our new efforts are not increasing length of stay, and that there is no inappropriate increase in our use of therapies.

What about other early warning systems to prevent low cardiac output state and cardiac arrest? Currently, there are emerging systems which are trying to develop electronic tools to help physicians recognize low cardiac output earlier. There's a company called Etiometry, or T3, which came out of work from Peter Lawson and the Boston Children's Group, which has tried to develop an algorithm to recognize low oxygen delivery states.

And there's also been some work, which I'll allude to here from Baylor, which tried to use an algorithm with certain important patient variables and a real time processing of physiologic data to try to predict deterioration in their cardiac population, specifically patients with parallel circulations. So to make that clear, essentially patients with single ventricle physiology who are either pre-operative or after their Norwood surgery or aorta pulmonary shunt from having deterioration.

So some of the things they looked at was heart rate and heart rate variability, respiratory rate, sats. They also looked at other hemodynamic measures, like filling pressures, blood pressure. And so you can see that very close to the event, they had a high ROC, but they weren't really able to predict hours out, which is really what you want, that a critical event was going to occur.

There is ongoing work here, which was started by my predecessor, Dr. Ricardo Munoz, in developing an early warning system to try to predict a deterioration in the same patient population. And the name for that study was C-WIN, and we're hoping to continue the work on that project. In particular, our goals are going to be, one, to try to refine that tool, which was primarily developed to predict deterioration in the single ventricle population and see if we can look at that population, and then expand it to our entire cardiac congenital heart cohort.

And in addition, we'd like to try to see if we can improve our tool moving away from what they did here, which was an expert-based data set to taking that expert-based dataset and using machine learning to further refine the tool. I should also mention that Chris Horvath who is in our pediatric critical care division, is also doing those same things in looking at early warning tools for the entire hospital, as well as looking for the development of an early warning system for our patients in the pediatric intensive care unit.

What about recognizing patients who are at risk and trying to initiate services early? Does that make a difference? Adult studies have demonstrated that there is benefit to early mobilization and use of therapy tools, particularly physical therapy and occupational therapy in critically ill patients. They've been able to show that there is a decreased length of stay, decreased ventilator days, and improved functional status at discharge.

In the pediatric population, there's really limited data. Historically, that may be because maybe we're a little too kind in pediatrics, and we're concerned about causing pain to patients by mobilizing them and getting them up and moving. I think there's also legitimate and very real concerns about moving and mobilizing patients who have invasive instruments in them, like intratracheal tubes, arterial lines, central venous lines. But there are suggestions that are emerging, and interestingly, it's coming from our sickest patient population, which is our ECMO patients, that mobilization is important and that it can improve outcomes.

And certainly, we're taking clues from our adult colleagues. I think probably one of the biggest improvements in lung transplant care has been how patients with lung disease, who require extra corneal support, are managed. We've moved from a time where those patients were very poor candidates for a lung transplant to now they're extubated, maintain on extracorporeal support, and mobilized. And I don't think it's surprising to see that those patients are now performing much better in the post-transplant period. And maybe there's something that we can learn from that.

There is a small study that just came out of Japan, which looked at early post-operative physical therapy and whether it made any benefit to motor outcomes in infants with both cyanotic and acyanotic congenital heart disease. It's a little bit of a busy slide. But essentially what they showed here is that the higher the scores on this nine-grade mobility assessment, the better the patient's doing. And you can see that there is an inflection downward, which was after the operation, and that it improves before the patient was discharged.

There was one patient from each group, which didn't show any improvement with this early initiation of physical therapy. But for the most part, they were able to show short-term gains in gross motor function for their patient group. And I think this is a really encouraging signal, and hopefully it's something that all units will be starting to practice.

Highlighting what we're doing here at Children's Hospital, there's a couple quality initiatives that are being led by our group, which includes Dr. Yuliya Domina, Tracy Baust, who helps with PC4 as well as with a lot of data collection for us, and our physical therapist started an early mobility implementation in the pediatric cardiac ICU.

So the goal of this was several-fold. It was to provide education to providers about how physical therapy services could be initiated and what were the benefits of those services. There was discussion with providers about recognizing the risks that invasive devices can bring for critically ill patients and how that may impact physical therapy, but looking at ways to overcome those barriers. And then also examining what was the use of those services after those educational efforts were made.

And they were able to see a nice increase in utilization of therapy services, and there was increased provider comfort with mobilization in the ICU setting. And interestingly enough, providers started to feel more comfortable with mobilizing patients that had invasive devices, which includes arterial lines and central venous lines. Obviously, more work will need to be done to see whether these efforts are going to improve motor outcomes. But I think these are great early efforts by our team in the cardiac ICU, and I thought it was important to highlight them.

In addition, the same group has been looking at the development and implementation of an in-patient neurodevelopmental program, which would span both the cardiac ICU and our acute care patients on the ward. The idea was to form a multi-disciplinary cardiac neurodevelopmental team to incorporate individualized and family integrated care.

So what do we mean by that? So education was provided to both the families and the staff regarding neurodevelopmental issues that are recognized in our congenital heart population as well as what could be potential benefits of therapies in this patient group. And then patients underwent neurodevelopmental assessment, and therapies were initiated if appropriate.

The early data from this shows that there has been improved awareness of neurodevelopmental issues in our patient population by initiating this educational initiative. I don't think it's surprising to see that the families are retaining the information better once they're out of the ICU due to probably the decreased anxiety. And people talk about trauma and PTSD that a lot of these families feel during their ICU stay, and I'm sure that impairs their ability to learn.

Again, we'll have to follow this up and see whether this makes a difference in the neurodevelopmental outcomes in our group. And especially for our highest risk patients, which are those in ECMO, we just had a discussion at the last ECMO meeting about ensuring that there is adequate follow-up, particularly neurodevelopmental follow-up for our sickest patients, meaning those who have required ECMO during their hospitalization.

And at last, I thought I talk to you a little bit about a discussion that I heard at the Pediatric Cardiac Intensive Care Society, which talked about some animal data. And it looked at a novel therapy to try to prevent neurologic injury-- at least I should say, novel to me. I think that this is something that's been looked at for a while, but has gained some steam recently. And that is there are some animal data that suggests that hydrogen, or H2 gas, may mitigate ischemia reperfusion injury by an antioxidant effect.

Essentially, there is histologic data which suggests that there is decreased cerebral edema and neuronal injury, and that these H2 gas exposed animals also exhibited improved scores with neurologic testing, which is one of the most interesting things is that people have actually come up with neurologic testing that you can do in mice and swine.

And obviously, there are some downsides to using this hydrogen gas, high concentrations, particularly above 5%, make this gas highly explosive. And so, there have to be safety mechanisms put into place to make sure that it can be done and done in a safe way that won't blow up the operating room. But I think that these animal data is interesting.

So there is one study-- in fact, there's several studies that come out of China, but one of them I found particularly interesting, which is using this hydrogen sulfide gas in a cardiac arrest model. So essentially what they did was they took rats, they induced ventricular fibrillation. And then they resuscitated the rats, and the rats were randomized to be a sham group.

So the sham group did not have cardiac arrest, but they had all the same other procedures that the rest of the animals did. The subjects that had cardiac arrest were either given standard care or standard care plus hydrogen gas. And then they followed those animal subjects up with neurologic scoring. They looked at their survival. And then they did a necropsy after a period of about five days to look and see what was the degree of cerebral edema and neuronal injury.

So what they were able to show, you'll see on this first graph, was that the patients with this kind of checkmark were the patients from the hydrogen gas that there was evidence of decreased cerebral edema in the patients that were exposed to hydrogen gas. I didn't show it here, but they also had markers of neuronal injury. And the hydrogen gas exposed rats also have less markers of neurologic injury. They performed better on the neurologic testing. And then also not shown here was that the survival after cardiac arrest was better in the hydrogen gas group.

So that's interesting, but does it really apply to us in our patient population? So it was discussed at the Pediatric Cardiac Intensive Care Society meeting was a study that was led by John Kheir at Boston Children's Hospital. You may know him for his work looking at essentially artificial red blood cells that will improve oxygen delivery, but he's also done some work with this hydrogen gas. And essentially what they did was they took neonatal swine, and they randomized the swine to receive hydrogen gas or standard care while being exposed to 75 minutes of deep hypothermic circulatory arrest.

So for those of you in the audience who are not in our cardiac group, deep hypothermic circulatory arrest can certainly lead to brain injury. And the longer the period of deep hypothermic circuitry arrest, for sure we know the greater the inflammatory state. And so they picked a significantly exaggerated period of DHCA in this patient group frequently. If hypothermic circulatory arrest has to be used, that time is always attempted to be limited and has tried to be limited into periods that are less than 30 minutes. So essentially, they picked an extremely long period of circulatory arrest to ensure that these patients were-- or I should say subjects-- were really going to have brain injury.

So the hydrogen gas was administered during pre-bypass anesthesia, during the bypass period, and then they kept the swine intubated for an additional 24 hours after the exposure to DHCA, and continued to expose the randomized group to hydrogen gas. The subjects were then extubated, and then they underwent testing, which included neurologic testing, MRI, and a necropsy to look at whether there was evidence of neural injury.

So little bit of a busy slide, but essentially on the top what it's showing is that the markers of neurologic dysfunction on testing were decreased in the hydrogen gas group. They saw that there was brain injury by MRI in the control group. And clinically, that subject group had a high incidence of seizures, whereas the hydrogen gas group had less evidence of injury, in particular white matter injury. And essentially, I think only one subject in that group had seizures. And then when they looked at the histologic injury score, the hydrogen gas group performed better.

While this is not necessarily ready for prime time, there's still a lot of work to be done, including safety work, there may be a time where we consider looking at human subjects testing for hydrogen gas in a variety of settings, which could include episodes that we know cause hypoxic-ischemic injury, which would be patients after cardiac arrest which could be outside of our general population, using this gas in the OR, in the ICU for patients that are in a low-flow state or after cardiac arrest. But this is still pie in the sky ideas. But I thought it was interesting, and I wanted to bring it to your attention.

So in summary, children with congenital heart disease are at increased risk for neurologic impairment. This includes learning disabilities, motor deficits, and behavioral problems. Although the early stage really focused on the impact of surgical advance and intraoperative management, we now know that multiple factors play a role in neurodevelopmental outcomes.

And really, there are several targets for initiatives in cardiac ICU care which may benefit neurologic outcomes, and these include how we're using our sedatives and which agents we choose, prevention of low cardiac output states and cardiac arrest, improved identification of high risk patients and early initiation of therapies, and maybe sometime in the future, novel therapies which may reduce the damage that's associated with these low-flow states.

I want to thank the group, in particular, the leadership in the Heart Institute. Victor, Jackie, and Vivek first for inviting me to speak, but more importantly, for believing enough in me to have me come here and join you as part of the team. Certainly would also like to thank the cardiac ICU team, who it's been really a pleasure to get to know over the last month. And I'm so looking forward to continuing to get to know you better. And then also the executive team at Children's Hospital. Thank you very much.