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It's my honor to introduce our speaker today Dr. Brandon Foreman. Dr. Foreman is associate professor of neurology and rehabilitation medicine, associate professor of neurosurgery and associate director of the neuro critical care research all at the University of Cincinnati. He doesn't really need introduction. I think most all of you already know him. But in any event, let me just say that he's is a very important pioneer in the field of neurocritical care and multimodal neuro monitoring making outstanding contributions to research, education, and clinical

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care. Please join me in welcoming Dr. Foreman to present pressure, volume, and flow filling in the missing piece of brain physiology and multimodal neuro monitoring. Dr. Foreman. [Applause] All right. Well, thank you guys for coming for the lunch and staying for the talk. Thank you Dr. Bowman for having me do this. It's a pleasure to get to speak to you guys on something that is really interesting to me certainly and hopefully it'll be interesting to you by the end of it which is cerebral blood flow and specifically blood flow in the context of multimodality

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neuro monitoring or bedside continuous monitoring. Let's see if I can get this to work. There we go. Here are my disclosures. I do have a couple disclosures on here, but the most important down at the bottom, you know, I work with Hemedex collaboratively, but this is I'm not getting any money for this. This is my own data, my own experience, and that's what I want to impart to you guys, of course. So no conflicts of interest with regard to the device we'll be talking about,

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which is the Hemedex device. But here are the three things that I want to go through. So one is to talk about the mechanisms of blood flow regulation as it relates to your patients in neurocritical care and how secondary brain injuries result from microvascular pathology in contrast to a lot of the larger vessel medium vessel pathologies that we think of. We're going to talk about the key role of cerebral blood flow, brain water content and brain temperature in relation to the mechanics of pressure flow and volume as it goes to the brain and particularly

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as it's disrupted after injury. and we'll talk about integrating all of this of course with clinical neuro monitoring how it interrelates with intracranial pressure and with brain tissue oxygen etc. So we'll start with the core of this which is how does cerebral blood flow impact contribute to and relate to secondary brain injury. As everyone is well aware because you all do this for a living secondary brain injury is incredibly common. It's about a quarter of all of our patients

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regardless of disease process and when it occurs it tremendously increases morbidity and mortality. A lot of the patterns that we think of as secondary brain injury, a lot of the pathophysiology we think of as secondary brain injury is extraordinarily common in and of itself. So if you look at things like elevated intracranial pressure, this occurs in some 90% of folks at some point or another during their course after traumatic brain injuries in particular. But other things that we consider secondary brain injuries such as low CPP or hypoperfusion,

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metabolic crisis, brain tissue hypoxia, seizures, spreading depolarizations, these all occur in far more than half of the patients that you take care of in the neuro ICU. But ultimately when I talk about secondary brain injury, it's an umbrella term, right? It means a whole bunch of different things. But there is a final common pathway. So regardless of which pathophysiology you're talking

about all these very common things that we see the underlying pathophysiology is really the inability

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of the brain to match its supply and its demand at the end of the day whatever the cause for that is and that's what results in neuronal cell death and ultimately functional and cognitive disability. Well, we know from pre-clinical models and I'm going to focus on traumatic brain injury, but what I do want to point out is a lot of the brain injuries that we take care of, including things like spontaneous intracranial or excuse me, aneurysmal subarachnoid hemorrhage all have very similar underlying microvascular pathology. Right? So, when we talk about diffuse injuries, a lot of

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what I'm talking about applies, but I'm going to focus on traumatic brain injury because that's my world. I live in Ohio and people drive very badly. So, I deal a lot with traumatic brain injury. In any case, so in pre-clinical TBI models, it's very clear that traumatic brain injury causes microvascular injury and specifically histologically there's evidence of micro thrombi of endothelial irregularities. When you look at people who have died from their trauma, they have capillaries with decreased luminal diameter. But they spare these larger vessels like

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the pial blood vessels. And in survivors with TBI, there's, you know, been some really nice studies from the Cambridge group that I'll highlight that really show that ischemia is quite common, but it doesn't look like you might expect it to look like intravascular micro thromboses. Some of these microvascular pathologies occur in such a way that they cause selective areas of neuron neuronal necrosis, islands of necrosis or stroke that occur throughout the brain. I sort of liken it to ARDS of the brain if you want to consider it that way. It's patchy. It's

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heterogeneous. And what the Cambridge group did is they looked at PET scans specifically for markers of ischemia such as oxygen extraction fraction, cerebral blood volume, and addition of cerebral blood flow. And they did this across some 68 patients over multiple days after their traumatic brain injury. What they found was there's a tremendous heterogeneity in regions of the brain, some of which are disparate or diff distant from the site of injury that show evidence of ischemia or changes related to increased blood flow and increased cerebral oxygen metabolism as

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you can see in that green circle with a decrease in oxygen extraction fraction versus other areas contralateral in this case to the contusion with low blood flow and increased oxygen extraction fraction suggestive of ischemia. Right? So this is happening in areas that are distant from or structurally relatively normal or healthy after traumatic brain injury. And in an earlier study from the same group, one of the things that was interesting to me is that the areas of ischemic brain volume where blood flow is low don't map on to the areas of hypoxic brain injury.

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So what you can see in the PET scans shown down below is they've kind of resolved or put in relief the ischemic brain volume there in the middle versus the areas of hypoxic brain injury there on the right and they don't match up. They don't line up. So it's not only the areas that are sort of patchy and heterogeneous in terms of the injury post trauma the secondary brain injuries but it's even the pathology that's occurring is distinct. So we want to monitor for secondary brain injury.

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How do you do this? How do you infer in fact that there is this underlying

process of supply and demand mismatch and ultimately how do you discern whether microvascular injuries occurred and how might you be able to treat it? Right? So where I'm at the University of Cincinnati, we try to do comprehensive neuro monitoring. And this is sort of the dumb schema that I think about conceptually in terms of what I'm monitoring. Essentially what we're trying to do is capture some measure of mechanics which is pressure and flow, metabolism, how's the brain using oxygen and

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glucose and function. How is the brain functioning when you can't rely on your neurological exam? And when I talk about multimodality neuro monitoring, what I'm referring to is access, clinical access, me being able to look at and discern a set of measurements that's directed toward identifying those secondary brain injury patterns that we want to try to mitigate. And to mitigate them, we want to use that data to guide us in individualized care. And there's consensus about this,

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right? We did an eDelphi consensus process really aimed at what is multimodality neuro monitoring. When I say that word, what does it mean? And it might mean different things to everybody in the room. You have different equipment than I do for instance or maybe you use things non-invasively, preferentially. Doesn't really matter. What we wanted to know is how do you define it? And one of the core pieces is not just how you define it, but how do you decide it's going to be useful for

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you? And one of the key things of course everyone had consensus about is this kind of data, this kind of monitoring is really the most useful for patients who are at risk for those secondary brain injuries. And the purposes again there was clear consensus which I thought was interesting is not only guiding individualized management, but there at the bottom you can actually see abstaining from or deescalating potentially harmful management. And that's really critical. You need to understand

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what's going on with the patient in order to give them the right therapy and not a potentially dangerous one that they don't need. So if you want to measure microvascular injury or more I guess generally you want to measure cerebral blood flow there's a number of ways to do this of course that we're all familiar with but they all have problems. So our radiographic measurements of blood flow obviously are intermittent. You can get them once every couple of days once every day

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if you really want to radiate people or if you have a PET scanner in your ICU. That's awesome. You can do that as much as you want, but most of us don't. And so there's a lot of elegant ways to measure global and local blood flow in, you know, using these techniques radiographically, but they're not practical for monitoring. I can't scan someone ahead of their secondary brain injury. I want to know when it's developing, right? And so there's a lot of continuous measures

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that we often use, but these all infer blood flow. So they're not a direct measurement, right? So TCDs are velocity, not flow. If you look at things like the brain tissue oxygen monitor, it certainly has a component of blood flow that mediates the oxygen delivery and content of the interstitial space, but it's not a direct blood flow monitor because there's other aspects of that particular measurement. And things like EEG can be very useful for long-term ischemia monitoring, but

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there's a lot of complexity in terms of how the EEG and cerebral blood flow

interplay or interact. But there is there's one monitor and that's the Hemedex course who's sponsoring this lunch that actually does allow you to measure continuous cerebral blood flow from a region of brain using the catheter that you can see here. So the way this regional blood flow works is continuously measured and it uses the principle of thermal diffusion flowmetry. And what that means is you've

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got an active self-heated thermistor and it tracks the thermal dissipation of that heat measuring the power that it takes to maintain constant temperature at that thermistor. And then there's a second one that tracks the temperature of the baseline temperature of the brain to compensate for changes in temperature. When you place this, you put it into the skull, usually through a bolt. That's how it's anchored. And it sits some two and a half to three centimeters below the inner table

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of the skull, typically in subcortical white matter. You can see in panel A there that it's in this scout film that it's sits in an area that sort of reflects a voxel of about 3 cubic millimeters excuse me, centimeters. And so you're getting a regional area of blood flow. You're not getting the individual capillary beds obviously you're getting an aggregate of the blood flow in that area. And if we've talked about you know these small patchy areas of necrosis and ischemia that occur you're capturing an aggregate areas of patchy heterogeneous abnormal blood flow

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using this catheter as close as you can get it. In panels B and C you can see where the catheter sits. They're in kind of the purple and the axial and the coronal films. They're sitting right next to in this case several other monitors that you'll see kind of throughout the talk including intracranial pressure, brain tissue oxygen, microdialysis, etc. There's not a whole lot of centers that actually use the blood flow monitor. In one survey, it's only about 5% of centers globally actually use thermal diffusion cerebral blood flow or the Hemedex device in

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clinical care. There's not a lot of publications on this stuff either. And so there's been in total in a systematic review from Frank Zeiler, at all you know about 150 patients in the literature of which we ended up studying about a fifth of those ourselves. So there's not a lot of data and its utility therefore is a little bit challenging to figure out what to do with the cerebral blood flow information given its complexity and that's what I want to impart a little bit about

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and empower you to better understand how this relates to our multimodality monitoring. Well, what do we know about cerebral blood flow in particular after trauma? There's been you know a number of studies using this intermittent radiographic data of cerebral blood flow after trauma that suggest that there are three phases or three kind of typical phases that occur after trauma. One is the hypoperfusion phase which occurs during that first 24 hours or so. So you get a traumatic injury and your blood flow is actually decreased for a period of about 24 hours

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after which you get a hyperemic phase for the next you know two three four five days and subsequently you enter this what's called vasospasm phase and it's distinct from aneurysmal vasospasm in many regards but it is considered a vasospasm phase but even though you know patients with TVI have lower global cerebral blood flow than controls say low blood flow in this context does not equal ischemia, ischemia is defined by your oxygen extraction fraction and your CMRO2, right? And that's a really really key distinction. So while you've got this blood flow absolute blood flow

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measurement, it really needs to be interpreted in context. And one of the big contexts is if you take a healthy brain and you block off blood flow, stroke, right? Then what you find is that the ischemic core is very clearly related to cerebral blood flow, your cerebral blood goes blood flow goes down to zero you have an ischemic core those are clearly related but in traumatic brain injury it is a little bit different so this is from Lonni et al that's part of that that paper I showed you

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earlier with the PET scans from the Cambridge group and what they're showing is the y-axis has the ischemic brain volume that they were able to measure over time on the x-axis, so you can see the bulk of or a large proportion of the ischemic brain volume developed in the first couple of days. But there's ischemic brain volume, the dots that are above that dash line throughout the 10-day period they monitor these folks. So ischemia develops, secondary brain injury, right, is what they're picking up on develops for more than a week after traumatic brain injury in

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some cases. But if you overlay that blood flow that we were just talking about, right? So blood flow now is on the other y-axis represented by those colored dots that we just looked at, what you can see is the ischemic brain volume does not match up with the absolute blood flow, right? In fact statistically there was no direct correlation between the two and so the question is why? if I have a stroke I know my blood flow and it decreases causes you know ischemic infer why does the same thing not happen in TBI and the answer is probably because there's normally

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multiple regulatory mechanisms that direct your blood flow in a way that is you know very stable and very tied to your metabolic demand. But when you injure that when you disrupt the supply and demand matching that occurs during, you know, with normal brain you end up with a much more heterogeneous response. You end up with something that's not a one-to-one CBF to infarct sort of response. It's not uniform. When you have nice uniform flow and you block it off, you create infarct. If you have nonuniform heterogeneous flow, it's going to cause all kinds of problems,

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but not in a way that you can reliably predict. It becomes a very complex system. Part of the complexity as a result is that studies have clearly shown that both high cerebral blood flow and low cerebral blood flow both appear to relate with poor outcome. So again, it's not a one-to-one relationship. You've got these regulatory mechanisms that have broken down leading to much more complex cerebral blood flow problems that variably cause other issues such as edema or ischemia or hypoxia. And so both low and high are associated with unfavorable outcome.

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Another complexity is it depends on where you're measuring. The blood flow in different tissue is quite a bit different. So if you're in subcortical tissue, the blood flow is at baseline lower and the ischemic threshold is quite low. It's less than 8 mills per 100 grams per minute. We're all used to seeing these beautiful CT maps, right? Where the normal cerebral blood flow is somewhere on the order of 25 or so. That's cortex. This is the spread of cerebral blood flow data that we've pulled from our patient populations, some 120 or so patients. In this

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case, the histogram of all of the blood flow measurements that we have taken over the course of care for these patients and this is sampled every second. So it's tremendous amount of data, but you can see the histogram here. There's a

clear peak in sort of the normal cerebral blood flow range, but this long tail of hyperemia and a proportion of patients with ischemic brain volume. There was a study from Kelly some years ago and they kind of highlighted that there's not really a clear correlation between CBF being low and poor outcome such that you get, you know,

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better outcomes as your CBF gets higher. And so, you know, there's a little complexity here, too, because the question becomes, so well, what do you do about blood flow if it's too high, if it's too low? How do I know for that patient if it's too high or too low? And so when you look at the very, very low blood flow and the very poor outcomes, you can see that really there's not a clear, if you put a linear regression line across this, it's basically zero, right? And I'll show you an

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example of why blood flow and ischemia don't necessarily match up and why blood flow and outcome don't necessarily match up directly. It's because you're dealing with dynamic physiology and you're dealing with this heterogeneous disregulated blood flow. This is an example actually from a publication of ours that shows the on top the series of CT scans from a young patient with traumatic brain injury. His admission CT scan you can see there at the level of the central valley and on post trauma day two he's come up to us in the neuro ICU and we put in a multimodality

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monitoring bolt because he remains comatose and on the scan we were surprised to see these areas highlighted in the white triangles rather of frank hypodensity I didn't aggressively window this I promise those are actually chunks of really hypodense tissue and when we started recording in panel B there. That's our multimodality neuro monitoring recording over 4 hours. The first thing we noticed is that the brain tissue oxygen was lower than it should be. The CPP was actually within a normal range as was the ICP, but our cerebral blood flow was absolutely in

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the toilet. It was as low as you can go, right? It was very, very low below the ischemic threshold. And so the decision was made to raise the CPP as a first try to see if we could improve things. And we can see over the first two three hours as we start a presser which is there on the red arrow is that the cerebral blood flow markedly improves. There's a tremendous improvement in not only the absolute blood flow but also the variation of that blood flow and within a day or so repeating the CT those hypodensities went away. Right? So again this is a very complex sort of

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pathology when you talk about microvascular flow and microvascular flow disruption. So pressure, volume, and flow is what we're talking about in part because all of those components go into how you're percolating blood through the brain in the capillary beds, which is what you want it to do. You want it to percolate through capillary beds. And so this is really the focus. And I'm going to turn your attention to something completely different for a minute to make this point. I'm going to talk about espresso because I love espresso. I

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don't know if you guys like espresso. I'm sorry about the coffee. It's not espresso. But making espresso is this really beautiful art where you grind coffee and you press it tightly into a puck. It's almost solid, right? And then you slam it with 130 pound force per square inch or nine bar and the water percolates through this puck and it picks up all these beautiful coffee chemicals and spits it out into your cup. And that's how you get this wonderful delicious syrupy espresso, right?

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So you start with your grinds, you tamp it into this solid thing and you percolate the coffee out of it. So pressure, volume, and flow is what you end up kind of dealing with. And you can graph it, which is really cool. This is actually a shot being made where you stick the puck into the espresso machine and turn on the lever. And in green you have, of course, I have a graph, right? In green you have the pressure. This is what happens when you start your espresso machine. Pressure ramps up to nine bar and that's in green and there's a flow. In order to get that pressure,

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you start pouring water into onto the puck and the pressure builds up because the puck is this very solid thing, right? And so you can see the flow there in blue. The flow is consistent as the pressure starts to build up and at some point that flow begins to go through the puck. The pressure builds to the point where it can shoot its way through this puck. And what you start to see is the pressure begins to decline. As the puck, which initially has a lot of resistance in yellow there, the CVR in this case is the analogy I'm going to make. As the resistance builds first and then

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goes away, that water starts to go through the puck more and more easily, the pressure begins to decrease. And you can see the volume of what's in your cup increases at the same time down there in the bottom in the blue and maroon. Right? Does that make sense? Everybody buy that? So, let's make an analogy now. And I've got it labeled up there. Right? Let's say the pressure is your arterial blood pressure 130 millimeters of mercury and as that increases right you have some flow that's going through your brain as it gradually sort of progresses there's a period of

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time where maybe it falls just a touch at the top of your pressure but I don't think that happens in our brain but it consistently flows through and the pressure begins to decline as it gets to the other side because you've gone through this porous medium of your brain tissue picking up all the solutes and the delicious chemicals that exist there, right? And you come out the other side with a brain volume or a blood volume rather on the other end. But this is a porous media problem

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and this is modeled in other disciplines actually in which you want to optimize the pressure and the flow and the volume. And so in coffee, the goal is to have this beautiful even distribution of water going through these water channels that develop in the puck when you get it hit it with enough pressure, right? And that gives you even extraction. You're pulling out the same amount of chemicals for every drop of water that's going through there. But here's the problem. If you kind of mix up your coffee grounds poorly, you have some areas where the water just finds a

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channel and shoots through and it doesn't pick up any coffee chemicals except for like the really bitter, nasty ones. And then you have other areas where the water just can't get through at the same time. And by the time it finally exits, it has picked up every nasty chemical it can find in your cup. And so when you go too fast, it's called under extraction. It tastes sour and disgusting. And if you go through way too slowly, it tastes just bitter and tannic. But if you have flow that's fairly even going through the entire puck, it's really this nice, delicious balance,

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right? So slow flow and high flow both in this case actually lead to something that we don't want, right? We want nice homogeneous flow picking up the same amount of chemicals, regulating what's coming into that cup. And that's what your essentially what your brain is, right? It's a porous media problem. It's a puck, it's a puck of coffee. That's your brain. And these dense capillary beds,

right? Blood has to flow through those. It has some ready-made channels, which is

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great, but they're all very tiny, and pushing through them is going to depend primarily on pressure. And so, you've got to flow through that capillary about as evenly as you can because if you don't, then you end up with some significant problems and specifically the microvascular pathology we've been talking about. So normally you have many of these regulatory mechanisms helping this flow to be fairly homogeneous. You have things like autoregulation. You have things like your sympathetic tone. You have vasodilation from things like carbon dioxide and of course

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your CMRO2 your neurovascular coupling is going to mediate how much flow is going through these capillary beds to modulate how much is nicely and homogeneously flowing through there. But if you disrupt that for any reason, if you traumatically injure that capillary bed, the microvasculature, now you've got areas where you can't flow through or you're flowing way past it and it's going too fast and you can't extract the oxygen you need or you extract every bit of oxygen because it's

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just sitting there in the capillary bed. And if you aggregate all those areas where you're not getting enough oxygen or you're flowing too fast to have any sort of ability to extract the oxygen, you end up with diffusion hypoxia, right? Or you end up with areas where you don't have enough flow altogether and you have ischemia and this phenomenon has been termed capillary transit time heterogeneity. You see it all on CTPs all the time. But this is happening at the microvascular level and it results in a lack of homogeneous flow and you can't generate normal

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physiologic pulsatility and variability. You can't get rid of the nice interstitial fluid that normally flows with that pulsatility, right? And so you have lymphatic dysfunction. All of this stuff results from the microvascular injuries that we don't see and have trouble measuring, mitigating, and detecting, right? In our clinical care, CBF is super tightly regulated, but it can't regulate itself when you have capillary tissue transit time heterogeneity. The regulatory mechanisms that I just mentioned, you can't actually see if you're monitoring the

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brain and specifically if you're looking at blood flow signals directly. And so, I'll show you an example of this is a multimodality monitoring panel over six hours. And each of these different lines is a trend for a different measurement that we're making. And red's heart rate, orange is arterial blood pressure, etc. You can see the labels there. And so we can see all these regulatory mechanisms in action. And of course, how they become dysfunctional. So first box here, this is a heart rate that is becoming more variable. There's increased autonomic input

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presumably, right? So if the heart rate is going from relatively flat to a little bit more variable, you can kind of intuit it that there's some sympathetic change. The CBF which is in purple that's what we kind of focus on that's fairly normal and it has a fair amount of variability itself right so there's this nice rich frequency content if you look at it under the microscope or just zoom in you can see what that looks like right you've got arterial pulsations in aggregate across these capillary beds that you're measuring from ultimately. But

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then you have decreased CPP that results from a big spike in your ICP right and

when this occurs you have a decrease in your cerebral blood flow as you fall below the lower limits of autoregulation and that's creating a change not only in the absolute value of the CBF but also the frequency content of that CSF becomes sort of attenuated. You've got some CO2 reactivity down in the blue you can see the CO2 let me get to it I don't highlight it that's okay but you can see the CO2 actually drops as well and when the CO2 drops the depth of the change

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blood flow actually becomes markedly more conspicuous. Right? So your blood flow drops with this lower CPP. You blow off your CO2 and it drops even further and there's a complete blunting of or cessation of those arterial pulsations as you get to the ischemic range. All right. Oh, I do highlight it. Hey, look at that. All right. As the CO2 comes up, there's an increase in the cerebral blood flow to some degree. Autoregulatory dysfunction which you can see down in the auto the orange box that's the PRx or the index of autoregulatory dysfunction

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we happen to use confirms that blood flow has fallen below that lower limit of autoregulation and so we try to get that back right so we've talked about several of these mechanisms from sympathetics to CO2 to autoregulation there's also neurovascular coupling and so the EEG in this case the suppression ratio starts to go up the CMRO2 is actually probably lower so our blood flow recovers it gets up to normal it's still kind of blunted in terms of the variability there until our suppression ratio starts to become zero again. In other words, you have less sedation on board,

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higher CMRO2, and now our blood flow has gotten back to where it's fairly variable in a normal physiologic way. It's within range, right? So, all of these different regulatory mechanisms are all combining and contributing to what's happening to your blood flow signal. It's not as simple as saying that's an ischemic blood flow. There's a lot of dynamics to consider and that's actually a fun part of all this, right? Is that you see this stuff in real-time and you can

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manage it or address it. One of the barriers to microvascular flow of course is also external or you know extrinsic compression and other factors such as edema and intercranial pressure elevations and things like this that all contribute to cerebrovascular resistance. And this is a term that it reflects the relationship between CPP and cerebral blood flow. You can only measure this of course if you have actual blood flow measurements. And so if you do this, if you measure the CVR and you look at how much time you spend with a specific resistance, so the higher the resistance,

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the more difficulty your blood is having getting through, right? So you're blasting pressure into the puck and it's not getting through, right? But the more time you have with an elevated CVR, for instance, there's a correlation potentially with poorer outcome, which is indicated by the colors that get closer to red. You guys are all familiar with these heat map plots probably from work from Giza at all that have been replicated over the years. The idea is the burden of or a dose of elevated cerebral vascular resistance seems to be portend poorer outcome. In blue there

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are the patients who have a cerebral vascular resistance and actually did well. Right? So there's a correlation with better outcome and that seems to be a stable cerebrovascular resistance of about three to five. And then if you have very low resistance the flow is just you know going through these channels you've got shunting essentially through those capillary beds at least in that region of the brain those also had an association poor outcome. So now you've got you know not only

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the flow but also the pressure that kind of comes into play. One of the aspects that you know cause a lot of problems with regard to pressure and flow in our TBI patients of course is cerebral edema. The water content of brain can actually be measured through the same device that you're measuring blood flow. This value that's measured is called the K constant if you will the thermal conductivity. Basically it's a measure of how efficiently heat is moving through any material in this case the brain. It's a physical property of everything you have a K constant. But it varies

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with the composition of that. Of course brain is you know brain tissue but that includes lipids and it includes blood and it includes all the other stuff that goes into the brain. It also varies with temperature and things like this, but you can measure that and it gives you an idea of how much water is in that substance you're measuring. And of course, that's an analog of cerebral edema, and so you can measure this as a K constant and sort of transfer it to this percentage of brain water

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content. Normal brain water is, you know, 2/3 70% of your body certainly and your brain as well. And after injury that can increase and it averages somewhere in the order of 77% brain water. That's edema. And that's been shown in the study from Sang-Bae Ko who actually helped develop this value or measurement. And what you can see is as the brain water content really goes above 72-73. It has a much clearer association with cerebral edema than when those K values those brain water content values are lower. And this is a dynamic measurement. So this gets generated every time

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that the Hemedex probe recalibrates. So you have a blood flow signal that'll record for 30 minutes to two hours at which point it says let's make sure we're accurate. Let's make sure we're compensating for things like temperature changes and it measures the K or conductivity at that moment. And so every 30 minutes to two hours you have a K value representation of the water content of the brain. So in the red line there that's kind of an imputed so to speak K value. Just kind of highlighted the course of the K value that you can see over time and in this particular

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patient with traumatic brain injury of course what you can see is the K value is going up as in green the intercranial pressure is really becoming quite refractory and in the where did they go oh there we go in the vertical lines you have some interventions right and so the first vertical line actually has hypertonic saline administered here for this massive elevation in ICP and the ICP gets better and you can see the K constant actually falls which is what you'd expect right you want to

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be able to treat brain water or cerebral edema but the ICP goes right back up in this patient with a refractory intracranial hypertension they give another bolus of hypertonic saline you see it does nothing right this is actually really important if your treatment is not helping time to move on to something else right the only way to measure this you can't get someone in the CT scanner every hour on the hour and so in this case we were able to do other things and so we gave Diamox which as

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you expect probably didn't do anything and then finally required a pentabarb bolus to get the ICP under control and that stabilized this K constant kind of throughout their course. If you look at aggregate, if we when we pulled all the K values in our TBI patients, you can see this time trend from hour zero to hour 120 or so after traumatic brain injury, there's a clear peak in the K

value and it happens at about hour 55 to 60, which you know that's the mantra that we're all taught,

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a cerebral edema peaks at 2 or 3 days after an injury and there is an aggregate response to hypertonic saline, but there's only about 50% of the folks that we looked at who had hypertonic saline that responded. That means 50% of the folks didn't and that's really critical information, right? Here's another example where our ICP is actually fairly normal. So this is a very long recording. This is 12 hours of recording and in green you can see the ICP is pretty low. It's below this horizontal line which is sort of a line or threshold of elevated ICP. And despite

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that there was this sudden change here at the red line where you can see the NPIs mapped here over time suddenly change and the left NPI drops to zero. That's what happens at that red line. And so the team was alerted and they said well IP is normal but geez okay let's give hypertonic saline. And they did which is great because they were able to reduce the cerebral edema that was pressing on that aspect of the brain that we were measuring. It wasn't a pressure phenomenon necessarily. It was an edema phenomenon. But they had a decompressive hemicraniectomy. So

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this is a patient where blood flow is really the key thing here. And edema is the key thing here because that's going to cause the mass effect that presses against the midbrain. But it's not going to create a pressure situation just yet until it reaches critical mass. And the blood flow right above it you can see goes up which is what you would expect. You increase flow in that area too. Now these probes as I mentioned you know the ischemic threshold is different in some cortical white matter versus gray matter. The amount of water in the tissue that's subcortical versus

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cortical is actually different as well. So you have more water natively in the cortex. You have big bags of neurons with water in them, right? And so the other kind of function of the K constant if you will is that you can tell where your probe is. So if you're measuring a blood flow value of 12 in subcortical white matter and you know it's subcortical white matter, that's probably okay. But if you're measuring a CBF of 12 in cortical gray matter and you know it's in cortical gray

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matter that's probably not as okay, right? So you have different thresholds depending on the tissue and being able to intuit that or infer that is actually really helpful. So this is a patient over this is I think a day and a half of monitoring and you can see their K values are mapped down here. They're 5.2 two, they're right, you know, their edema, right? The water content's above 72% and it is increasing as you'd expect, but it's low. And then there's this sudden jump after they've

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been manipulated. And unfortunately, the catheter actually migrated a bit more superficially. The K value jumped and it's actually up in now what is cortical gray matter territory and continues to increase. So that edema, the same edema that's been happening the whole time continues to happen. It's just your baseline has changed because your tissue type has changed. That's actually really important. It's not that difficult to figure out. There's two very distinct distributions of K

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values in the white matter versus the gray matter and there seems to be a dividing line. If that K value is above 5.36 or so, you're probably in gray matter and you can sort of interpret things at that point differently if it's

appropriate to do so. The normal brain water contents differ, the ischemic thresholds differ not tremendously. The trend is really critical and you can use that trend but this gives you additional information that can help you interpret that data more clearly if you use that sort of idea of there's a different ischemic threshold there's a different

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edema threshold and map the time you spend with elevated ICP for instance here in a or the time you spend with hypoperfusion or the time you spend with brain tissue hypoxia or autoregulatory dysfunction these pretty clearly correlate with tissue specific edema right. And so I think that's a key thing as well. Edema, just like cerebral blood flow, is something that you want to try to optimize. And blood flow in general, whether you're in subcortical white matter or gray matter, again, this blue band or the patients who had a correlation with better outcome really is,

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you know, it's important to be in the middle, not too low, and not too high. And so there's these thresholds of ischemia and hyperemia that you can see correlate with poorer outcome out here both in subcortical white matter and in cortical gray matter as well. So Hemedex has been working on a number of different visualizations. How do you visualize this relationship between cerebral edema and ischemia or blood flow hyperemia and edema ICP? How does that relate to the edema that's happening right now or the hyperemia that you're seeing? Is

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that an ischemic tissue causing your ICP over time to rise? And so there's a number of ways that you can identify this stuff in real time in patients. And this is a kind of an example of a couple of different ways to look at this. In the first graph I'll draw your attention to. This shows you low in blue normal or you know kind of middle-range blood flow and in yellow hyperemic blood flow. And you can see in this particular patient, this is a patient with traumatic brain injury. In this

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particular patient, they have a pretty broad range of hyperemic and ischemic CBF that's been measured, you know, again, every second continuously over time, but their proportion of time is not super high outside of these ranges. In fact, you know, it's about 90% of the time they're in this kind of middle range. If you look just below that, you can see a plot of how the CBF looks over hours. In this case, you're going on three and a half days. And here in red you can see the blood flow and in blue underneath it you can see the K value. So for this patient the blood

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flow which the axis is over here on the y- axis to the right is actually pretty normal. There's a lot of variability and the K value is rising as you would expect for someone with evolving edema. But their blood flow is preserved and fairly normal throughout most of this course. And that's a really important thing. You can have edema but as long as you're preserving your blood flow that's probably okay. You're getting through those capillary beds potentially. On the upper side you

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can see the kind of relationship between how blood flow is impacting edema. So again, are you having ischemic tissue that it's edematous because it's ischemic or are you having hyperemic tissue that's edematous because of the you know oncotic pressure that's shoving water and solutes outside of the cells into the interstitial space and we can see on average is that the K value in this particular patient you're in white matter those K values are lower than 5.36 and there is a relationship

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wherein low in blue low blood flow values have a higher K constant or higher brain water content higher CBF values hyperemia has a higher K value. And then the sweet spot here in this case, the middle range here, the average in that middle range of 30 ms per 100 grams per minute has the lowest K value. Right? I'm not going to call this a CBF opt based on the K value, but that's kind of you might want to think about it that way. And then down on the bottom, what you can see mapped is the ICP and the cerebral blood flow. And there's kind of four quadrants. There's low flow

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and high ICP. Low flow and normal ICP, excuse me, low ICP and normal flow. So, I got my axes mixed up here on the Y- axis is CBF. So, normal flow, low ICP, low flow, low ICP, and then over here, high flow, high ICP, high flow or low flow, high. Does that make sense? You got four quadrants. There you go. It's kind of like BOOST. Think about it like BOOST, right? Is that okay? Can we think about it like BOOST? ABC and D. All right. But what we can see in this particular patient is they're all in the good quadrant. This is the A quadrant. Your ICP is normal. CBF is normal. This

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patient did really well. They had a GOS of five at 3 to six months, which is fantastic. Okay. Contrast this visualization with another patient. Same visualization. In this case, you can see the values of CBF have shifted. There's a lot more right around this sort of lower CBF range about a third of the time they spend with ischemic brain tissue. You can see here that initially in that first day there's a CBF that's normalish. It's variable. And then look what happens. This thing

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just tails off. Your CBF is becoming essentially ischemic. But what confirms this is that K value which again is in white matter goes up in a delayed fashion. So just like you have stroke and then you have edema that occurs a day or two later your secondary brain injuries will cause a delayed increase in cerebral edema and that's exactly what you're seeing here. So you can see this ischemia developing over time and then you can see the manifestations of that occurring over time. The mean K values again sort of map onto this idea of if you're hyperemic or ischemic it does

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create cerebral edema. And if you look at where they're at in terms of their ICP versus CBF, they have a lot more time spent with a higher ICP and a lower CBF. This patient, of course, didn't do so well and they ended up dying at the end of their course. So, if I say, you know, this is complex, you get the idea. But the dynamics are there and they're easy to see if you can monitor that stuff continuously, which is why I really like having those measurements. And high and low CVF, as I mentioned, don't seem to correlate with outcome too much. But if you look at this scatter

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plot I showed you earlier where that kind of suggested that there's all these values with the black arrows and those are actually times in which the high blood flow correlated with high ICP and if you take those away if you just talk about blood flow the relationship is a little bit more linear with outcome. So what is it about those hyperemic intracranial hypertension patients that's a little bit different and what I would suggest is it's autoregulation and of course the center TBI folks and others have pretty clearly shown that when it comes to ICP the thing

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that mediates at least mortality seems to be the preservation or disruption of autoregulation as you can see in these two panels if you have intact autoregulation your outcome in terms of favorable and unfavorable is about the same regardless of your ICP as it increases over time in contrast if you have autoregulatory failure there's very clear split where an ICP you know tends to

be different in those with unfavorable versus favorable outcome. So pressure autoregulation is another really critical thing that you can see with cerebral blood flow measurements in a way that's

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a lot more direct rather than sort of inferring it with the assumptions that we make. In this case, if you look at the a panel over a couple of hours in a patient with again traumatic brain injury, they have an ICP that's elevating at the same time that their CPP is actually falling, right? And presumably that CPP is falling below the lower limits of autoregulation, which is part of why there's vasodilatation as you can see from the kind of standard Lassen curve sort of thing that we often think about neurocritical care. you move your blood flow or your CPP in this case down

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toward the lower limits of autoregulation. You have vasodilatation, you have increased blood volume, you have increased ICP. So we think that's happening but if there's vasodilatation why is there not an increase in blood flow like hyperemia and all this other stuff or at least why aren't we maintaining our blood flow right you actually see the blood flow drop which really kind of hits home that that is a lower limit of autoregulation that you're falling off of in this particular case. So in this patient we start at pressors the CPP goes up. We push ourselves onto

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the autoregulatory plateau or ICP comes down but look what happens to our blood flow. it is restored very very nicely and even once we blow off some CO2 the blood flow is preserved. So you know in this setting we can really see where we're at on the autoregulatory plateau. You can map it actually as well. The actual Lassen curve right is CBF on the y-axis and map or CPP on the x-axis and that's this is from a single patient you can very clearly see where their autoregulatory plateau is

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right they have a lower limit below about 70 and an upper limit above 85.In an aggregate you can show this certainly it doesn't have to just be one patient although that's what you would be looking at presumably at bedside right you'd be looking at the autoregulatory plateau of any given patient. And we often think about autoregulation as dynamic not static so when I say static I mean there's you know, a longer change in blood flow or CPP in that particular patient over 5, 10,

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15 minutes. And that's what we're kind of looking at and treating with regard to those changes in ICP. But a lot of what we measure or consider autoregulatory function is based on dynamic measurements. And what I mean by that is they're short interval measurements. So if you take a look and zoom in on the ICP and the blood pressure, you can see that there's these kind of fluctuations that occur every 30, 40, 50, 60 seconds, right? This is normal physiology. These happen, but they

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are nice little tests of autoregulation, right? When you suddenly change your blood pressure, something is going to change with regard to flow and presumably volume and presumably ICP. Which if you look at those two together and correlate them, that's called your PRx, which you're all familiar with probably at this point. And if those are not related, that's great. You probably are autoregulating. So that blood pressure can do whatever it wants and the ICP is not necessarily going to go with it. On the other hand, if they're going together, as you can see, in this particular

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case, your PRx is high because they're more correlated. And you can do the same with cerebral blood flow. It's very similar kind of thing. You can we called it

a CBFx when we looked at it. But you similarly can generate an optimum CPP or a place at which the autoregulatory function at least that dynamic autoregulatory function is sort of optimized. And just like in you know the studies from the Cambridge group defining the PRx and showing that it tended to reflect an optimum CPP of around 70 to 80. You can show the same thing with blood flow measurements directly and

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they change over time with patients. They differ between patients. So it becomes really important the more direct you can actually figure out what your auto regulation is honestly the better right and at the very least it's fantastic corroboration of this more indirect measurement that we often make as through the PRx. Very quickly I'll talk about brain temperature because the Hemedex does measure brain temperature. It impacts things like cerebral edema. that impacts things like CMRO2 which can drive blood flow. So it ends up being important. This is a histogram of more than

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200 of our patients what their temperatures look like. These are all of your patients. Many of them have fever. Most of them are normal. It's a nice Gaussian almost distribution which is fantastic. But it is really important actually to know what your brain temperature is doing because it does impact a lot of these other things. Not just blood flow but if you're affecting edema for instance, you're affecting your ICP, right? So this is a patient who came in with a pretty severe brain

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injury and got decompressed and what you can see is that the temperature in this patient goes up very fairly rapidly and pretty profoundly. He's got massive fever that develops and at the same time the EEG as represented by the alpha delta ratios here slows way down. Right? So you've got cortical dysfunction that's occurring as a result of this fever. your CMRO2 has increased dramatically but the actual cortical function has slowed precipitously and that's because you've got this metabolic vulnerability that we've been talking about supply and demand mismatching

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they go on to depolarize right so temperature is really really important it's metabolically very impactful. Here's an example of how this looks in another patient who we've got microdialysis there in black including glucose measurements and glycerol and in the red arrow we actually gave there some insulin had been given just as part of a routine order set unfortunately and you can see that the glucose actually dropped unfortunately and at the same time there's this massive fever

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that develops substantially higher than the core temperature represented down here the dash line's on the same place so the core temperature actually is barely febrile look at the brain temperature it's massive right so you got two pretty profound metabolic insults that are occurring at the same time which is really really I think important to be able to recognize some of these things. There's a transient rise in glycerol that happens suggesting there's even some neuronal breakdown

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that occurs. So fever is really important. It impacts not just blood flow but all of these other parameters as well. And knowing that this is the problem. It's brain fever, not core fever. This person has a temperature 383. No one's doing anything about that. But when your brain temperature is 39 almost, that's a big problem. And these can happen if you're not measuring the brain specifically. The ICP also increased slowly over time as you can see here. I mean this was not a benign thing and when the fever improves all that other stuff tended to

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look a lot better including the glycerol and the ICP and everything else. But sometimes the brain temperature is lower than the body temperature and that can be a sign of something like mitochondrial dysfunction. If you're not using your mitochondria to create the energy you need, you're not generating the thermal reactions that those infer right and so you actually can see that as well. This is a day's worth of recording. And what I want to highlight here is that the temperature in

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the brain is actually substantially excuse me down here the temperature in the brain's riding along this dash line you can see the temperature in the body is actually much much higher interestingly enough and if you look at the blood flow it is profoundly low but this patient wasn't ischemic if you look at their lactate pyruvate ratio it is very high it's 40 or so which is around what we get concerned about for ischemia but the pyruvate is actually high they're not using any of

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the pyruvate this is a patient who's profoundly metabolically suppressed and their CBF is low, their temperature being different than their core temperature actually kind of tells that story. But you have to have all of that sort of information to be able to tell. All right, as we're getting on in time, what I want to do is move toward some of the CBF dynamics that we often see. But I am going to skip over a few cases and just highlight some of the things that that I wanted to show when

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you're looking at this data in real time, you'll start to see a lot of different relationships that again I think are really important if you're going to make a management decision for like carbon dioxide levels in your patient, right? You want to know that you're not blowing off too much CO2 causing ischemia for instance. So it becomes really important to see things like CO2 reactivity that can develop over time. Things like this fluctuation in end tidal CO2 which are clearly

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impacting your ICP become important to see. And in this case, you know, we decided to hyperventilate this patient with these big ICP elevations and look what happens to our CBF. That was not the intervention for this patient, right? So those dynamics become incredibly important. There's dynamics that that can inform what's happened to a patient who's suddenly gotten worse. In this case, their CBF is relatively normal. And then an event happens where our ICP suddenly spikes, our lactate pyruvate ratio jumps up, our glycerol jumps up. So we have someone who's got profound

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metabolic crisis, ischemia, neuronal breakdown, massive elevation ICP and their CBF. If you look before that event and after they've clearly become ischemic and the question is what in the hell happened in that particular case, well they got an EVD right before all this happened and in fact you know they developed a pretty substantial hemorrhagic conversion of a contusion there. So you know that sudden change to ischemia even in the absence of microdialysis tells you that something has clearly gone on. There's been a pathophysiologic change. So with that I'm

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going to move on a little bit to individualizing management because I think that's the other key piece of this and I'll show you one last case and then we'll wrap up. This is a patient who has as you can see a right-sided bolt. We've got a whole lot of monitoring here including heart rate, blood pressure, ICP, etc. And what I want to point out is the CBF here in purple. It's riding pretty high above this dash line which in this case is hyperemic and at the same time their PbtO2 is

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below the dash line which is hypoxic. So you've got hyperemia and hypoxia, right? So what's happening? Are we dealing with that shunting stuff we were talking about, right? So the flow is actually too high. You can't extract the oxygen sufficient to increase your PbtO2. Or is it something else? Do we have vasodilation because the CPP up here is riding around 55 to 60. So we're at the lower limits of autoregulation. We're just vasodilated and blasting blood flow through there. I don't know, right? You don't know. And that's the important part of all this

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is you got to generate a hypothesis and do something about it. In this case, we said, "Well, let's try pressors. Let's start with that. Let's get the CPP up". What happens? And when we do that, here's the CPP that's starting to go up and our PbtO2 goes up. So, our brain tissue oxygen is better, which is awesome. Our PRx showing us that we had autoregulatory dysfunction actually gets better as well. So, we have pushed ourselves up on the plateau. But unfortunately,

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our hyperemia, if anything, is getting worse. And look at our K value. So, we have cerebral edema now that's developing as a result. So, what do we do? Well, let's try something else. We got some benefit there. That's great. Leave the CPP. Now, let's try dropping our CO2. Let's get the hyperemia under control that way. So, we drop the CO2. Maybe we overshot. I don't know. Our ICP looks great. We really fixed that. But look at our CBF, right? And gradually this sort of

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normalizes thankfully. And we kind of let the CO2 ride. And this normalizes. In fact, kind of goes back to where it was at before. But we know what we need to do, right? So, this is a person who doesn't need more vascular tone. We don't need to modulate the CO2 that low. They need that CPP. We can keep it there. And we just need to watch to make sure that, you know, we're not developing further edema from the hyperemia as it continues by doing that kind of stuff, hypothesis testing,

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right? And figuring out what your targets are, what you should do in that patient. Let's keep our CO2 back to kind of where it was. Let's keep our CPP at 75 or 80. And let's watch the blood flow. Make sure the edema is not worsening because maybe they'll respond hypertonic. Right? You just made like three hypotheses, which is great. And if you do that and you feed it forward, whoever is taking care of your patient clinically, maybe that's you, maybe that's someone else, then

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you can iteratively try out those hypotheses, see if what works, and then make another care goal for that patient, individualizing their management. When you do this, this is some work from Brian Appavu and kids where they started reporting on all this information, making those hypothesis, writing them down, saying, "Here guys, you're in the ICU. You're not going to have time to stare at a day's worth of multimodality monitoring data. But here's what I found. Try this and see what

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happens because I think your CO2 needs to be a little bit lower for this reason. And this is what you should see if it's going to work. When you do that, you know, in this particular case, it was a small case series. They weren't powered to show any differences in outcome, but they did reduce mechanical ventilation days and ICP days. They were making decisions that allowed them to liberate earlier in terms of ICU care. We've been doing the same thing. We went back and looked at our patients. And when we report this stuff, there are so many relationships that you will see

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if you're looking at data this way. And the CBF is really the lynch pin for a lot of that stuff in my monitoring data and in the way I use this clinically. But we were able to not use as much intervention for ICP. We definitely changed our CO2, which was significantly different, but we also had less time with ICPs that were elevated because we were reporting forward, you know, here's what's happening with your CBF. Here's what you might try. And those patients actually did better which I was a little bit surprised about. But when we started reporting

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this stuff out individualizing management based on CBF and our other multimodality neuro monitoring parameters there was a drop in the patients who had a proportion of patients with poor outcome using a statistical process control chart. As you can see here, before we started reporting the stuff, individualizing management after which we had a pretty clear improvement and a shift in our grata plots here based on a multivariate regression. So to sum and let you guys get out of here with one minute to spare, CBF can be measured continuously and you can see not just

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the absolute CBF which may be less important than its dynamics. how is it being regulated in that patient and what do you need to do about it in context of everything else the location of CBF monitor actually does matter and now you can tell where it is which is great and that regional edema is another important piece informing clinical decisions is empowered by knowing what your blood flow is which is really sort of that final piece that we don't often get with a lot of our methods that infer blood flow at least to me that's really really important and so hopefully that

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is interesting enough to come by the Hemedex booth which is where I'll be from 3:30 to 5 or so if you have any questions since I got us right to the end of time. And so if you want to ask questions, you want to come by and look at some of the stuff in detail, I'm happy to do that with you. But I'll let you go since we're at 1:15. Thank you all for being here. I appreciate it. Hope lunch was good. I'll see you at 3:30.