The Problem with Physiology (and Why You Should Rethink Your Practices)

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The physiology you abide by, that you govern by, has problems.

When I went to medical school, information about the way physiology should rule the management of myocardial infraction was widely available to us. Now all of that has been removed from textbooks, and we make fun of it. But the question that arises is whether we are any better at practicing critical care medicine. I think not.

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We are obsessed, for example, with oxygen delivery for sepsis. We think that organs only fail when there is inadequate oxygen, so we become obsessed with the need to deliver more oxygen. We have moved on to maximizing oxygen delivery with early goal-directed therapy as a consequence of that physiological belief. *The New England Journal of Medicine* published what was called a pivotal study, but is it really true, is it really helpful, is it carrying the truth for us, is it salvation or mumbo-jumbo? (2001;345[19]:1368; http://bit.ly/2RaxXNm.)

As I will show you, it is mostly mumbo-jumbo. It has taken us 15 times the number of patients and three large multicenter trials in three different jurisdictions around the world to kill this idea based on physiology. But many paradigms malfunction when physiology rules your behavior. Protein C is low in sepsis, so we have to replace it. Albumin decreases edema because it increases colloidal osmotic pressure, so it should be good for traumatic brain injury. A high intracranial pressure is abnormal and dangerous physiology, so we should decrease it by taking the vault of the skull off our patients.

I've got bad news for you: You fix physiology, you try to normalize glucose, and you kill people. Seventy-three Kiwis and Canadians died who otherwise would not have because of mad physiology. Give protein C in sepsis to replace the low levels, and what do you get? One large randomized controlled trial had people spending a bucketful of money to buy protein C, but patients had more bleeding episodes and no benefit. Another study looked at albumin in TBI; this is the post-hoc analysis of the SAFE trial. (*N Engl J Med* 2007;357[9]:874; http://bit.ly/2O3UmK6.) They found increased mortality in patients who received albumin compared with saline. That's because we are looking at only one aspect of physiology. Because that's how we do physiology: We look at one thing and forget about the rest.

But if you give commercially available albumin to animals, you immediately see a rise in ICP because it is a hypotonic solution. Let's decompress the brain. That's a great idea: The ICP is high, we want it to go down, so surely this is a great thing. Can we do it? Of course. Decompressive craniectomy is an effective way of lowering intracranial pressure. We decrease the duration of mechanical ventilation and the duration of ICU stay, but we blow away the patient's brains.

Obsessed with Fluids

Who thinks it makes sense to open the skull and let the brain just expand by 7 cm and tear one billion axons in five seconds? Obviously, we do. We can measure increased caloric expenditure in critically ill patients, so we're going to feed them early and aggressively. We know they have low glutamine levels, so we're going to give glutamine back. We deliver early feeding and measure the increase in caloric input, but it's a stupid thing to do. This increases the time in ICU, on mechanical ventilation, and in the hospital, and this is a completely pointless activity. If you give trophic feeding—just 20 ml an hour for the first seven days—to patients with severe ARDS, as they did in the EDEN trial, it makes no difference at all. (*JAMA* 2012;22;307[8]:795; http://bit.ly/2PfVuiJ.) Again, mad physiology leads to mad behavior.

The same is true for low glutamine; we're going to replace it. Pity that it's a bad idea because it increases the chance of killing people. Again, mad physiology and mad behavior. But there is nothing madder than the world of intravenous fluids. It beats them all. Let's apply the white man's cure of sepsis to African children: aggressive, large amounts of fluid boluses. Oops. We killed a few African children with physiology. (*N Engl J Med* 2011;364[26]:2483; http://bit.ly/2ApcB9j.)

We're so obsessed with fluids that we even think giving people mashed potatoes or corn in water intravenously will save their lives. Does it matter that we made some kidneys not work well, not to mention all of the side effects of skin and nerve deposits? Why does this happen? Are doctors stupid? No, they just can't tolerate the thought that they don't really know what to do.

But there's something else. Physiological gain is immensely seductive in the ICU where we practice a new art called numerology. That's because we bow down to attribution bias, the anecdotal and selective observation of favorable effects attributed to intervention, which then gives us undue confidence that something is going to work. Does that sound familiar? There is more to physiology that makes it particularly seductive, like its immediacy bias, the observation that a favorable effect is so immediate, so obvious, and so strong that it must be true. And we ignore what will happen in 15 or 30 minutes.

We make the measurable important, not the important measurable. IV fluids are fantastic for this. We give boluses all the time, and we get excited about them.

We say the patient is a lot better and that we have this thing called responsiveness to intravenous fluids. We look at the literature, we look at pulse pressure variation, stroke volume variation, and we go for it. Look, there is a beautiful ROC there, it's great, it's the right thing to do. Except that all the studies that measured its effectiveness immediately after it was given. What's going to happen in 15 minutes?

15 Minutes of Fame

Here is what happens in 15 minutes: You're back to baseline. Same for stroke volume: You're back to baseline in 20 minutes. So what do we do for the next 23 hours and 40 minutes? Presumably, do it again. And again. And again. Do fluids actually do anything at all? Is it the fluids or is it that we are just putting cold fluid into somebody's veins? The answer: It's the cold. (*Acta Anaesthesiol Scand* 1993;

37[8]:768.) If you give volunteers the same amount of warm or cold intravenous fluids, the pressure effect, which lasts for only a short time, is all due to the cold. You might be just as effective putting ice cubes on patients. If you give warm fluid instead, you increase the cardiac output. Why? Because you're warming the patient up and causing vasodilatation.

We are threatened by that thinking. The biggest menace to knowledge is not that you don't know, it's that you think you know. We're hard-wired to believe this. Psychologists call it overclaiming bias, our tendency to overestimate our knowledge. It's a well-defined psychological syndrome. We overclaim if we believe we are expert in something. And we super-overclaim if we believe we are specifically knowledgeable in a specific domain. If you tell people this is wrong, they'll still overclaim. And if you tell them they're really good, their ability to overclaim becomes unimaginable. (*Psychol Sci* 2015;26[8]:1295.) They even believe—and say—they have been to places that don't actually exist. It's amazing. We live in a world of rational astrology, following beliefs whether or not they are true. Could be true, could be false; we don't care.

Physicians bow to attribution bias, which imparts undue confidence that something is going to work

Intravenous fluids are a classic example. Some ideas may turn out to be true, but we behave as though it doesn't matter. The whole of society works like that. Breakfast is the most important meal of the day? Who randomized people to have it or not? Apples are really good for you. Really? What about oranges? Where are the randomized controlled trials? Oxygen is good for myocardial infarction. Says who? It's a constant stream of madness. As Mark Twain said, "It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so."

Don't worry; here's what you do. Look at the literature in detail. Consider biological plausibility. Follow carefully evaluated evidence. Be open-minded and balanced. Be skeptical without being unduly cynical. Accept doubt with a smile. Practice the known medicine of the time with the understanding that truth will inevitably be the source of derision in the future. Fight tooth-and-nail to enroll patients in high-quality randomized controlled trials so that the known medicine of today can be improved. **EMN**

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