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Editorial

Goldilocks and the three post-cardiac arrest subjects

"So first she tasted the porridge of the Great, Huge Bear, and that was too hot for her; and she said a bad word about that. And then she tasted the porridge of the Middle Bear, and that was too cold for her; and she said a bad word about that, too. And then she went to the porridge of the Little, Small, Wee Bear, and tasted that; and that was neither too hot nor too cold, but just right; and she liked it so well that she ate it all up; but the naughty old Woman said a bad word about the little porridge-pot because it did not hold enough for her."

The Story of the Three Bears (1837); Robert South Southey (1774–1843)

Clinical trials conducted in the intensive care setting are often neutral [1]. To some extent, this may be explained by issues of statistical power, recruitment, and outcome selection common to all clinical trials. However, the role of heterogeneity of disease severity or unmeasured patient factors may play a larger role [2]. In conventional trial designs, population-average treatment effects are compared between arms. If a particular therapy helps a third of subjects, hurts a third of subjects and is inert in the remaining third, it will appear to have no benefit compared to placebo.

It is easy to imagine how this could play out when testing treatments for the post-cardiac arrest syndrome [3,4]. Consider a subject with devastating anoxic brain injury – why would we expect to observe benefit from any depth or duration of targeted temperature management (TTM)? By contrast, consider a minimally injured subject that briskly localizes to noxious stimuli but does not follow commands– would we not anticipate recovery regardless of the depth or duration of TTM? At a population level, identification of a positive treatment effect from any therapy requires enrollment of subjects with treatment-responsive disease. In the case of post-arrest care, these might be patients with moderately severe injury that could recover if secondary brain injuries were prevented, but would otherwise succumb to their illness. A hindrance in resuscitation science is that we struggle to reliably identify subjects in this 'sweet spot': we are still working to define and standardize measures of illness severity, and too often must rely on historical case features (e.g. shockable, witnessed, bystander CPR) as crude estimates.

In this issue of *Resuscitation*, Nakatani et al. report a secondary analysis of registry data on 431 comatose subjects resuscitated from out-of-hospital cardiac arrest and treated at 15 tertiary care hospitals in Japan between 2011 and 2013 [5]. Each subject had cerebral near infrared spectroscopy (NIRS) recorded at hospital arrival and was treated with 12–24 h of TTM to 32–34 °C. Other aspects of post-cardiac arrest critical care were left to the discretion of treating clinicians, but generally conformed to the 2010 American Heart Association guidelines [6]. The authors retrospectively stratified NIRS-derived regional cerebral oxygen saturation (rSO_2) into three groups: 'normal' (rSO_2 > 60%), 'intermediate' (rSO_2 41–60%), and 'abnormal' (rSO_2 < 40%). The primary outcome was 90-day all-cause mortality, and the secondary outcome was 90-day CPC 1–2. Favorable subject characteristics and outcomes declined across rSO_2 categories in a stepwise fashion, suggesting that rSO_2 did estimate illness severity. The authors conducted extensive modeling adjusted for typical covariates, including propensity-score matching, inverse-probability weighting, and Rubin causal modeling.

Ultimately, treatment with TTM was associated with lower all-cause mortality after propensity adjustment in the 'intermediate' group (rSO_2 41–60%), whereas the 'normal' (rSO_2 > 60%) and 'abnormal' (rSO_2 < 40%) groups did not appear to benefit from TTM. Although these results were stable in several sensitivity analyses, the authors could not adjust for all potentially relevant aspects of post-cardiac arrest care (e.g. oxygenation, ventilation, hemodynamics, sedation, neuromuscular blockade, prognostication, etc.). We also do not know the proximate cause of death for subjects. Establishing whether TTM reduced death from neurologic reasons in the intermediate rSO_2 group would support the authors' postulated mechanism for benefit.

This hypothesis-generating study demonstrates a nuanced approach that resuscitation scientists could adopt. By quantifying disease severity, treatments can be targeted at those patients likely to respond. Moreover, a measure like NIRS that can be sampled continuously at the bedside could also be used to titrate the dose or duration of care based on real-time need and treatment responsiveness. A subject with severe anoxic brain injury should be treated differently than a subject with primarily systemic ischemic reperfusion injury or a subject with severe myocardial stunning. Such hypothesis-generating results should be followed up with a trial designed to assess, in an *a priori* fashion, the impact of our standardized post-cardiac arrest regimens on different phenotypes and combinations of injury patterns within the post-cardiac arrest syndrome.

Because brain injury is the major cause of morbidity and mortality after resuscitation from cardiac arrest, rSO_2 is appealing because it monitors the end-organ of particular interest. rSO_2 appears to estimate local oxygen delivery. As such, it may approximate the severity of many of the processes believed to contribute to preventable secondary brain injury after cardiac arrest, including deranged cerebrovascular autoregulation, increased microcirculatory critical opening pressure and perivascular edema resulting in diffusion-limited oxygen delivery [7,8]. Moreover, insofar as TTM reduces cerebral metabolic rate of oxygen, patients with low but non-lethal rSO_2 values might be particularly

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expected to benefit from rebalancing oxygen supply and demand.

Although NIRS is non-invasive, carries physiologic face validity, and supported by growing observational evidence it is far from the only measure of post-arrest illness severity that could be used to guide patient care or inclusion in clinical trials. Other methods might include instruments such as the Out of Hospital Cardiac Arrest (OHCA) score [9], Cardiac Arrest Survival Post-Resuscitation In-Hospital (CASPRI) score [10], Good Outcome Following Attempted Resuscitation (GO-FAR) [11], or Pittsburgh Cardiac Arrest Category (PCAC) [12,13]. Bedside assessment like electroencephalography, lactate clearance, ejection fraction, or measures of other acute end-organ dysfunction might also be used, depending on the putative mechanism of the therapy in question

The resuscitation science community should prioritize achieving a consensus on the scales, scores, instruments, and beside estimates we will use moving forward to accurately and reliably measure post-cardiac arrest illness severity. Furthermore, the Utstein-style guidelines for uniform reporting of cardiac arrest data [14] should include these consensus measures. Only then will we be able to formally acknowledge and embrace the heterogeneity within and across different domains of post-cardiac arrest illness and advance our post cardiac arrest treatment paradigm.

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Joshua C. Reynolds*
Michigan State University College of Human Medicine, Grand Rapids, MI, USA
E-mail address: reyno406@msu.edu

Jonathan Elmer
University of Pittsburgh, Pittsburgh, PA, USA

* Corresponding author at: 15 Michigan Street NE, 7th Floor, Grand Rapids, MI, 49503, USA.