

The “sweet spot” for physiological targets in critically ill patients

Steve A R Webb, Paul J Young and Rinaldo Bellomo

Titration of various therapies to achieve a target range or a threshold level of a physiological variable is an integral component of managing critically ill patients in the intensive care unit. There are many examples of this type of titration. Inspired oxygen concentration (F_{iO_2}) and positive end-expiratory pressure (PEEP) are manipulated to achieve particular oxygen concentration targets measured by arterial blood gas levels or pulse oximetry in patients receiving mechanical ventilation. Tidal volume or applied inspiratory pressure, as well as respiratory rate, can be adjusted to achieve a target P_{aCO_2} . Intravenous fluid and vasoactive drug administration is titrated to achieve a range of related targets, including arterial blood pressure, cardiac filling pressures, cardiac output, venous oxygen saturations, and clinical markers of perfusion, including urine output. In patients undergoing dialysis, the “dose” can be adjusted to achieve different levels of creatinine clearance. The caloric target for feeding, the composition of the nutrition and route of feeding can be adjusted to achieve nutritional targets. Insulin can be given to achieve a target range of blood sugar level. In patients with, or at risk of, elevated intracranial pressure (ICP), a variety of treatments can be used to achieve a target ICP and cerebral perfusion pressure. Elevated body temperature, above a threshold, can be reduced with antipyretic medication or external cooling, and hypothermia can be corrected through external warming. The dose and choice of sedative medications can be adjusted to achieve a target level of consciousness. In patients with anaemia, a threshold can be used as a trigger for transfusion.

The relationship between these physiological targets and patient-centred end points is more complicated than was initially believed when these therapies were first introduced into clinical practice.¹ Early approaches to ICU therapies involved the concept of “normalisation” of physiology.² Observational studies of patients who were critically ill also identified certain physiological values as being more commonly associated with survival, leading to the use of “survivor levels” as targets.³ There are now sufficient examples from randomised controlled trials (RCTs) to show that titration to normalise physiological values or to achieve physiological values more commonly associated with survival cannot be regarded as valid universal principles of intensive care medicine. There are multiple well conducted RCTs that have compared two or more levels of a physiological target, thresholds for treatment, or a “dose” of therapy. These studies have reported that normalisation or achievement of “survivor levels” either achieves no difference or results in

poorer survival.⁴⁻¹⁰ Indeed, with the possible exception of early goal-directed therapy in sepsis (an unblinded single centre study¹¹), there are no studies in which either of these approaches have improved patient-centred outcomes such as survival or functional independence. In fact, the converse has often been found. For example:

- in patients with acute respiratory distress syndrome (ARDS), mechanical ventilation with a tidal volume of 6 mL/kg of ideal bodyweight results in lower mortality than a tidal volume of 12 mL/kg of ideal bodyweight, even though the latter results in a more normal P_{aCO_2} level;⁴
- a transfusion threshold of 70 g of haemoglobin per litre results in better outcomes than a higher transfusion threshold;⁵
- normalisation of blood sugar levels results in three more deaths per 100 patients treated;⁶
- titration of cardiac output to “survivor levels” in patients with septic shock is either ineffective or increases mortality;^{7,8}
- although not necessarily generalisable, lowering ICP by decompressive craniectomy in some types of traumatic brain injury worsens neurological outcomes;⁹
- although derived from a subgroup analysis, there is no evidence that treating patients with hypoalbuminaemia with albumin rather than saline improves survival;¹² and finally
- administering intravenous resuscitation fluid to African children with sepsis and who have clinical signs of hypovolaemia reduces survival compared with giving no intravenous resuscitation fluid at all.¹³

If anything, it appears that less intensive manipulation of physiology is actually associated with better outcomes than more intensive approaches. Clearly, this principle cannot be extended to its logical extreme, as complete failure to manipulate physiology in the ICU would undoubtedly result in high mortality.

We believe several inferences can be drawn. First, the only way to understand the relationship between titration of a therapy to achieve a particular physiological target and patient-centred outcomes is to undertake pragmatic clinical trials¹⁴ that would randomly allocate patients to different targets and measure patient-centred outcomes. Second, the plausible effect size between different targets, while still clinically relevant, may be small, so studies designed to evaluate different physiological targets may require substantial amounts of statistical power. Third, for many physiological

targets, it is reasonable to postulate that a U-shaped curve describes the relationship between a target and patient-centred outcomes. In patients with ARDS who are receiving controlled mechanical ventilation, we know that a tidal volume of 6 mL/kg of ideal bodyweight is superior to 12 mL/kg of ideal bodyweight.⁴ However, this defines only two points on a graph expressing the relationship between tidal volume and 28-day mortality (Figure 1A). It seems reasonable to presume that a tidal volume of 0 mL would result in high mortality! It also seems reasonable to presume that tidal volumes higher than 12 mL/kg of ideal bodyweight, at some extreme level, would result in higher mortality than a tidal volume of 12 mL/kg does. This defines two more points on a curve, which has a U-shape (Figure 1B). However, what is not known is the optimal tidal volume. It is possible that 6 mL/kg of ideal bodyweight is optimal (Figure 1B), but it might be that 4 mL/kg (Figure 1C), or 8 mL/kg is actually optimal (Figure 1D); or it may be that the base of the curve is flat across a range of tidal volumes (Figure 1E). Further, it is not known whether the optimal tidal volume differs in a systematic way based on definable characteristics of the patient, such as age, sex, nature of initiating critical illness, or pulmonary compliance.

There is evidence, at least in Australia and New Zealand, that the risk-adjusted outcome for patients treated in ICUs is improving over time.^{15,16} However, this improvement is occurring despite a paucity of RCTs showing that candidate interventions being tested are superior to standard care.¹⁷ We propose that an important objective of research, and one that is likely to lead to evidence to improve patient outcomes, should be to define the “sweet spot” that characterises the

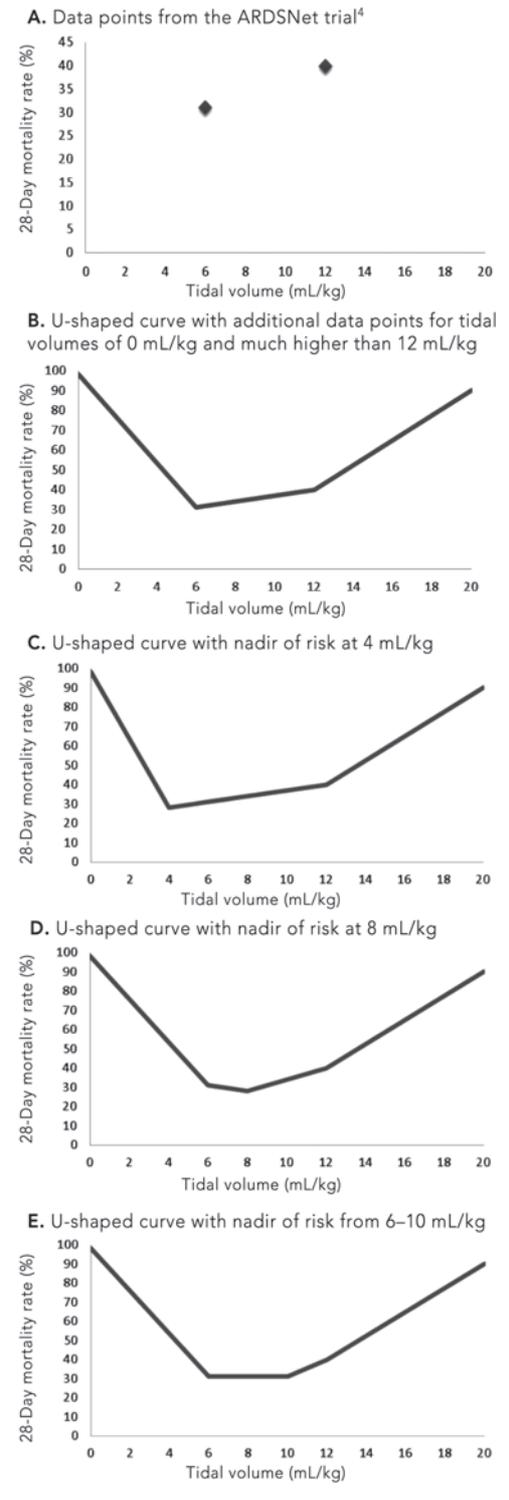
range for many different physiological targets that optimise survival and other patient-centred outcomes, and to determine if the optimal target differs between different categories of patients.

Conducting RCTs to determine the optimal targets for physiological manipulation will be challenging. It is likely that novel trial designs that maximise statistical power and adaptability, including the capacity to adapt their design based on possible differential treatment effects in identifiable subgroups, offer the best likelihood of generating this evidence. Designs such as Bayesian adaptive trials^{18,19} and cluster crossover trials^{20,21} are particularly suited to answering these questions. Trials groups such as the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), Canadian Critical Care Trials Group (CCCTG), and the ARDS Network (ARDSNet) have been at the forefront of conducting trials that disproved the universality of the principles that normalisation or titration to “survivor levels” would improve patient outcomes.^{4-6,9}

These groups are likely to be at the forefront of this new wave of research to determine optimal targets, and it is possible that generating sufficient statistical power will require collaboration between these and other clinical trials networks within a framework of networks-of-networks such as the International Forum for Acute Care Trialists (InFACT)²² and the International Severe Acute Respiratory Infection Consortium (ISARIC).²³

The prerequisites for this work are falling into place. Novel Bayesian adaptive designs and cluster crossover trials are being actively investigated as potential study designs for patients who are critically ill (Andrew Forbes, Monash University and Derek Angus, University of

Figure 1: Possible relationships between tidal volume and mortality in mechanically ventilated patients with acute respiratory distress syndrome



ARDSNet = ARDS Network.

Pittsburgh Medical Center, personal communications). A first priority will be a better understanding of the targets that clinicians actually use in clinical practice, as clinical trials should first be conducted within the range of targets that are in widespread clinical use.²⁴ The use of opt-out consent as the default approach to informed consent should be considered where two or more targets are within accepted clinical practice, and their use is currently distributed quasi-randomly without consent. With such an approach, the only requirement should be to provide information and an easy way to decline to participate.

Several million patients are treated in ICUs throughout the world each year. These patients receive an array of different therapies that are titrated to physiological targets, and this is done largely in the absence of any evidence that any particular target is better than another. Even for targets for which we have some evidence from RCTs comparing two alternatives, we do not know the “sweet spot” that corresponds to best outcomes. Multiple programs of research will be necessary to provide high-quality evidence about the targets that work best so that clinicians can provide patients with the best possible care.

Author details

Steve AR Webb, Intensive Care Specialist,¹ and Clinical Professor^{2,3}

Paul J Young, Intensive Care Specialist,⁴ and Honorary Senior Research Fellow⁵

Rinaldo Bellomo, Clinical Professor,³ and Intensive Care Specialist and Director of Research⁶

1 Intensive Care Unit, Royal Perth Hospital, Perth, WA, Australia.

2 School of Medicine and Pharmacology and the School of Population Health at the University of Western Australia, Perth, WA, Australia.

3 Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, VIC, Australia.

4 Intensive Care Unit, Wellington Hospital, Wellington, New Zealand.

5 Medical Research Institute of New Zealand, Wellington, New Zealand.

6 Intensive Care Unit, Austin Hospital, Melbourne, VIC, Australia.

Correspondence: steve.webb@uwa.edu.au

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