Editorials

Does the patient need more fluid?

In this issue of Critical Care and Resuscitation, Dr Harvey and colleagues look for indices which might be used to flag intravascular depletion.[1] They report on three. The first is systolic pressure variation, which is the difference between the maximum and minimum systolic pressures across the ventilatory cycle. The second, systolic area variation, was adapted by the authors from stroke volume variation, a parameter already available to users of the PiCCO system (Pulsion Medical Systems, Munich, Germany). The difference is that although both systolic area and stroke volume variation use arterial pulse contour analysis,[2] the latter is calibrated further by transpulmonary thermodilution to convert area above diastolic pressure into stroke volume. The third index is the initial distribution volume of glucose, which is a 'snapshot' of the rapidly equilibrating component of the extracellular space. Whereas variation in systolic pressure and systolic area are dynamic indices, the rapid glucose space can only be static. In this study of mechanically ventilated patients post cardiac surgery, the important finding was that none of the three indices could predict a response to fluid loading.

The question of intravascular filling preoccupies critical care practitioners everywhere. Most supplement their clinical evaluation (e.g. fluid balance, skin turgor, jugular venous pressure, urine output) with more sophisticated indices of myocardial preload, particularly in the presence of organ dysfunction. Preload parameters abound, and vary in their invasiveness.[3] Some can be sampled continuously as in the case of central venous pressure and left ventricular ejection time (which when measured by oesophageal Doppler is FTc, or 'flow time corrected for heart rate ').[4] Others must be sampled intermittently, as with pulmonary artery occlusion pressure (PAoP),[5] right ventricular end-diastolic volume,[6] transpulmonary thermodilution indices such as intrathoracic blood volume and global end-diastolic volume,[7] and echocardiographic estimations of ventricular end-diastolic area.[8,9]

None is an absolutely reliable reflection of left ventricular end-diastolic fibre length, the Holy Grail of preload measurement. Perhaps because of this, traditional static measurements of filling pressure such as right atrial pressure and PAoP are known to be unreliable as individual predictors of the response to fluid loading.[10,11] Disappointingly, this also applies to static area and volumetric measurements such as right ventricular end-diastolic volume, and left ventricular end-diastolic area and volume.[12-17] It seems that all static indices need further calibration to become genuine descriptors of intravascular filling. The traditional method has been to alter intravascular volume as a forcing function, in other words to use fluid challenges. Even then there is a need for regular recalibration, since action thresholds change along with fluctuations in myocardial compliance, intrathoracic pressure and vasomotor tone. At times this can be counterproductive, for example in acute lung injury or severe myocardial dysfunction, when excessive fluid loading has serious consequences.

More recently it has been realised that during the respiratory cycle, a range of preloads is tested repeatedly against rapid response markers of ventricular output such as systolic pressure, pulse pressure and stroke volume.[18] In each case the signal from these markers is stronger in mechanical ventilation, where the sudden increase in intrathoracic pressure on inspiration reduces venous return, right ventricular preload and right ventricular ejection. After a delay of a few heartbeats, left ventricular filling is also reduced through its series connection with right ventricular output and via ventricular interdependence.[19] By these mechanisms stroke volume oscillates with imposed fluctuations in intrathoracic pressure, after a phase lag. An under-filled vasculature responds with excessive swings in ventricular ejection.

Herein lies the rationale for adopting fluctuations in systolic pressure,[20-21] pulse pressure,[11] stroke volume,[22,23] peak aortic blood flow[14] and vena caval diameter[24] as dynamic indices of intravascular filling. Some have had considerable success in predicting the need for fluid loading.[18] As always there are caveats. To begin with, variation in systolic pressure suffers from one specific disadvantage - the direct transmission of intrathoracic pressure elevations to systolic pressure. Shifting the focus to the so-called ΔDown component may help to improve the signal to noise ratio.[21] Second, measuring variation in peak aortic blood velocity or vena caval diameter is largely impractical except as a snapshot, since it requires trans-oesophageal echocardiography and the presence of an expert operator.

Next are the artefacts potentially common to all such dynamic indices. Mechanical ventilation has complex effects on heart performance extending beyond simple preload oscillations. Increases in alveolar and intrathoracic pressure reduce left ventricular afterload by reducing transmural pressure.[19] The same applies to the right ventricle, with an added opposing increase in afterload due to inspiratory compression of pulmonary capillaries. Factors such as these affect specificity in

particular, especially when there is dysfunction of either ventricle or raised pulmonary vascular resistance. Pericardial restriction and overt tamponade are also confounding variables, again affecting specificity. Perhaps the more limited success of stroke volume variation in cardiac surgical patients,[25] along with Dr Harvey's recent lack of success with systolic pressure and stroke area variation,[1] can be explained in this way. To make matters worse, intrathoracic pressure fluctuations in critical illness are an inconstant forcing function, varying in parallel with alterations in tidal volume, airways resistance, and chest wall or lung compliance. Cardiac arrhythmias and valvular dysfunction can also have potent effects on ventricular ejection, further reducing the reliability of this type of test.

What about more direct volume quantification? Measurements of plasma volume, circulating blood volume or extracellular fluid volume demand meticulous attention to detail. They represent indicator 'spaces' rather than true physiological volumes, and all are sufficiently labour intensive to discourage most clinicians.[26] A timed indicator dilution and serial measurements are inevitably required. Only rapid and repeatable techniques can be of any use at the bedside. Nonetheless, there are strong advocates for the newer measures of plasma volume such as hydroxyethyl starch dilution,[27,28] and for faster, more repeatable circulating blood volume measurements, such as carbon monoxide dilution.[29,30]

When it comes to extracellular fluid volume, clinical measurements must be confined to its rapidly equilibrating component, which is about 20% of total body water and about half of the total extracellular volume.[26] Even so, this method has its supporters. In fact proponents of the rapid glucose extracellular compartment make virtue of necessity.[31] They hypothesise that pure blood volume measurements are physiologically less relevant in under-perfused states because of redistribution to a 'peripheral' compartment, normally made up of poorly perfused tissues. The argument goes that, because the rapid glucose space is restricted to the plasma plus that portion of the extracellular space in immediate dynamic equilibrium with plasma, it is a more 'central' number than circulating blood volume with its peripheral 'backwater' component, and therefore a more realistic index of fluid status. In one study of oesophageal cancer surgery patients, the rapid glucose space had better sensitivity and specificity for the adequacy of intravascular filling than measurements of plasma volume.[31] However, to take a contrary view, such a finding might also reveal the error introduced by using plasma volume as a substitute for circulating blood volume.[32]

To complicate matters further, the desirable intravascular volume across the broad spectrum of critical illness is unpredictable, depending as it does on vasomotor tone, myocardial compliance, intrathoracic pressure and juxta-cardiac pressure. Critical care practitioners are often confronted with relative intravascular depletion due to mediator-induced loss of vasomotor tone, coupled with actual plasma loss expanding the interstitial and trans-cellular spaces. Examples include sepsis, anaphylaxis and interventions like cardiopulmonary bypass, each of which activates complex vaso-active inflammatory cadences.[33-35] With so many variables operating, settling on one action threshold for any indicator space does not seem feasible. Certainly, Dr Harvey and colleagues could find no relationship between the rapid glucose space and fluid responsive hypotension post cardiac surgery. Perhaps again, only a fluid load as a forcing function can put these numbers in their clinical perspective.

Finally, for many years one simple manoeuvre has been employed by many 'hands-on' critical care practitioners to evaluate intravascular volume status – the response to passive leg raising. The auto-transfusion is only modest, but it has the advantage of providing a genuine increase in venous return without fluid loading.[36]

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The toxic shock syndrome: inhibiting superantigens or treating their adverse effects?

While the search for a drug that would improve mortality in the treatment of sepsis had appeared to be largely futile, suddenly the results of the Phase III, mult-

icenter Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial appear,[1] capturing the imagination of clinicians who constantly survey the therapeutically arid 'sepsis' landscape. The fact that an infusion of drotrecogin alfa (activated) resulted in reductions in the plasma levels of D-dimer and serum levels of interleukin-6 (i.e. markers of coagulopathy and inflammation, respectively) in a phase II study,[2] encouraged the PROWESS authors to evaluate "whether the administration of drotrecogin alfa activated would reduce the rate of death from all causes at 28 days in patients with severe sepsis and have an acceptable safety profile". The authors performed the study and concluded that recombinant human activated protein C (drotrecogin alfa activated) significantly improves 28-day mortality rates in patients with severe sepsis.[1]

That drotrecogin alfa activated has significant antithrombotic, anti-inflammatory and profibrinolytic effects is an attractive prospect, particularly as many cite a beneficial immune modulation to be the 'Holy Grail' for the treatment of SIRS and sepsis.[3-6] Although the PROWESS study had many flaws[7] and has yet to be validated, it would appear that the genie is out of the bottle: drotrecogin alfa activated is not only being used for patients with severe sepsis, it is also being used for other conditions. For example, in previously excluded disorders (e.g. severe sepsis in solid organ transplantation)[8] and meningococcal purpura fulminans.[9] In this regard the toxic shock syndrome (TSS) would appear to be ideally suited to benefit from such an agent, and in this edition a report of its use in a case of TSS is presented.[10]

Toxic shock syndrome is caused by the production, absorption and widespread distribution of a *Staphylococcus aureus* toxin, or toxins, including the superantigen toxic shock syndrome toxin-1 (a potent inducer of interleukin-1, interleukin-2 and TNF-α).[11,12] In 99% of cases, the patients are young menstruating women wearing a tampon. In the other 1% of cases, it is described in prepubertal, postmenopausal female patients and in male patients with staphylococcal infections.[13] The patient usually presents with a sudden onset of pyrexia, vomiting, watery diarrhoea, sore throat (or very tender mouth), headache, disorientation, myalgia, distended abdomen with pain suggestive of peritonitis and an erythematous rash. This is followed by the development of hypotension, oedema and, in severe cases, shock, acute respiratory distress syndrome, acute renal failure and disseminated intravenous coagulation. The erythematous 'sunburn-like' or scarlatiniform rash is present during the acute phase of the illness and about 10 days later there is desquamation of the skin, particularly of the palms and soles. The acute phase lasts for 4-5 days, whereas the convalescent phase may last for several weeks.

After attempting to halt the continued production of toxin from the infected focus (e.g. irrigating the vagina or wound and removal of foreign bodies and tampons, etc), therapy is largely supportive. Shock is treated conventionally with fluids and inotropic agents. Antistaphylococcal antibiotics do not appear to improve the patient's outcome,[14] although they do reduce recurrences and are usually administered for up to 5 days.[14] Corticosteroids have also been advocated although their place in therapy is not yet proven.[15]

The streptococcal toxic shock syndrome (STSS) is caused by streptococcal infections that produce streptococcal pyrogenic exotoxin A (a superantigen that is also potent inducer of TNF-α and interleukin-2),[16] and has clinical features similar to the TSS. The discovery that intravenous immunoglobulin (IVIG) reverses the hyperproliferation of T cells, neutralises superantigens,[17] (although this effect may vary between the different IVIG products[18]) and down-regulates the production of TNF-α,[19] has prompted some to use IVIG (2 g/kg in two doses[20] or 1 g/kg on day one and 0.5 g/kg on day two[21,22]) to reduce morbidity and mortality associated with the STSS.[23] One recent randomised, double-blind, placebo-controlled trial in patients with the STSS reported a reduction in mortality from 30% to 14% when using 1 g/kg IVIG followed by 0.5 g/kg at 24 hours and 0.5 g/kg at 48 hours (as well as clindamycin 600 mg 8-hourly and penicillin up to 12 g daily).[24] While, IVIG has been suggested in the treatment of patients with TSS,[25] currently there are no reports of its use in this condition.

Unfortunately, case reports using a new therapeutic approach that is associated with a good clinical outcome, suffer from implying the tenuous logic of *post hoc ergo propter hoc*. Perhaps the same may be said of editorials. For example, in the current case report,[10] if IVIG rather than drotrecogin alfa activated was used, and the patient survived, this editorial may not have reasoned the case for drotrecogin alfa activated for patients with the TSS.

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Oversedation and agitation in the intensive care unit: vacillate or automate

The present interest in sedation and analgesia in the intensive care unit has a short history. Despite the initial tendency of intensivists to sedate patients heavily, recent publications have caused intensivists to reconsider this approach and assess whether a more holistic approach including human contact and judicious use of sedatives and analgesics may have greater advantages for the patient.

With a wide variety of pharmacological agents now available for sedation and analgesia, the potential for confusion continues. The choice of agent, or agents, may depend on many factors including the need for sedation and analgesia, the pharmacodynamics and pharmacokinetics of the drug, or drugs, in question, the route and ease of administration and the tolerance profile and cost. A recent publication reported the differences in the clinical use of sedative and analgesic drugs, alone or in combination, in Western European intensive care units.[1] Not surprisingly, the authors revealed substantial differences in the drugs used for sedation and analgesia as well as sedation scales used to monitor levels of sedation.

Australian data reveal similar inconsistencies. An Australian survey performed in 1997,[2] revealed that the

most common form of sedation was a combination of benzodiazepines and narcotics. In the majority of units (94%), nurses were responsible for titrating and administering sedation, and in most units (63%) the aim was to lightly sedate patients. The methods of sedation varied, with few units using sedation scales (17%), and the most common complication reported was over sedation (32%). A more recent Australian study,[3] confirmed that a continuous infusion was still the preferred mode of drug administration, with morphine and midazolam the favoured agents. Sedation scales were used in 43.2% of units and protocols for sedation were used in only 23.3% of units. Complications of sedation were audited in only 11.6% of units.

These data are not supportive of the notion that daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation have advantages.[4] A previous publication by Kollef *et al*,[5] also suggested that the use of continuous intravenous sedation was associated with prolonged mechanical ventilation.

In recent years numerous sedation scales have been validated and instituted in intensive care units. Brattebo and colleagues,[6] evaluated the effect of a scoring system and protocol for sedation on duration of mechanical ventilation in a surgical intensive care unit and found that the introduction of a sedation scale decreased patient ventilator days. Australian data also suggest that the introduction of a sedation scale may decrease ventilation hours as well as sedative and analgesic use in the intensive care unit.[7]

The review by Shaw and colleagues,[8] alludes to recent publications in intensive care sedative practice and addresses, in particular, the problem of agitation control. Apart from clinical intuition and experience, it is suggested that objective measurements of agitation such as heart rate variability and blood pressure variability are of value in evaluating agitation in the intensive care unit. Movement as an indicator of agitation is also discussed and digital imaging to measure patient motion is implied as a further quantified measurement to determine patient agitation. It is then suggested that a model of the essential dynamics of the agitation system can be used for developing an automated sedation infusion protocol. In this model, input from objective agitation measurements is used to drive a syringe pump to minimise agitation.

As exciting and innovative as this technique may be for drug administration in sick patients, clinicians may be repeating the same mistakes made with the introduction of the Swan-Ganz catheter. That is, physiological measurements displayed on screens may not necessarily be good for patient management.[9]

The critically ill patient is has a multitude of reasons for autonomic instability, and some of these, such as occult haemorrhage, may be life threatening. An automated approach, with drug administration initiated when haemodynamic change occurs may have profound clinical ramifications. The integration of movement and motor activity as a means of evaluating sedation and agitation is not a flawless suggestion. For example, excessive motor activity in a patient with metabolic derangement and seizures, delirium tremens or epilepsy would not warrant an automated approach. Decreased motor activity in a patient with myasthenia gravis, Guillain Barré or neuropathy of the critically ill would also pose unique challenges to this strategy of agitation control.

Intensive care patients are often scared, disorientated and lonely. They are surrounded by plastic tubes, ventilators, flashing lights and alarms. They have lost intimate contact with their loved ones. Appropriate clinician contact should be encouraged and facilitated. The reasons for agitation and anxiety need to be thoroughly established through communication, prior to automated drug administration.

Despite reservations about the clinical advantages of an automated approach to agitation and sedation in the critically ill, available evidence confirms that intensivists still vacillate when prescribing sedative and analgesic agents.[1,3] Currently less than 50% of Australian intensive care units have a definite protocol, or use a sedation scale when administering sedative and analgesic agents to a critically ill patient.[3] Perhaps the time is right for these units to collaborate in a multicentre trial where issues such as patient experiences, ventilation time, analgesic and sedative use, feed intolerance and possibly inotropic requirements can be assessed before and after introduction of a protocol and sedation scale. Until we have these answers we should continue as compassionate clinicians when treating the isolated and alienated critically ill patient.

It was more than a decade ago that I voiced my concerns to a senior mentor that, as an internist, I found it difficult at times to relate to heavily sedated and monitored patients. The reply was: “Remember they are still patients with feelings and emotions - treat them as such and communicate if you can”.

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Antibiotic prophylaxis. How, when and why

Surgical site infections (SSI) are amongst the commonest nosocomial infections and are associated with increased antibiotic use, increased cost and length of stay and increasing antibiotic resistance. Extensive literature documents the effectiveness of perioperative antibiotics in a variety of situations and prophylactic antibiotic use remains a major indication for antimicrobial use in critical care units. However, audits of prophylaxis show widespread variation from guidelines, particularly with respect to choice of antibiotic, timing and duration.

The risks versus benefits of antibiotic prophylaxis will depend on the risk of SSI and its potential severity (e.g. prosthetic infection), the effectiveness of prophylaxis and the consequences in terms of antibiotic cost, resistance and toxicity. SSI is associated with the extent of operative contamination (i.e. clean, clean-contaminated or contaminated fields) and host factors such as advanced age, obesity or malnutrition, diabetes, ascites, low haematocrit, disease severity, prolonged pre-operative stay, infection at distal sites, and pre-existing nasal colonisation with *Staphylococcus aureus*. Many of the comorbidities above can be captured in the simple ASA score which is strongly predictive of SSI risk.

Intra-operative factors influencing SSI risk include sterile technique (e.g. skin preparation, surgical scrub, aseptic barriers), operative technique related to haemostasis and debridement and duration of the procedure. Surgical experience is clearly associated with lower SSI risk and surveillance and feedback to surgeons also appears to lower infection rates. The use of autologous rather than homologous blood transfusion reduces infection rates after colorectal surgery,[1] and control of intra-operative temperature and glucose and avoidance of operative drains may also prevent SSI.

Post-operatively, the risks for SSI have been less defined, but interventions of likely benefit include attention to handwashing, limiting the duration of prophylactic antibiotics, early removal of drains, minimising the duration of intravenous and urinary catheterisation and correction of host factors associated with SSI.

Notwithstanding the importance of considering and correcting, where possible, the risk factors described above, appropriate antimicrobial prophylaxis plays an important role in controlling SSI, reducing morbidity and mortality, cost and length of stay whilst reducing overall antibiotic use. The benefits can be quite dramatic: for example in colorectal surgery, where antibiotic prophylaxis has been well studied, the number needed to treat to prevent 1 death from infection is only 17.[2]

Antimicrobial prophylaxis is most strongly recommended in colorectal surgery and prosthetic hip/knee surgery and is generally recommended for cardiothoracic, head and neck, most upper gastrointestinal, obstetric and gynaecology procedures, prostatectomy, vascular surgery, closed fracture fixation and neurosurgery. The choice of antimicrobial agent should be directed against likely causative organisms. For most procedures not involving the lower gastrointestinal tract a first generation cephalosporin (e.g. cefazolin) is appropriate, with addition of metronidazole for the former. Targeted prophylaxis against specific pathogens such as methicillin resistant *S. aureus* may be needed in some hospitals for certain high risk procedures or if the patient is known to be previously colonised.

The administration of antimicrobial should be timed to achieve high drug levels at the time of incision. Dosing commencing later has a rapidly reducing benefit and 'post-operative prophylaxis' has no benefit. In most situations a single dose only of antibiotic is required, but for prolonged procedures (> 3 hours) with major blood loss a further operative dose can be given. There is no indication for ongoing prophylaxis post-operatively or 'until drain removal' for any surgical procedure.[3]

The prevention of SSI associated with surgical implants is of particular importance because of their severity, associated morbidity and mortality and usual requirement for prosthetic removal to effect cure. Problems in assessing clinical efficacy of preventative

strategies relate to the prohibitively large sample sizes required, difficulties in distinguishing superficial from deep infection and microbiological diagnosis of infection particularly with organisms that are common laboratory contaminants.[4] These problems are exemplified in the paper by Lucey and Myburgh in this issue,[5] who found, in comparison to a retrospective control period, a reduction in positive CSF gram stains and cultures in patients with external ventricular drains following introduction of a management protocol including drain management and short term use of cephalothin commencing prior to insertion. The analysis is complicated by small numbers, inclusion of replacement drains which are likely to be associated with higher infectious risks and limited microbiological and clinical data. The low rate of positive gram stains is surprising, suggesting some of the CSF isolates, particularly coagulase-negative Staphylococci, may have been contaminants. Many of the isolates in the pre-protocol group (e.g. *Acinetobacter, Serratia, Enterococcus* spp. and coagulase negative Staphylococci would also not be expected to be reliably inhibited by Cephalothin. The management protocol called for daily surveillance of CSF, although for technical and administrative reasons approximately half the potential samples were not received and similar surveillance occurred pre and post-protocol. Unfortunately, routine surveillance of CSF in patients with external ventricular drains does not appear to be helpful or warranted,[6] and manipulation may increase the risk of introducing infection. Drains were replaced at similar intervals routinely in both groups, but whether this prevents infection or justifies the small procedural risks is unknown. For centrally-placed intravenous catheters it is clear that routine replacement does not reduce infection and is not indicated.

The majority of patients (8/12 and 13/15 in the pre and post-protocol periods respectively) received antibiotics making it unlikely that antibiotic use *per se* reduced infection risk. However, the management protocol was clearly associated with less inappropriate continuation of antibiotics post insertion. Jacobs and Westerband,[7] found higher septic morbidity and pneumonia rates in head injury patients receiving prophylaxis for the duration of monitoring, illustrating the potential hazards of inappropriate antimicrobial prophylaxis. Thus the management protocol may have beneficial effects in this regard. Finally, it is likely that improved adherence to sterile techniques during insertion and manipulation of drains contributed to the findings observed post-protocol.

A number of studies have attempted to determine the impact of prophylactic antibiotics on infection related to intracranial pressure monitors. In a recent meta-analysis of 85 reports only 2 studies met the predetermined inclusion criteria and these 2 were too small to produce significant results.[8] A subsequent review of 215 patients found an overall infection rate of 7.4%, but no difference between those receiving prophylaxis and those not.[9]

Until, or unless, well-conducted studies are performed emphasis on preventing these infections should focus on full surgical sterile technique during insertion, minimising the duration of monitoring and meticulous local care and sterile technique during manipulations. A single dose of 1 g Cefazolin, Cephalothin or Flucloxacillin would be a reasonable option prior to insertion, but administration beyond this single dose can probably not be justified.

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