Optimising organ perfusion: the high-risk surgical patient and the sick ICU patient.

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Abstract

Maintenance or prompt restoration of an oxygen supply sufficient to facilitate adequate cellular metabolism is fundamental in maintaining organ 'happiness'. This is particularly relevant when metabolic needs alter markedly, for example, in response to major surgery and critical illness. The consequences of inadequate tissue oxygenation are local complications such as wound and anastomotic breakdown, organ dysfunction and death. At present, heavy reliance is placed upon surrogate markers of tissue oxygenation such as blood pressure and hyperlactataemia that are insensitive to early organ compromise. Advances in oxygen sensing technology will facilitate monitoring in various organ beds and allow more precise titration of therapies to physiologically relevant endpoints. Clinical trials will obviously be needed to evaluate any impact on outcomes, however accurate, on-line monitoring of the adequacy of tissue oxygenation offers the promise of a paradigm shift in resuscitation and perioperative practice. This review will explore current evidence for goal-directed therapy in the optimisation of organ perfusion in high-risk surgical and critically ill patients, and offer arguments to support the potential utility of tissue oxygen monitoring.

Introduction

Much has been written about haemodynamic optimisation of both the critically ill ICU patient and the high-risk surgical patient. Diverse strategies and monitoring approaches have been advocated and discarded, and no clear consensus has been reached despite decades of research.

While presenting different challenges, high-risk surgical patients and sick ICU patients share some commonalities that warrant their joint consideration. High-risk surgery accounts for only 12.5% of surgical procedures, yet over 80% of surgical deaths[1]. Alongside increased mortality, this cohort is at greater risk of post-operative complications including poor wound healing, anastomotic breakdowns, surgical site and chest infections, prolonged ileus and delayed discharge from hospital. Independent of preoperative risk, the occurrence of a complication within 30 days of surgery was associated with a 69% reduction in long-term patient survival[2]. Likewise, sepsis, as an example of critical illness, accounted for >50,000 ICU admissions in England in 2015 with a hospital mortality exceeding 30%[3]. There is also a considerable long-term morbidity and mortality risk; about a third die in the year after sepsis, a sixth experience severe persisting weakness, psychiatric or cognitive issues, and only half make a complete or near-complete recovery[4].

Inadequate organ perfusion with resultant tissue hypoxia represents a common pathway to poor outcomes in both surgical and ICU patient groups. How best to identify and respond to perfusion abnormalities remains unresolved, and this continues to generate considerable debate and controversy. The notable absence of actual perfusion targets within organ beds has hampered progress. Clinicians rely

upon (i) indicators suggesting circulatory stability such as blood pressure, heart rate and cardiac output, (ii) surrogates of blood volume status such as fluid responsiveness, respiration-induced variations in pulse pressure and stroke volume, and central venous pressure, and (iii) markers of the adequacy of organ perfusion such as urine output, serum lactate and central venous saturation (SvO_2).

Such global measures do not account for between-organ variations; the perfusion of some tissue beds is compromised earlier than others, e.g. gut and skin as compared to brain. In the case of lactate, the measured blood level depends on the balance between production and utilization; lactate is an important energy substrate, particularly at times of cellular and metabolic stress. Hyperlactataemia may not occur until significant perturbation has occurred(5).

A goal-directed approach is physiologically coherent. Some studies, mostly single-centre, have signalled improved survival and decreased complication rates across a range of surgical sub-specialties(6–9), and in critically ill patients with sepsis(10). However, outcome improvements have not been consistently reproducible, especially in large, multi-centre trials(11–14). Does this lack of benefit represent an overall failure of the concept or reflect inadequacies in the monitoring technologies utilized, lack of user expertise, inappropriate study design (e.g. using fixed drug or fluid dosing), targeting the wrong goals, unsuitable patient selection, failure to adhere to the study protocol, or combinations thereof? Are these negative studies a victory of real-world pragmatism over theoretical purity, for example, selecting sample sizes based on unrealistic treatment effects, or enrolling lower-risk patients to meet recruitment schedules? In this review we shall explore the current evidence base for goal-directed

therapy in the optimisation of organ perfusion in high-risk surgical and critically ill patients, and offer a rationale supporting the potential utility of tissue oxygen monitoring.

Prediction tools for post-operative complications

A predicted postoperative hospital mortality risk above 5% is a widely accepted definition of high-risk surgery(15). Patient factors such as frailty, nutritional status, cardio-respiratory and metabolic fitness, and pre-existing organ dysfunction, alongside surgical factors such as emergency or urgent surgery, and the anticipated degree of surgical complexity, blood loss and extent of tissue trauma all contribute to this risk prediction.

A variety of scoring tools have been developed to quantify surgical risk preoperatively, both to inform critical care resource allocation and shared decision-making. The American Society of Anesthesiologists' Physical Status classification (ASA-PS I-V) is probably the mostly widely used system for categorising risk pre-operatively(16). While this score can predict post-operative outcomes for populations(17), it does not provide an individualised risk prediction of an adverse outcome. Other models such as P-POSSUM do attempt to predict individual risk but this tool is predicated on intra-operative findings to better assess postoperative risk(18). The Surgical Outcomes Risk Tool (SORT), developed by colleagues at our institution from the 2011 NCEPOD 'Knowing The Risk' dataset, utilises six pre-operative variables to provide a predicted 30-day mortality risk for patients undergoing non-cardiac, non-neurological surgery with better discrimination than either ASA-PS or the Surgical Risk Scale(19).

Aside from scoring systems and risk prediction models, preoperative cardiopulmonary exercise testing (CPET) has been used to appraise perioperative risk. The original paper focussed on identifying patients who would not need postoperative critical care(20). This was based on an anaerobic threshold (AT) ≥11 ml oxygen consumed per kg body weight per minute, a value previously identified in patients with moderate-to-severe heart failure(21). Seemingly 'unfit' patients with an AT below this cut-off had an 18% postoperative mortality versus <1% in those with AT values above. However, a recently published prospective cohort study examining 1401 patients enrolled from 25 hospitals across four countries failed to show any utility of AT measurement in predicting either death or myocardial infarction within 30 days of non-cardiac surgery, or moderate-to-severe postoperative complications(22). A lower peak oxygen consumption value during preoperative CPET did predict pulmonary complications, surgical site infections, unexpected ICU admissions, and re-operations but interestingly, was not associated with postoperative cardiac complications. Perhaps such a 'fit versus unfit' paradigm, based on dichotomised AT values is an over-simplification. A category of intermediate fitness and risk must also exist, characterised by a range of AT values falling either side of this cut-off(23). Nevertheless, a lack of cardiorespiratory reserve and an inability to adequately increase oxygen delivery and consumption in the face of increased metabolic stress should plausibly identify a patient at increased risk of postoperative complications.

Oxygen delivery and tissue hypoxia

Oxygen is essential to sustain cellular respiration in all eukaryotic life forms, including humans. More than 90% is consumed by mitochondria, predominantly for generation of ATP by oxidative phosphorylation, but also for production of reactive oxygen species and heat production via ATP-uncoupled respiration. Importantly, the contribution of these latter processes may increase significantly under conditions of inflammation and critical illness but are rarely considered within the general concept of whole-body oxygen delivery and consumption.

The oxygen cascade describes the progressive, step-wise diminution of oxygen partial pressure from inspired air to mitochondrion. Established dogma dictates it is this pressure gradient that drives tissue oxygenation, however, this neglects the centrality of cardiac output in maintaining oxygen delivery to meet tissue needs.

Tissue hypoxia is a major pathophysiological determinant of outcome in both high-risk surgical and sick ICU patients. An initial increase in oxygen consumption is characteristic of the stress response following a surgical insult. Failure to meet this increased demand, with consequent development of a conceptual tissue oxygen debt, is detrimental; an increased incidence of complications, organ failure and death correlate with an increasing severity and duration of tissue hypoxia(24). Likewise, early, non-resuscitated sepsis is often characterised by hypotension, hyperlactataemia and reduced central or mixed venous oxygen saturations (SvO_2). These abnormalities imply, but do not conclusively prove, compromised organ perfusion with increased anaerobic metabolism and tissue hypoxia. Failure to

significantly improve circulatory status following seemingly adequate resuscitation prognosticates for poor outcome(25).

Goal-directed therapy in sepsis

Based on such observational findings, early correction of organ hypoperfusion using protocolised 'early goal-directed therapy' was advocated by Manny Rivers and colleagues(10). Their strategy utilised aggressive fluid resuscitation ± blood transfusion ± dobutamine, and specifically targeted central venous oxygen saturation ($ScvO_2$) alongside other physiological variables over a 6-hour period. A prospective, randomised, controlled trial (PRCT) in patients with presumed sepsis presenting to their emergency department demonstrated significant improvements in survival rates(10). This study however generated multiple questions, for example why mortality reduction was seen only in patients dying acutely from sudden cardiovascular collapse rather than multi-organ failure. Nonetheless, this concept was enshrined within the early resuscitation bundle of the Surviving Sepsis Campaign guidelines(26,27) until three multi-centre PRCTs (ProCESS, ARISE, ProMISe) failed to replicate morbidity or mortality benefit over the standard-of-care limbs (11–13). To provide balance to the debate, the patients in these three trials were much less sick despite using the same entry criteria; baseline $ScvO_2$ values were much higher with the UK study reporting that a third of the enrolled patients would not normally have been admitted to a critical care unit(11). The large majority of patients did not have any cardiac output monitoring to more accurately titrate fluid and drug therapy. It is reasonable to assume that the general quality of patient care (including resuscitation)

has improved over the intervening 15-20 years. Indeed, little between-group differences were seen in therapeutic interventions in the latter studies. This may also be in part related to a considerable proportion (>25-30%) of the protocol groups not achieving the targeted physiological endpoints. This is problematic for studies in which a treatment goal is the intervention under scrutiny.

Whether improved compliance to the protocol would have made a difference to outcomes remains moot. Nonetheless, it remains a generally accepted maxim that early recognition of a septic (or any other critically ill) patient followed by prompt and appropriate cardiorespiratory intervention is beneficial. Important questions remain as to what intervention is optimal and what physiological endpoint(s) should be targeted.

Perioperative goal-directed therapy:

Resuscitation to predefined physiological targets has long been standard practice in intensive care units. This is increasingly widespread, though not universal, in the peri-operative setting, even though outcome studies predate those undertaken in the critically ill. In a landmark PRCT, targeting supra-normal peri-operative oxygen delivery (>600 ml/min/m^2) in a high-risk surgical cohort using fluid and dobutamine, initiated preoperatively, halved complication rates and reduced mortality by 75%(24). Comparable findings have been replicated in a number of other studies using fluid and dopexamine or epinephrine to achieve similar oxygen delivery targets(6,7).

The fall from grace of the pulmonary artery flotation catheter following the negative UK multicentre PAC-MAN study(28) and other similar trials led investigators to seek

new and less-invasive ways of both monitoring and augmenting oxygen delivery, and to seek different endpoints. Some studies have targeted a stroke volume at the top of the Starling curve either intra- or post-operatively. Our group and others, utilising oesophageal Doppler, demonstrated reductions in postoperative complications and hospital length of stay in abdominal, cardiac and orthopaedic surgical populations (9,29–32). While not all oesophageal Doppler-guided optimisation studies have demonstrated outcome improvement, a recent systematic review found postoperative complications were reduced in patients undergoing colorectal and high-risk surgery but not in those undergoing intermediate-risk surgery (33). Similar studies with other technologies have yielded more variable outcomes. This may reflect the risk status of the patients studied, but also methodological issues relating to either the technology(34,35), the intervention, or the choice of targeted endpoint. For example, multiple perioperative studies using a regimen including a fixed dose infusion of dopexamine have all failed to show benefit so the underlying rationale behind this approach needs to be questioned(14,36,37).

Summarising the above, general improvements in perioperative anaesthesia and haemodynamic management mean than lower-risk patients are likely to do well regardless of optimisation, unless some untoward catastrophe occurs, as adequate tissue perfusion is likely to be maintained throughout. Even in higher-risk patients, 30-day mortality rates are now relatively low in developed countries(22). The focus should perhaps be on a reduction in postoperative complications rather than mortality. Limitations in the monitoring technology being utilized must be fully appreciated by the user. For example, changes in arterial compliance related to use of

vasopressors, rapid major blood loss or large volume fluid administration will invalidate trends in cardiac output assessed by non-calibrated pulse contour or bio-reactance devices(38,39).

Finally, selection of appropriate treatment endpoints, and safe interventions to achieve perfusion targets, appear key. The use of a fixed rate vasoactive infusion can hardly be described as haemodynamic *optimisation*. The ongoing debate surrounding liberal versus restrictive perioperative fluid regimens fails to consider individual patient needs. From a physiological standpoint, the patient needs the right amount of an intervention to ensure adequate tissue perfusion. Too little or too much may both prove deleterious. These issues will be discussed in more detail below.

Enhanced recovery after surgery (ERAS), critical illness and fluid regimens

A healthy debate has raged over the past two decades over the volume of fluid needed by a patient, both perioperatively and during critical illness. An association between a positive sodium and water balance and increased mortality and rates of complications has been reported perioperatively(40,41) and in patients with sepsis(42). This study by Boyd and co-workers is instructive; they reported a median positive fluid balance after 4 days ranging from 1.5 litres in the 'driest' quartile to 20.5 litres in the 'wettest'. A quarter of patients in this 'wet' quartile received more than 36 litres of fluid. At just 12 hours, median net fluid balance varied from 710 ml to 8150 ml in the two extreme quartiles. Mortality was twice as high in the wet quartile. While acknowledging that sicker patients are more likely to require, or at least be given, more fluid, a marked difference in outcomes remained even after adjustment for illness severity.

Baseline practices in the reporting institution, or even country, are generally overlooked. In the three Early Goal-Directed therapy (EGDT) trials in septic shock(11–13), fluid volumes were greater in the US study compared to both Australia and the UK. Traditional users of low volume fluid replacement have reported outcome benefit from additional (titrated) fluid administration, whereas the opposite appears true in places where fluid use has been traditionally more liberal. For example, Venn and colleagues reported improved outcomes when more fluid was given intra-operatively to patients undergoing hip fracture repair, from a median 1392 ml to 2051 ml titrated to an optimised stroke volume[43]. Conversely, Branstrup and colleagues reported a reduced rate of postoperative complications with fluid *restriction*; a median fluid volume of 2740 ml was administered on the day of colorectal resection compared 5388 ml in the 'liberal' fluid cohort(44).

Despite a paucity of high-quality evidence, recent consensus statements have advocated fluid restriction for patients undergoing abdominal surgery as part of 'enhanced recovery' protocols(45–47). However, the story becomes more confusing with the recent publication of the RELIEF trial, a large PRCT of 3000 high-risk patients undergoing major abdominal surgery(48). Outcomes, notably acute kidney injury, were *improved* in the liberal fluid group who received a median 6.1 litres in the first 24 hours following commencement of surgery compared to those receiving 3.7 litres in the fluid restriction group.

Surrounded by such conflicting findings, to couch questions pertaining to optimisation of tissue perfusion simply in terms of '*wet versus dry*' is arguably reductionist thinking *par excellence*. Notably, few of the recent large perioperative trials have utilized more

sophisticated monitoring. For example, in the RELIEF study only 1-in-7 of the enrolled patients received any form of intraoperative cardiac output monitoring. Intraoperative measurement of lactate and $ScvO_2$ was not reported, while only 30% had a post-operative lactate measurement performed. It is thus conceivable that some 'dry' patients may have been seriously under-perfused while some 'wet' patients may also have been under-perfused or overloaded with excessive fluid. Likewise, pursuit of arbitrary physiological surrogates of organ perfusion, or targeting of pre-specified values of oxygen delivery may not necessarily achieve the unmeasured goal of adequate tissue oxygenation, and may even prove deleterious if excessive volumes of fluid or inotrope are used(49).

The wet-dry debate in the early resuscitation of septic patients has recently entered the public arena with forceful criticism of the ongoing US CLOVERS (Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis) trial by Public Citizen, a consumer advocacy organisation. In this study, patients are being randomised to receive predominantly fluid or vasopressors for initial resuscitation; Public Citizen argue the need for a third group receiving standard of care rather than either extreme [(50)].

A more nuanced approach acknowledges the enormous heterogeneity among these patients and abandons the concept of rigid one-size-fits-all protocolism. Comorbidities and variable cardiorespiratory reserve coupled with widely-differing metabolic derangements and fluid shifts, alongside often unpredictable circulatory responses to sedative agents and anaesthetic interventions, dictate the need for a more bespoke management with appropriate targeted monitoring. Such an approach reframes the debate in terms of cellular wellbeing with haemodynamic optimisation

of the high-risk surgical and sick ICU patient guided by verified, objective markers of tissue oxygenation.

Tissue oxygen monitoring

Our current ability to detect evolving shock and tissue hypoxia at an early stage is limited. Physiological adaptation to blood loss, heart failure and other low output states can effectively camouflage deterioration, especially in young, fit people who have considerable cardiorespiratory reserve. Animal and clinical studies confirm conventional haemodynamic measures such as heart rate and blood pressure are poor markers of early tissue hypoperfusion, as is serum lactate[5,51–53]. While global blood flow monitoring gives some indication of the adequacy of tissue perfusion, it does not offer detail at the tissue level, the impact of any microcirculatory perturbations nor, as mentioned earlier, variability in blood flow between organ beds or the susceptibility of particular organs to tissue hypoxia.

In recognition of these limitations, investigators have turned to regional and tissue oxygenation monitoring in patients including gastric tonometry[54], near-infra-red spectroscopy[55], side-stream dark field imaging of the microcirculation[56], and tissue oxygen tension monitoring of subcutaneous tissue[57] and conjunctiva[58], albeit with limited success. None of these modalities have become established in routine clinical practice due to technical and reliability issues, and complexities of measurement.

Our lab has worked for over a decade with Oxford Optronix, a small British company, to develop a bedside tissue oxygen (PtO_2) monitor inserted into the bladder wall via a modified Foley catheter. This device is shortly to undergo clinical trials. PtO_2

represents the partial pressure of oxygen of the interstitial space of a given tissue and varies between different organ beds[59]. As PtO_2 is a measure of the local oxygen supply/demand equilibrium to that tissue bed, the normal range in healthy animals reflects the balance between blood flow to that organ and its aerobic metabolic activity. Thus resting muscle PtO_2 will be much higher than liver PtO_2 as the liver is more metabolically active and its blood supply mainly constitutes a portal circulation containing deoxygenated haemoglobin after its earlier passage through the gut [60].

PtO_2 falls when tissue oxygen delivery cannot meet the metabolic requirements of predominantly mitochondrial respiration and rises in situations of relative metabolic inactivity such as during the established organ failure of sepsis[61]. In rodent models of haemorrhage-reperfusion and hypoxaemia-reoxygenation[61,62], PtO_2 was sensitive to changes in perfusion status across a variety of organ beds ranging from superficial, accessible tissues such as bladder and muscle to deeper, more vital organs (liver and renal cortex). Upon translation to a 55-60 kg porcine model(5), the fall in bladder PtO_2 preceded conventional clinical markers of shock such as blood pressure and lactate, thus offering further encouragement for its utility in human patients. These data raise the prospect that PtO_2 monitoring may offer an 'early warning system', detecting incipient shock prior to current modalities used in routine clinical practice.

As noted earlier, a static PtO_2 value represents the balance between local oxygen supply and demand. Additional information regarding this balance can be obtained with a dynamic assessment of circulatory sufficiency and organ perfusion. One such example is the use of an 'oxygen challenge' test, i.e. a short period of hyperoxia. The predictable rise in PtO_2 in different organ beds following hyperoxia in healthy animals

was blunted during various shock states including hypovolaemia and resuscitated sepsis[63]. While this response was expected in hypovolaemia, the blunted tissue response that persisted despite resuscitation in sepsis implies local microcirculatory dysfunction or shunting. Notably, the degree of blunting was in line with illness severity and prognosis[64]. A similar blunted response was prognostic in septic patients[65]. A small, single centre study used goal-directed therapy in septic patients to target a positive oxygen challenge response above a certain threshold, reported improved survival [66].

Tissue oxygen monitoring thus has a strong foundation in both basic science and clinical research. Animal models have allowed testing over diverse tissue beds, from brain and kidney to conjunctiva and muscle. Some studies have assessed responses to cardiorespiratory insults in different anatomical compartments of the same organ bed[67]. Superiority has been demonstrated in early detection of inadequate tissue perfusion compared to conventional monitoring modalities. The oxygen challenge test further enhances this diagnostic capability, allowing early recognition of complex perfusion abnormalities such as those observed in sepsis[65]. Findings in these pre-clinical models suggest the bladder, an easily accessible, superficial organ, can act as a 'canary' tissue bed that accurately reflects changes in deeper, more vital organs.

Prior technologies have failed to become established in routine clinical practice, so resolution of practical, technical and reliability issues is paramount. Monitoring of tissue oxygenation has evolved from polarographic Clark electrodes to modern devices based on photoluminescence quenching. Disadvantages of the Clark electrode technique are the need to calibrate *in vivo*, and the consumption of oxygen by the

electrode itself that makes it less accurate at lower values of PtO_2. Modern photoluminescence technology uses a small, transition-metal containing optode sensor. Following luminescence with incident light, this signal is quenched by oxygen. With partial pressures of oxygen inversely proportional to the decay half-life of the luminescent signal, lower oxygen tensions will result in a longer half-life. This basic physical concept offers three advantages. It can be incorporated into the Stern-Volmer equation to calculate PtO_2 in real-time, *in vivo* calibration is not needed, and detection of tissue hypoxia is increasingly accurate with longer half-lives at lower values of PtO_2.

Potentially, this technology may prove invaluable in optimising organ perfusion in patients undergoing high-risk surgery and in the critically ill. A failure to maintain adequate organ perfusion and tissue oxygenation is a major determinant of outcome in these patients, yet trials targeting supra-physiological values of oxygen delivery have often proven disappointing. Arguably, the choice of targeted endpoint, the monitoring technology, and the patient population are responsible for the conflicting findings. PtO_2 may thus offer an early diagnostic capability of local oxygen supply/demand imbalance, and a theranostic role by guiding the choice of intervention and titrating the dose (of fluid, drug, ventilator setting) to an acceptable but not excessive level. Early mortality following elective surgery is low in developed countries yet morbidity, delaying hospital discharge or requiring readmission, is still problematic and impacts both on the patient and the efficiency of the healthcare system. This morbidity may be severe, necessitating intensive care (re-)admission but even relatively minor morbidity can have a significant impact. An accurate, continuous means of measuring the adequacy of tissue perfusion would represent a Holy Grail of

haemodynamic monitoring. Whether PtO_2 monitoring, or another novel technology, fulfils this dream remains to be seen. However, there is a definite and urgent need to progress from the current status quo.

Author contributions:

TP and DB planned and co-wrote the first draft of this article.

AD provided advice and expertise on the technical and basic science aspects. He edited the section on 'tissue oxygen monitoring'. In addition, he provided the graph used in figure 1.

MS provided editorial guidance and was responsible for final draft revision.

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References:

1. Pearse RM, Harrison DA, James P et al. Identification and characterisation of

the high-risk surgical population in the United Kingdom. *Crit Care*. 2006;**10**:1–6

2. Khuri S, Henderson W, DePalma R, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg. 2005; 242:326-41
3. Shankar-Hari M, Harrison DA, Rubenfeld GD, Rowan K. Epidemiology of sepsis and septic shock in critical care units: Comparison between sepsis-2 and sepsis-3 populations using a national critical care database. *Br J Anaesth.* 2017;**119**:626–36.
4. Dyson A, Simon F, Seifritz A et al. Bladder tissue oxygen tension monitoring in pigs subjected to a range of cardiorespiratory and pharmacological challenges. *Intensive Care Med*. 2012;**38**:1868–76.
5. Prescott HC, Angus DC. Enhancing Recovery From Sepsis: A Review. JAMA. 2018;319:62–75.
6. Boyd O, Bennett ED, Grounds RM. A Randomized Clinical Trial of the Effect of Deliberate Perioperative Increase of Oxygen Delivery on Mortality in High-Risk Surgical Patients. *JAMA J Am Med Assoc*. 1993;**270**:2699-707
7. Wilson J, Woods I, Fawcett J et al. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. *BMJ*. 1999;**319**:1099-103
8. Lobo S, Salgado P, Castillo V et al. Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. *Crit Care Med*. 2000; **28**: 3396-404
9. Sinclair S, James S, Singer M. Intraoperative intravascular volume

optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ*. 1997; **315**: 909–912

10. Rivers E, Nguyen B, Havstad S et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**:1368-77
11. Mouncey P, Osborn T, Power G, Harrison D, Sadique M, Grieve R. Trial of Early, Goal-Directed Resuscitation for Septic Shock for the ProMISe Trial Investigators*. *N Engl J Med*. 2015; **372**: 1301-11
12. Yealy D, Kellum J, Huang D et al. A Randomized Trial of Protocol-Based Care for Early Septic Shock. Process trial. N Engl J Med. 2014; **370**: 1683–1693.
13. Peake S, Dellaney A, Bollomo R et al. Goal-Directed Resuscitation for Patients with Early Septic Shock. Arise Trial. N Engl J Med. 2014; **371**: 1496-506
14. Pearse R, Harrison D, MacDonald N , Gillies M, Blunt M, Ackland G. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery a randomized clinical trial and systematic review. *JAMA - J Am Med Assoc*. 2014;**311**:2181–90.
15. Boyd O, Jackson N. How is risk defined in high-risk surgical patient management? *Crit Care*. 2005;**9**:390–6.
16. ASA House of Delegates on October 15, 2015. American Society of Anesthesiologists - ASA Physical Status Classification System. (2015). Available at: http://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system. (last accessed 21 September 2018)
17. Wolters U, Wolf T, Stützer H, Schröder T. ASA classification and perioperative variables as predictors of postoperative outcome. *Br J Anaesth*. 1996;**77**:217–22.

18. Prytherch D, Whiteley M, Higgins B, Weaver P, Prout W, Powell S. POSSUM and Portsmouth POSSUM for predicting mortality. *Br J Surg*. 1998;**85**:1217–20.
19. Protopapa K, Simpson J, Smith N, Moonesinghe S. Development and validation of the Surgical Outcome Risk Tool (SORT). *Br J Surg*. 2014;**101**:1774–83.
20. Older P, Smith R, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. *Chest*. 1993;**104**:701–4.
21. Weber K, Janicki J. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. *Am J Cardiol*. 1985;**55**:22A–31.
22. Wijeysundera D, Pearse R, Shulman M et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet*. 2018; **391**:2631-640.
23. Rose G, Davies R, Davison G et al. The cardiopulmonary exercise test grey zone; optimising fitness stratification by application of critical difference. *Br J Anaesth.* 2018;**120**:1187–94.
24. Shoemaker W, Appel P, Kram H. Role of oxygen debt in the development of organ failure sepsis, and death in high-risk surgical patients. *Chest*. 1992;**102**:208–15.
25. Shoemaker WC. Physiologic Patterns in Surviving and Nonsurviving Shock Patients. *Arch Surg*. 1973;106:630.
26. Dellinger RP, Levy MM, Rhodes A et al. Surviving Sepsis Campaign. *Crit Care Med*. 2013;**41**:580-637

27. Rhodes A, Evans LE, Alhazzani W et al. Surviving Sepsis Campaign. *Crit Care Med*. 2017; **45**:486-552

28. Harvey S, Harrison DA, Singer M. Assessment of the Clinical Effectiveness of Pulmonary Artery Catheters in Management of Patients in Intensive Care (PAC-Man): A Randomised Controlled Trial. *Lancet* 2005; **366:472**–7.

29. Mythen M, Webb A. Perioperative Plasma Volume Expansion Reduces the Incidence of Gut Mucosal Hypoperfusion During Cardiac Surgery. *Arch Surg.* 1995; **130**: 423-9.

30. McKendry M, McGloin H, Saberi D et al. Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery. *BMJ*. 2004; **329**: 25

31. Gan TJ, Soppitt A, Maroof M et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiol*. 2002; **97**: 820-6

32. Kuper M, Gold S, Callow C et al. Quality improvement report: Intraoperative fluid management guided by oesophageal Doppler monitoring. *BMJ*. 2011; **342**: 3016

33. Reanimación R, Ripollés-Melchor J, Casans-Francés R et al. Goal directed hemodynamic therapy based in esophageal Doppler flow parameters: A systematic review, meta-analysis and trial sequential analysis. *Rev Esp Anestesiol Reanim*. 2016;**63**:384-405.

34. Thiele R, Bartels K, Gan T-J. Inter-device differences in monitoring for goal-directed fluid therapy. *Can J Anesth Can d'anesthésie*. 2015; **62**:169-81

35. Broch O, Bein B, Gruenewald M et al. Accuracy of Cardiac Output by Nine

Different Pulse Contour Algorithms in Cardiac Surgery Patients: A Comparison with Transpulmonary Thermodilution. *Biomed Res Int.* 2016;**2016**:3468015

36. Takala J, Meier-Hellmann A, Eddleston J, Hulstaert P, Sramek V. Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. European Multicenter Study Group on Dopexamine in Major Abdominal Surgery. *Crit Care Med*. 2000;**28**:3417-23
37. Jhanji S, Vivian-Smith A, Lucena-Amaro S, Watson D, Hinds C, Pearse R. Haemodynamic optimisation improves tissue microvascular flow and oxygenation after major surgery: A randomised controlled trial. *Crit Care*. 2010;**14**:R151.
38. De Pascale G, Singer M, Brealey D. Comparison of stroke volume measurement between non-invasive bioreactance and esophageal Doppler in patients undergoing major abdominal–pelvic surgery. *J Anesth*. 2017; **31**:545-51.
39. Grensemann J. Cardiac Output Monitoring by Pulse Contour Analysis, the Technical Basics of Less-Invasive Techniques. *Front Med.* 2018;**5**:64
40. Tambyraja A, Sengupta F, MacGregor A, Bartolo D, Fearon K. Patterns and clinical outcomes associated with routine intravenous sodium and fluid administration after colorectal resection. *World J Surg*. 2004;**28**:1046–51.
41. Silva J, De Oliveira A, Nogueira F et al. The effect of excess fluid balance on the mortality rate of surgical patients: A multicenter prospective study. *Crit Care*. 2013;**17**:R288.
42. Boyd J, Forbes J, Nakada T, Walley K, Russell J. Fluid resuscitation in septic

shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med*. 2011;**39**:259-65.

43. Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P. Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. *Br J Anaesth.* 2002;**88**:65-71.
44. Brandstrup B, Tønnesen H, Beier-Holgersen R et al. Effects of Intravenous Fluid Restriction on Postoperative Complications: Comparison of Two Perioperative Fluid Regimens - A Randomized Assessor-Blinded Multicenter Trial. *Ann Surg*. 2003;**238**: 641-48.
45. Feldheiser A, Aziz O, Baldini G et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand*. 2016; **60**:289-334.
46. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr*. 2012;**31**:783-800.
47. Scales K. Intravenous fluid therapy in adults in hospital (CG174). *Natl Inst Clin Excell*. 2013;**23**:S6-8.
48. Myles PS, Bellomo R, Corcoran T et al. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. *N Engl J Med*. 2018;**378**:2263-74.
49. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D. Elevation of Systemic Oxygen Delivery in the Treatment of Critically Ill Patients. *N Engl J Med*. 1994;**330**:1717-22.
50. https://www.citizen.org/media/press-releases/federal-regulators-must-halt-

unethical-reckless-sepsis-trial-funded-nih (last accessed 21 September 2018)

51. Levy B, Gibot S, Franck P, Craviosy A, Bollaert P-E. Relationship between muscle Na+ K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet*. 2005;**365**:871–5
52. James J, Luchette F, McCarter F, Fischer J. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet*. 1999;**354**:505-8.
53. Londoño J, Niño C, Díaz J et al. Association of Clinical Hypoperfusion Variables With Lactate Clearance and Hospital Mortality. *Shock.* 2018;**50**:286–92.
54. Gomersall C, Joynt G, Freebairn R, Hung V, Buckley T, Oh T. Resuscitation of critically ill patients based on the results of gastric tonometry: a prospective, randomized, controlled trial. *Crit Care Med*. 2000;**28**:607-14.
55. Creteur J, Carollo T, Soldati G, Buchele G, De Backer D, Vincent JL. The prognostic value of muscle StO_2 in septic patients. *Intensive Care Med*. 2007;**33**:1549-56.
56. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med*. 2002;**166**:98-104.
57. Drucker W, Pearce F, Glass-Heidenreich L et al. Subcutaneous tissue oxygen pressure: a reliable index of peripheral perfusion in humans after injury. *J Trauma*. 1996;**40**:S116-22.
58. Kram H, Shoemaker W. Method for intraoperative assessment of organ perfusion and viability using a miniature oxygen sensor. *Am J Surg*. 1984;**148**:404–7.
59. De Santis V, Singer M. Tissue oxygen tension monitoring of organ perfusion:

rationale, methodologies, and literature review. *Br J Anaesth*. 2015;**115**:357–65

60. Dyson A, Stidwill R, Taylor V, Singer M. Tissue oxygen monitoring in rodent models of shock. *Am J Physiol Heart Circ Physiol*. 2007;**293**:526–33.
61. Boekstegers P, Weidenhofer S, Kapsner T, Werdan K. Skeletal muscle partial pressure of oxygen in patients with sepsis. *Crit Care Med*. 1994;**22**:640-50.
62. Dyson A, Stidwill R, Taylor V, Singer M. The impact of inspired oxygen concentration on tissue oxygenation during progressive haemorrhage. *Intensive Care Med*. 2009;**35**:1783–91.
63. Tremper KK, Waxman K, Shoemaker WC. Effects of hypoxia and shock on transcutaneous PO_2 values in dogs. *Crit Care Med*. 1979;**7**:526-31.
64. Dyson A, Rudiger A, Singer M. Temporal changes in tissue cardiorespiratory function during faecal peritonitis. *Intensive Care Med*. 2011;**37**:1192–200.
65. Yu M, Morita SY, Daniel SR, Chapital A, Waxman K, Severino R. Transcutaneous pressure of oxygen: A noninvasive and early detector of peripheral shock and outcome. *Shock*. 2006;**26**:450–6
66. Yu M, Chapital A, Ho HC, Wang J, Takanishi D. A prospective randomized trial comparing oxygen delivery versus transcutaneous pressure of oxygen values as resuscitative goals. *Shock*. 2007;**27**:615-22
67. Whitehouse T, Stotz M, Taylor V, Stidwill R, Singer M. Tissue oxygen and hemodynamics in renal medulla, cortex, and corticomedullary junction during hemorrhage-reperfusion. *Am J Physiol Physiol*. 2006;**291**:F647-53.