Review

Pitfalls in haemodynamic monitoring in the postoperative and critical care setting

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Summary
Haemodynamic monitoring is a vital part of daily practice in anaesthesia and intensive care. Although there is evidence to suggest that goal-directed therapy may improve outcomes in the perioperative period, which haemodynamic targets we should aim at to optimise patient outcomes remain elusive and controversial. This review highlights the pitfalls in commonly used haemodynamic targets, including arterial blood pressure, central venous pressure, cardiac output, central venous oxygen saturation and dynamic haemodynamic indices. Evidence suggests that autoregulation in regional organ circulation may change either due to chronic hypertension or different disease processes such as traumatic brain injury, cerebrovascular ischaemia or haemorrhage; this will influence the preferred blood pressure target. Central venous pressure can be influenced by multiple pathophysiological factors and, unless central venous pressure is very low, it is rarely useful as a predictor for fluid responsiveness. Central venous oxygen saturation can be easily increased by a high arterial oxygen tension, making it useless as a surrogate marker of good cardiac output or systemic oxygen delivery in the presence of hyperoxaemia. Many dynamic haemodynamic indices have been reported to predict fluid responsiveness, but they all have their own limitations. There is also insufficient evidence to support that giving fluid until the patient is no longer fluid responsive can improve patient-centred outcomes. With the exception in the context of preventing contrast-induced nephropathy, large randomised controlled studies suggest that excessive fluid treatment may prolong duration of mechanical ventilation without preventing acute kidney injury in the critically ill.

Key Words: circulation, fluid therapy, haemodynamics, inotropes, outcomes

Haemodynamic monitoring is a vital part of daily practice in anaesthesia and intensive care. The ability to optimise haemodynamics to ensure adequate organ perfusion and improve clinical outcomes is one of the many holy grails in anaesthesia and intensive care. Although there is evidence to suggest that goal-directed therapy may improve outcomes in the perioperative setting[1], which haemodynamic targets we should aim at to optimise patient outcomes remain elusive and controversial.

Apart from the traditional haemodynamic targets such as blood pressure, urine output, central venous pressure and cardiac output, there are many haemodynamic parameters that are increasingly available to anaesthetists and intensivists, including central venous oxygen saturation and dynamic indices. This narrative review aims to summarise the pitfalls of different haemodynamic targets, and in so doing, assess whether the aim to find a single ideal haemodynamic target for all patients in different perioperative and critical care settings is, in fact, an unrealistic goal.

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Accepted for publication on November 5, 2015

Arterial blood pressure

Arterial blood pressure is the most common haemodynamic target we use for our patients on a daily basis. Although normal blood pressure for patients at different age groups has been well established, the optimal blood pressure for patients with different pathological conditions remains unclear. While intuition tells us that aiming at a normal blood pressure is a sensible haemodynamic target, we should not assume that bringing a patient's blood pressure to normal range will improve outcomes. This is because many interventions that change blood pressure, either directly or indirectly, can induce harms which may outweigh any potential benefits of getting the blood pressure back to normal. Furthermore, an optimal blood pressure for different individuals may also be different, making the strategy of 'one-size-fits-all' potentially problematic.

Recent studies have focused on whether autoregulation at regional organ perfusion level is preserved, and if so, a normal blood pressure target may not be essential or beneficial. In the setting of septic shock, a recent randomised controlled trial (RCT) showed that a higher mean arterial pressure (MAP) (80 to 85 mmHg) was not associated with a reduction in mortality compared to targeting a lower MAP

(60 to 65 mmHg)[2]. Nevertheless, in the subgroup of patients with chronic hypertension in this study, maintaining a higher MAP was associated with a reduced risk of acute kidney injury requiring renal replacement therapy (31.7% versus 42.2%). This suggests that the autoregulation for optimal renal perfusion has shifted rightward or towards a higher level in patients with chronic hypertension. This study also showed that using catecholamines to maintain a higher MAP was associated with an increased risk of atrial fibrillation. Whether clinicians should aim at a higher MAP for patients with chronic hypertension in septic shock would thus depend on whether the benefits of reducing acute kidney injury outweigh the risks of precipitating atrial fibrillation (6.7% versus 2.8%) and possibly coronary ischaemia (acute myocardial infarction 1.8% versus 0.5%). Conversely, a higher MAP (75 to 85 mmHg) is no more effective than a lower MAP (50 to 60 mmHg) during cardiopulmonary bypass in reducing acute kidney injury after on-pump cardiac surgery[3].

The optimal blood pressure target for patients with brain injury is complicated. Cerebral bloodflow is normally maintained over a range of blood pressures due to autoregulation. It has long been known that cerebral autoregulation can be impaired after different types of brain injury and hence, a certain threshold of cerebral perfusion pressure (CPP) is recommended (e.g. >60 mmHg). Recent evidence suggests that cerebral bloodflow autoregulation can vary substantially between patients after traumatic brain injury. The standard CPP target of >60 mmHg may not be adequate for some, but excessive for others, with a U-shaped curve for neurological outcomes in relation to the duration of CPP being suboptimal[4,5]. Pressure reactivity index can be assessed by adjusting the CPP and observing its effect on intracranial pressure over time[4,5], allowing an optimal CPP to be individualised and appearing more promising. Currently, there is still insufficient evidence to confirm that monitoring intracranial pressure and CPP after traumatic brain injury would improve patient-centred outcomes. For patients with spontaneous intracerebral haemorrhage, pooled results from RCTs suggest that keeping systolic blood pressure below 150 mmHg may reduce the risk of haematoma expansion within the first 24 hours of haemorrhagic stroke and improve neurological outcome compared to keeping systolic blood pressure <180 mmHg[6]. Similar approaches to blood pressure control do not, however, appear to influence neurological outcome for patients with ischaemic stroke[7].

Systemic hypertension occurs in many patients after carotid endarterectomy or carotid stenting, due to denervation or dysfunction of the carotid baroreceptors. In these patients, impaired cerebral autoregulation may fail to adjust to a sudden increase in cerebral blood flow immediately after relieving the carotid arterial obstruction, resulting in cerebral hyperperfusion with cerebral oedema if systemic hypertension is not treated promptly within the first few hours after surgery[8]. For patients who have had recent ischaemic stroke or bilateral critical carotid stenosis before surgery, cerebral hyperperfusion can be transformed into catastrophic intracerebral haemorrhage, and as such, aggressive antihypertensive therapy aiming at systolic blood pressure <140 to 160 mmHg, possibly better with beta-blockers than vasodilators, is advisable for these high-risk patients. The factors that should be considered when using arterial blood pressure as a haemodynamic target are summarised in Table 1.

Central venous pressure

Central venous pressure (CVP) has been used for many decades as a target to guide fluid therapy. Recent meta-analyses suggested that the utility of CVP as a surrogate marker of preload or fluid responsiveness is overrated[9]. While a very low CVP is likely to suggest a patient's cardiac output may be fluid responsive[10], a CVP between 5 and 20 mmHg has almost no predictive value. Even changes in CVP with fluid boluses have not been proven to predict fluid responsiveness[9]. This is not surprising given that CVP can be affected by multiple factors other than intravascular volume, including venous resistance, intrathoracic pressure, intra-abdominal pressure and pulmonary vascular resistance[11]. Indeed, in patients with right heart dysfunction (e.g. acute pulmonary embolism), use of fluid boluses to increase CVP to a high level may be harmful, as the right heart is very prone to dilate with excessive filling and the left heart can be paradoxically under-filled due to interventricular dependency[12]. Other studies have also shown that CVP has no discriminative value in predicting adequacy of systemic oxygen delivery for patients after major surgery[13] and is not reliable in predicting the size or collapsibility of the superior vena cava[14]. Despite the use of ultrasound technology, serious mechanical complications related to central venous catheterisation can still occur[15]. Perhaps, the potential benefits of CVP monitoring alone may not justify the associated risks of central venous catheterisation, if there are no other indications for central venous catheterisation such as reliable central vascular access for vasoactive medications.

Cardiac output

Cardiac output can be measured continuously by a pulmonary artery catheter, PiCCO® (Philips, Amsterdam, Netherlands) (or other pulse contour) monitor, or oesophageal Doppler so that fluid and inotropes can be titrated to a certain target[16–18]. It is important to appreciate that cardiac output is a measure of the circulation and not the heart itself. Hence, we should not assume a patient with a relatively normal cardiac index (e.g. 2.5 l/min/m^2) will have a normal heart[19]. In fact, it is possible for a dilated and failing heart to generate a stroke volume similar to a hyperdynamic but empty heart, for simple geometric reasons. Furthermore,

Table 1

Factors to consider when using blood pressure as a haemodynamic target in the perioperative and critical care setting

1.	Technical issues: optimal damping and no subclavian or femoral artery stenosis proximal to the arterial catheter.
2.	Arterial blood pressure waveform in addition to mean arterial pressure may give some indirect information to the haemodynamic status of the patients (e.g. a low diastolic blood pressure may imply vasodilatation, a small pulse pressure may suggest a small stroke volume, a wide variation in systolic blood pressure or pulse pressure in relation to positive pressure ventilation may suggest hypovolaemia)
3.	Potential benefits should be greater than harms induced by interventions or drugs used to maintain the blood pressure (e.g. atrial fibrillation from catecholamines)
4.	Presence of chronic hypertension may suggest that a higher mean arterial blood pressure for renal perfusion is needed
5.	Recent-onset intracerebral haemorrhage may benefit from a lower systolic blood pressure (<150 mmHg)
6.	Cerebral hyperperfusion syndrome and/or intracerebral haemorrhage after carotid stenting or endarterectomy for critical carotid stenosis may occur if systolic blood pressure is higher than 140 to 160 mmHg immediately after surgery

Table 2

Limitations of using central venous pressure (CVP) or dynamic indices to guide fluid therapy

1.	Mechanical complications related to central venous catheterisation should be considered
2.	Although a very low central venous pressure may indicate fluid responsiveness, the usual central venous pressure between 5 and 20 mmHg has very little predictive value for fluid responsiveness. A high central venous pressure in the setting of right ventricular failure due to right heart failure or acute pulmonary embolism can be harmful
3.	Dynamic indices can be affected by cardiac arrhythmias, the magnitude of changes in intrathoracic pressure or tidal volume (either during spontaneous or mechanical ventilation), use of vasopressors, and left ventricular dysfunction. A lack of dynamic respiratory variations in dynamic indices may thus, be more useful clinically, in indicating that the patient is fluid unresponsive. These dynamic indices may best be labelled as markers of 'fluid unresponsiveness' to guide clinicians in avoiding use of excessive intravenous fluid for their patients
4.	Dynamic indices appear less useful in paediatric patients
5.	Fluid responsiveness is not always equivalent to hypovolaemia, and there is insufficient evidence to suggest that giving more fluid therapy until patients are no longer fluid responsive can improve patient-centred outcomes
6.	Some intravenous fluids may have adverse effects on the coagulation or renal system, and excessive fluid therapy may prolong mechanical ventilation in the critically ill without preventing acute kidney injury (with the exception in the context of contrast-induced nephropathy)

a low normal cardiac output can also be achieved in the presence of a reduced stroke volume in the presence of tachycardia. With these limitations in mind, the cardiac output measured by different devices should be interpreted in the context of the patient's heart rate and left and right ventricular function as assessed by echocardiography. Although maintaining a relatively normal cardiac output in critical illness makes intuitive sense, whether interventions that are capable of improving cardiac output can improve patient-centred outcomes remains elusive, and likely to vary in different pathological conditions.

Central and mixed venous oxygen saturation (CvO_2 and SvO_2)

CvO_2 and SvO_2 have been used to reflect the balance between systemic oxygen delivery and consumption. If the systemic oxygen delivery is inadequate relative to the oxygen consumption, oxygen extraction is increased, resulting in a low CvO_2 and SvO_2. Venous oxygen saturation has been shown to correlate with other haemodynamic parameters, including cardiac output and central venous–arterial carbon dioxide gradient in patients with circulatory failure and after major surgery[20,21]. Based on the assumption that optimising CvO_2 and SvO_2 may reduce the risk of systemic oxygen debt, multiple RCTs incorporating a treatment algorithm aimed to optimise CvO_2 have been conducted. Surprising to many people, such a treatment algorithm has not been effective in reducing mortality in patients with severe sepsis in multicentre RCTs[22–24], despite the use of more intravenous fluid, blood transfusion and use of inotropes or vasopressors associated with the early-goal-directed-therapy (EGDT). The reasons behind why using CvO_2 as a therapeutic target was not effective in reducing mortality remain unclear. The first and foremost criticism of these trials is that patients who were recruited in these RCTs were already adequately resuscitated before the initiation of EGDT, with the mean baseline CvO_2 higher than what is considered acceptable (Australasian Resuscitation In Sepsis Evaluation [ARISE] trial: 72.7%, Protocol-Based Care for Early Septic Shock [ProCESS] trial: 71%, Protocolised Management in Sepsis [ProMISe] trial: 70%). This was very different from the CvO_2 of the patients (49%) in the report by Rivers et al, which showed that EGDT aimed to increase CvO_2 from 49% to CvO_2 >70% was associated with a reduction in mortality[25].

Second, the traditional physiology teaching states that arterial oxygen tension (PaO_2) contributes very little to the arterial oxygen content and hence, also systemic oxygen delivery. It is then assumed that PaO_2 would not affect the CvO_2 or SvO_2 and hence, PaO_2 is not important when using CvO_2 to guide fluid therapy, transfusion or inotropes. We have to understand that it is the PaO_2 that determines the arterial oxygen saturation (SaO_2), and likewise, it is the central or mixed venous oxygen tension that determines the CvO_2 or SvO_2, respectively. Because the venous oxygen tension normally lies on the steep part of the haemoglobin–oxygen dissociation curve, a small change in central and mixed venous oxygen tension can have a substantial effect

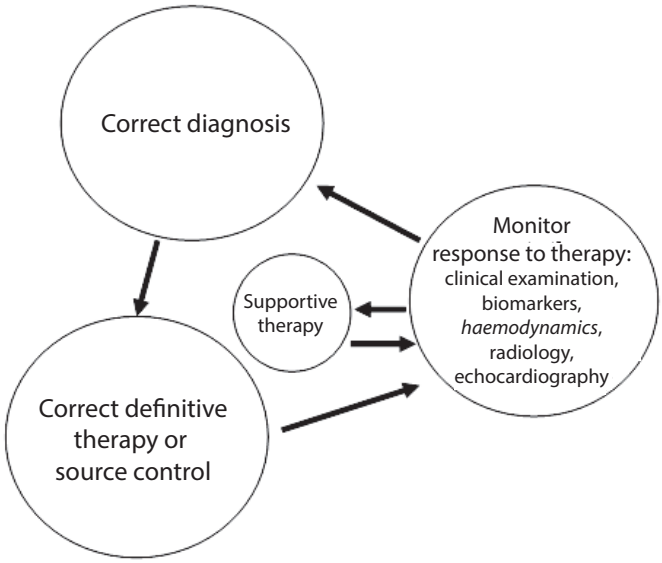

Figure 1: Monitoring haemodynamics as part of the diagnostic and therapeutic feedback loop in critically ill patients.

on CvO_2 and SvO_2. Even though PaO_2 does not contribute much to the arterial oxygen content, this does not mean that PaO_2 cannot affect central or mixed venous oxygen tension, and subsequently also the CvO_2 and SvO_2. Our previous work has clearly demonstrated that increasing PaO_2 by using a higher inspired oxygen concentration can have a substantial effect on CvO_2 and SvO_2[26], with an increment of up to 10% or more, rendering CvO_2 or SvO_2 useless as a marker of adequate cardiac output when there is hyperoxaemia[27]. This result was subsequently confirmed by similar studies and mathematical modelling[28–30]. Even in patients without obvious extreme hyperoxaemia, PaO_2 remains the most important factor in determining CvO_2 in patients after major surgery[13]. In fact, hyperoxaemia (mean PaO_2 >120 mmHg) was common in patients recruited in the RCT on EGDT[22], making the algorithm aiming at a high CvO_2 without considering the effect of hyperoxaemia on CvO_2 vulnerable to uncontrolled bias.

Third, the normal value of CvO_2 or SvO_2 in the presence of severe sepsis remains uncertain. This is because systemic shunts due to redistribution of microcirculation bloodflow or mitochondrial dysfunction at the cellular level can both increase CvO_2 or SvO_2 to a supranormal level (>90%) which is associated with an increased mortality[31]. This may also explain why EGDT may be more useful in the elective perioperative setting[1], where hypovolaemic or cardiogenic shock is more common than sepsis. If CvO_2 or SvO_2 is used to guide haemodynamic therapy, it is important to make sure that PaO_2 is not higher than the bare acceptable range (e.g. <60 to 70mmHg) and hypovolaemia or cardiac failure is the dominant mechanism of circulatory failure. It is best to understand that a low CvO_2 or SvO_2 is very suggestive of inadequate systemic oxygen delivery; but a normal CvO_2 or SvO_2 does not necessarily confirm the septic process is adequately treated in severe sepsis due to presence of systemic shunts. A relatively normal CvO_2 or SvO_2 (and also other haemodynamic parameters for this matter) should not automatically trigger a *laissez-faire* approach to the management of the patients with severe sepsis; an aggressive source control remains paramount.

Dynamic haemodynamic indices to predict fluid responsiveness

A wide range of dynamic haemodynamic indices, including pulse pressure or stroke volume variation, plethysmographic variability index, and respiratory variation of the diameter of the inferior or superior vena cava or jugular vein, have emerged in the past decade. Dynamic indices have theoretical advantages over static indices such as central venous pressure, pulmonary capillary wedge pressure or left ventricular diastolic volume because they reflect how venous filling or stroke volume changes with changes in intrathoracic pressure. However, as more and more studies about dynamic haemodynamic indices have emerged, the limitations of these indices have also become apparent.

Firstly, the predictive ability of these indices may be heavily influenced by the magnitude of the ventilating pressure or tidal volume used and whether the patient is spontaneously breathing[32,33]. A lack of respiratory variations in inferior vena cava diameter, central venous pressure or even pulse volume is clinically more useful in telling us that the patient is unlikely to be fluid responsive[34–36]. Conversely, presence of respiratory variations in these dynamic indices does not guarantee the patient is fluid responsive, especially when there is a large variation in intrathoracic pressure during the respiratory cycle. As such, these dynamic indices may be best labelled as markers of 'fluid unresponsiveness' rather than 'fluid responsiveness'. Secondly, because positive intrathoracic pressure has a different effect on stroke volume in patients with and without left ventricular failure, pulse pressure variation is not useful in predicting fluid responsiveness in patients with left ventricular failure[37]. Thirdly, pulse pressure variation or plethysmographic variability index can be affected by cardiac arrhythmias, or peripheral vasoconstriction from shock or use of vasopressor[38]. Fourthly, the performance of these dynamic indices appears to be limited in paediatric patients[33,39]. Finally, there is insufficient evidence to suggest that optimising fluid responsiveness can improve clinical outcomes[40]. We should not assume that any patients who are fluid responsive should receive more fluid until they are no longer fluid responsive[41]. In addition, some types of intravenous fluid may also have adverse effects on the coagulation or renal system[42,43], especially if a large amount of such fluid is used. With the exception in the context of preventing contrast-induced nephropathy[44], evidence suggests that excessive fluid treatment may prolong

duration of mechanical ventilation without preventing acute kidney injury in critically ill and surgical patients[45–47]. The limitations of using central venous pressure and dynamic indices to guide fluid therapy are summarised in Table 2.

Conclusion

There are many potential useful haemodynamic targets we can use for patients undergoing major surgery and in the ICU. Unfortunately, most of these haemodynamic targets are heavily context-dependent and may change over time, even for the same patient. Using the same haemodynamic target to treat patients with different acute diseases and chronic comorbidities is unlikely to achieve the best outcomes for all. Knowing the pitfalls of different haemodynamic targets does not suggest that we should abandon using these targets for our patients. It should be noted that circulatory failure or shock is not a disease itself, but a complication of an underlying pathological process. In this context, haemodynamic response to medical treatments should be considered as a part of a feedback loop to confirm whether the correct diagnosis is made, and appropriate source control and therapy have been delivered (Figure 1).

When clinical signs of the patients do not fit together (e.g. 'septic shock' from pneumonia without significant oxygen requirement, 'septic shock' with a relatively high central venous pressure without too much prior fluid therapy), or patients who fail to respond to initial resuscitation or require continued escalation of the doses of vasopressor, then it is mandatory to obtain more information from the patients. This may include, but is not limited to, further biochemical tests (e.g. lactate, troponin, brain-natriuretic-peptide), radiological imaging and echocardiography. Exclusion of obstructive shock, such as cardiac tamponade or acute pulmonary embolism, is particularly important. Different underlying diseases and context of the patients will invariably dictate what haemodynamic targets are more likely to be useful. Practically, a combination of clinical examination, biochemistry, radiological imaging and echocardiographic assessment will be pivotal in addition to targeting fluid and inotropic therapy to a certain set of haemodynamic targets in difficult cases. The potential harms of all interventions, including commonly used intravenous fluids and drugs, used to achieve the haemodynamic targets should also be carefully considered. A single ideal haemodynamic target for all patients in different perioperative and critical care settings may exist, we just have not found it yet. Until then, using multiple haemodynamic targets, tailored to a patient's underlying pathological condition, to guide haemodynamic support appears to be the best option we have.

Conflict of Interest

The author's research was funded by the Raine Medical Research Foundation and WA Department of Health through the Raine Clinical Research Fellowship. The author has no financial nor non-financial conflict of interests to declare in relation to the subject matter, drugs or equipment discussed in this manuscript. A summary of this manuscript was presented at the 6th Annual Scientific Meeting on Intensive Care in Kuala Lumpur on 14 August 2015.

References

1. Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. Anesth Analg 2012; 114:640-651.
2. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014; 370:1583-1593.
3. Azau A, Markowicz P, Corbeau JJ, Cottineau C, Moreau X, Baufreton C et al. Increasing mean arterial pressure during cardiac surgery does not reduce the rate of postoperative acute kidney injury. Perfusion 2014; 29:496-504.
4. Lang EW, Kasprowicz M, Smielewski P, Santos E, Pickard J, Czosnyka M. Short pressure reactivity index versus long pressure reactivity index in the management of traumatic brain injury. J Neurosurg 2015; 122:588-594.
5. Lazaridis C, Smielewski P, Steiner LA, Brady KM, Hutchinson P, Pickard JD et al. Optimal cerebral perfusion pressure: are we ready for it? Neurol Res 2013; 35:138-148.
6. Tsivgoulis G, Katsanos AH, Butcher KS, Boviatsis E, Triantafyllou N, Rizos I et al. Intensive blood pressure reduction in acute intracerebral hemorrhage: a meta-analysis. Neurology 2014; 83:1523-1529.
7. Lee M, Ovbiagele B, Hong KS, Wu YL, Lee JE, Rao NM et al. Effect of blood pressure lowering in early ischemic stroke: meta-analysis. Stroke 2015; 46:1883-1889.
8. van Mook WNKA, Rennenberg RJMW, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PAM et al. Cerebral hyperperfusion syndrome. Lancet Neurol 2005; 4:877-888.
9. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. Crit Care Med 2013; 41:1774-1781.
10. Heenen S, De Backer D, Vincent JL. How can the response to volume expansion in patients with spontaneous respiratory movements be predicted? Crit Care 2006; 10:R102.
11. Gelman S. Venous function and central venous pressure: a physiologic story. Anesthesiology 2008; 108:735-748.
12. Belenkie I, Dani R, Smith ER, Tyberg JV. The importance of pericardial constraint in experimental pulmonary embolism and volume loading. Am Heart J 1992; 123:733-742.
13. Litton E, Silbert B, Ho KM. Clinical predictors of a low central venous oxygen saturation after major surgery: a prospective prevalence study. Anaesth Intensive Care 2015; 43:59-65.
14. Cowie BS, Kluger R, Rex S, Missant C. The relationship between superior vena cava diameter and collapsibility and central venous pressure. Anaesth Intensive Care 2015; 43:357-360.
15. Goulding G. Unrecognised carotid arterial cannulation: prevention and management. Anaesth Intensive Care 2014; 42:696-699.
16. Litton E, Morgan M. The PiCCO monitor: a review. Anaesth Intensive Care 2012; 40:393-409.
17. Phan TD, Ismail H, Heriot AG, Ho KM. Improving perioperative outcomes: fluid optimization with the esophageal Doppler monitor, a metaanalysis and review. J Am Coll Surg 2008; 207:935-941.

18. Cowie BS. Does the pulmonary artery catheter still have a role in the perioperative period? Anaesth Intensive Care 2011; 39:345-355.
19. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F. Hemodynamic instability in sepsis: bedside assessment by Doppler echocardiography. Am J Respir Crit Care Med 2003; 168:1270-1276.
20. Silbert BI, Litton E, Ho KM. Central venous-to-arterial carbon dioxide gradient as a marker of occult tissue hypoperfusion after major surgery. Anaesth Intensive Care 2015; 43:628-634.
21. Ho KM, Harding R, Chamberlain J. A comparison of central venous-arterial and mixed venous-arterial carbon dioxide tension gradient in circulatory failure. Anaesth Intensive Care 2007; 35:695-701.
22. Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014; 370:1683-1693.
23. Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014; 371:1496-1506.
24. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015; 372:1301-1311.
25. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345:1368-1377.
26. Ho KM, Harding R, Chamberlain J. The impact of arterial oxygen tension on venous oxygen saturation in circulatory failure. Shock 2008; 29:3-6.
27. Ho KM, Harding R, Chamberlain J, Bulsara M. A comparison of central and mixed venous oxygen saturation in circulatory failure. J Cardiothorac Vasc Anesth 2010; 24:434-439.
28. Legrand M, Vallée F, Mateo J, Payen D. Influence of arterial dissolved oxygen level on venous oxygen saturation: don't forget the PaO2! Shock 2014; 41:510-513.
29. Ho KM, Silbert B. Impact of arterial oxygen tension on venous oxygen saturation. Shock 2014; 42:279.
30. Zampieri FG, Park M, Azevedo LCP, Amato MBP, Costa ELV. Effects of arterial oxygen tension and cardiac output on venous saturation: a mathematical modeling approach. Clinics (Sao Paulo) 2012; 67:897-900.
31. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Multicenter study of central venous oxygen saturation (ScvO(2)) as a predictor of mortality in patients with sepsis. Ann Emerg Med 2010; 55:40-46.
32. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. Intensive Care Med 2005; 31:517-523.
33. Yin JY, Ho KM. Use of plethysmographic variability index derived from the Massimo(®) pulse oximeter to predict fluid or preload responsiveness: a systematic review and meta-analysis. Anaesthesia 2012; 67:777-783.
34. Magder S. Bench-to-bedside review: An approach to hemodynamic monitoring--Guyton at the bedside. Crit Care 2012; 16:236.
35. de Valk S, Olgers TJ, Holman M, Ismael F, Ligtenberg JJM, Ter Maaten JC. The caval index: an adequate non-invasive ultrasound parameter to predict fluid responsiveness in the emergency department? BMC Anesthesiol 2014; 14:114.
36. Bodson L, Vieillard-Baron A. Respiratory variation in inferior vena cava diameter: surrogate of central venous pressure or parameter of fluid responsiveness? Let the physiology reply. Crit Care 2012; 16:181.
37. Shim JK, Song JW, Song Y, Kim JH, Kang HM, Kwak YL. Pulse pressure variation is not a valid predictor of fluid responsiveness in patients with elevated left ventricular filling pressure. J Crit Care 2014; 29:987-991.
38. Baker AK, Partridge RJ, Litton E, Ho KM. Assessment of the plethysmographic variability index as a predictor of fluid responsiveness in critically ill patients: a pilot study. Anaesth Intensive Care 2013; 41:736-741.
39. Weber T, Wagner T, Neumann K, Deusch E. Low predictability of three different noninvasive methods to determine fluid responsiveness in critically ill children. Pediatr Crit Care Med 2015; 16:e89-e94.
40. Richard JC, Bayle F, Bourdin G, Leray V, Debord S, Delannoy B et al. Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial. Crit Care 2015; 19:5.
41. Kox M, Pickkers P. "Less is more" in critically ill patients: not too intensive. JAMA Intern Med 2013; 173:1369-1372.
42. Pathirana S, Wong G, Williams P, Yang K, Kershaw G, Dunkley S et al. The effects of haemodilution with albumin on coagulation in vitro as assessed by rotational thromboelastometry. Anaesth Intensive Care 2015; 43:187-192.
43. Saw MM, Chandler B, Ho KM. Benefits and risks of using gelatin solution as a plasma expander for perioperative and critically ill patients: a meta-analysis. Anaesth Intensive Care 2012; 40:17-32.
44. Brar SS, Aharonian V, Mansukhani P, Moore N, Shen AY, Jorgensen M et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. Lancet 2014; 383:1814-1823.
45. Mekontso DA, Roche-Campo F, Kouatchet A, Tomicic V, Beduneau G, Sonneville R et al. Natriuretic peptide-driven fluid management during ventilator weaning: a randomized controlled trial. Am J Respir Crit Care Med 2012; 186:1256-1263.
46. Stewart RM, Park PK, Hunt JP, McIntyre RC Jr, McCarthy J, Zarzabal LA et al. Less is more: improved outcomes in surgical patients with conservative fluid administration and central venous catheter monitoring. J Am Coll Surg 2009; 208:725-735.
47. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006; 354:2564-2575.