Review

Year in review 2008: *Critical Care* - cardiology

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Abstract

We review key research papers in cardiology and intensive care published during 2008 in *Critical Care*. We quote studies on the same subject published in other journals if appropriate. Papers have been grouped into three categories: (a) cardiovascular biomarkers in critical illness, (b) haemodynamic management of septic shock, and (c) haemodynamic monitoring.

Cardiovascular biomarkers in critical illness

Cardiac troponins

Cardiac troponins (cTns) are highly sensitive and specific biological markers of myocardial damage. Elevated cTn is an independent predictor of adverse outcome and correlates with intensive care unit (ICU) and hospital lengths of stay among critically ill patients, regardless of the mechanism causing its rise [1-3]. However, because ICU patients often have increased cTn for reasons other than overt myocardial infarction (MI), raised cTn may be attributed to other conditions, and therefore the true incidence of myocardial damage in ICU may be underestimated.

Lim and colleagues [4] screened patients admitted to ICU by using cTn and electrocardiograms (ECGs) to determine the incidence of elevated cTn and MI and to assess whether these findings influence prognosis. In this study, patients were classified as having MI in the presence of elevated cTn and ECG evidence supporting a diagnosis of MI. Among 103 patients, 35.9% had a confirmed MI whereas 14.6% had an elevated cTn only. Patients with an MI or with elevated cTn without ECG changes had a longer duration of mechanical ventilation and ICU stay and higher ICU and hospital mortality rates compared with patients with no cTn elevation (odds ratio 27.3). Lim and colleagues [4] found that screening cTn measurements and 12-lead ECGs detected MI at a higher rate than clinical diagnosis alone, suggesting that the true incidence and associated mortality of MI in ICU patients are underestimated.

Brain natriuretic peptides

Increased levels of brain natriuretic peptide (BNP) and the biologically inactive N-terminal pro-BNP (NT-proBNP) are associated with impaired left ventricular (LV) function and ischaemia, pulmonary embolism (PE) and chronic obstructive pulmonary disease [5].

Coutance and colleagues [6] conducted a meta-analysis of studies in patients with acute PE to assess the prognostic value of elevated BNP or NT-proBNP levels to predict short-term overall mortality, PE-specific mortality and the occurrence of serious pre-defined adverse events. The study showed that elevated BNP or NT-proBNP levels may help to identify patients with acute PE and right ventricular (RV) dysfunction at high risk of short-term death and adverse outcome events. BNP and NT-proBNP had low positive predictive values (PPVs) for death (14%) but a high negative predictive value (99%), suggesting that BNP or NT-proBNP might be useful in identifying patients with a likely favourable outcome.

Kirchhoff and colleagues [7] prospectively studied the relationship between NT-proBNP, disease severity and cardiac output (CO) monitoring measured by transpulmonary

ALI/ARDS = acute lung injury/acute respiratory distress syndrome; BNP = brain natriuretic peptide; CCO = continuous cardiac output; CCO_{PAC} = continuous cardiac output by pulmonary artery catheter thermodilution; CO = cardiac output; CO_{TCP} = transcardiopulmonary thermodilution cardiac output; cTn = cardiac troponin; CVP = central venous pressure; ECG = electrocardiogram; IAH = intra-abdominal hypertension; ICU = intensive care unit; LV = left ventricular; LVD = left ventricular systolic or diastolic dysfunction; MI = myocardial infarction; MODS = multiple organ dysfunction syndrome; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAOP = pulmonary artery occlusion pressure; PCCO = pulse contour-derived cardiac output; $PCCO_{pre}$ = pre-calibration pulse contour-derived cardiac output; PE = pulmonary embolism; pHi = intramucosal pH; PiCCO = pulse contour cardiac output; PPV = positive predictive value; RAP = right atrial pressure; ROC = receiver operating characteristic; RV = right ventricular; $ScvO_2$ = central venous oxygen saturation; SV = stroke volume; SvO_2 = mixed venous oxygen saturation; SVV = stroke volume variation; $SVV_{FloTrac}$ = stroke volume variation calculated using the FloTrac/Vigileo™ system algorithm; SVV_{PiCCO} = stroke volume variation calculated using the $PiCCO_{Plus}$™ system; TEE = transoesophageal echocardiography.

thermodylution (pulse contour cardiac output, or PiCCO) in 26 trauma patients with no previous history of cardiac, renal or hepatic impairment. Patients were subdivided into two groups based on disease severity by using the multiple organ dysfunction syndrome (MODS) score: group A had minor organ dysfunction (MODS score ≤4) and group B had major organ dysfunction (MODS score >4). Serum NT-proBNP levels were elevated in all patients. NT-proBNP was significantly lower at baseline and at all subsequent time points in group A, whereas the cardiac index was significantly higher in group A at baseline and at all time points. The investigators also found a significant inverse correlation between cardiac index and MODS score and a positive correlation between MODS score and serum NT-proBNP levels. These pilot data hint at a potential value of NT-proBNP in the diagnosis of post-traumatic cardiac impairment.

BNP and NT-proBNP are frequently elevated in critically ill patients and both show a dispersion that is much larger than that of a non-ICU population. Coquet and colleagues [8] conducted a prospective observational study of medical ICU patients to evaluate the accuracy of NT-proBNP as a marker of cardiac dysfunction in a heterogeneous group of critically ill patients. Of 198 patients included, 51.5% had echocardiographic evidence of cardiac dysfunction. Median NT-proBNP concentrations were 6.7 times higher in patients with cardiac dysfunction (area under the receiver operating characteristic [ROC] curve 0.76). While adding ECG changes and organ failure score increased the area under the ROC curve to 0.83, NT-ProBNP was not independently associated with outcome. Despite the effects of age and creatinine clearance on NT-proBNP levels, a single measurement of the NT-proBNP level at ICU admission might rule out cardiac dysfunction in critically ill patients independently of age or renal function.

BNP or NT-proBNP may theoretically be useful in distinguishing pulmonary oedema due to acute lung injury/acute respiratory distress syndrome (ALI/ARDS) from hydrostatic or cardiogenic oedema. Levitt and colleagues [9] performed a prospective blinded cohort study in a mixed medical and surgical ICU to assess the diagnostic utility of BNP in a cohort of ventilated patients with convincing evidence of either ALI/ARDS or cardiogenic pulmonary oedema. BNP was measured immediately after enrolment and then daily for 3 days in patients with ALI/ARDS (defined as a pulmonary artery occlusion pressure [PAOP] of less than 16 mm Hg or a right atrial pressure [RAP] of less than 10 mm Hg and no echocardiographic evidence of new or worsening left ventricular systolic or diastolic dysfunction [LVD]) and in patients with cardiogenic oedema (defined as a PAOP of greater than 20 mm Hg or an RAP of greater than 14 mm Hg with a current echocardiogram documenting new or worsening LVD) [9].

BNP levels (at baseline and with repeated measurement) did not reliably distinguish ALI/ARDS from cardiogenic pulmonary oedema despite the efforts to clearly separate the two groups based on haemodynamic parameters. Given that ALI/ARDS and cardiac dysfunction are not mutually exclusive conditions, the clinical utility of BNP testing in this setting may well be limited [9].

Lactates and central venous oximetry

Lactates and central venous oxygen saturation ($ScvO_2$) – measured from the superior vena cava – are used as indicators of adequacy of tissue oxygen supply. Patients with high lactates, even in the absence of hypotension ('occult shock'), are at higher mortality risk. In patients with severe sepsis/shock and raised lactate levels, directing treatment to target $ScvO_2$ is associated with a significant survival benefit [10]. However, the key factor for improving survival is early recognition and intervention.

In a prospective observational pilot study of 124 patients requiring urgent pre-hospital care, Jansen and colleagues [11] studied the relationship between pre-hospital capillary or venous lactate levels and in-hospital mortality. Lactate levels were measured by the Emergency Medical Services (using a handheld device) on arrival at the scene (T1) and just before or on arrival at the emergency department (T2). Mortality was higher in those with T1 lactate of greater than 3.5 mmol/L compared with a lactate of less than 3.5 mmol/L (T1: 41% versus 12%; T2: 47% versus 15%). In multivariate analysis, only delta lactate and GCS were significantly associated with mortality, with hazard ratios (95% confidence intervals) of 0.2 (0.05 to 0.76) and 0.93 (0.88 to 0.99), respectively. These pilot data suggest that it may be possible to identify a group of patients at high risk *before* admission to hospital and that appropriate management at this very early stage may improve outcomes.

Low $ScvO_2$ values have also been associated with an increased risk of postoperative complications in high-risk surgery [12] and in severe sepsis [10]. Little is known, however, of the $ScvO_2$ profile of other patient groups. In an unselected group of unplanned ICU admissions, Bracht and colleagues [13] showed that, on ICU admission, 21% of patients had an $ScvO_2$ of less than 60%. In this group, an $ScvO_2$ of less than 60% was associated with an increased mortality (29% versus 17%, $P<0.05$) but not with ICU or hospital length of stay [13]. The mean ± standard deviation value of $ScvO_2$ for the septic group was 68% ± 12%, significantly higher than the 49% reported by Rivers and colleagues [10].

To compare ICU admission $ScvO_2$ values in Dutch ICUs with data from Rivers and colleagues [10], van Beest and colleagues [14] performed a prospective observational multicentre study. While the 'incidence' of low $ScvO_2$ is reported, the data actually reflect its 'prevalence'. The mean mixed venous oxygen saturation (SvO_2) and $ScvO_2$ values were greater than 65% and greater than 70%, respectively. Only

14% and 5% of the overall population had $ScvO_2$ values of less than 60% and less than 50%, respectively. Among septic patients, the prevalence of an $ScvO_2$ of less than 60% and less than 50% was even lower (6% and 1%, respectively), highlighting that the syndrome described by Rivers and colleagues [10] may be relatively uncommon in the ICU depending on the specific hospital setting but remains important as patients with an $ScvO_2$ of less than 50% exhibited the highest in-hospital mortality (57%) compared with an overall mortality of 32% [14]. These data raise concerns about the utility of an $ScvO_2$-guided therapy in severe sepsis patients admitted to ICU, as opposed to the emergency department, and will require further studies [15], particularly as SvO_2 and $ScvO_2$ are only indirect indices of global tissue oxygenation and do not provide any insight on the state of oxygen utilization in tissues [16].

In summary:

1. When used as a screening tool in critically ill patients, cTn and 12-lead ECG lead to a higher rate of MI diagnosis.
2. BNP or NT-proBNP levels may help to identify patients with acute PE and RV dysfunction with a likely favourable outcome, while a single measurement of the NT-proBNP level at ICU admission might rule out cardiac dysfunction in critically ill patients independently of age or renal function.
3. However, BNP or NT-proBNP levels do not distinguish ALI/ARDS from cardiogenic pulmonary oedema.
4. Both high lactates and low $ScvO_2$ are associated with higher mortality, but the percentage of ICU patients with an $ScvO_2$ of less than 50% is small.

Haemodynamic management of septic shock

Low gastric intramucosal pH (pHi) is a sensitive marker of splanchnic hypoperfusion and a good predictor of poor outcome in critically ill patients. In a randomised trial, Palizas and colleagues [17] studied 30 septic shock patients who were randomly assigned within 48 hours of ICU admission to two different resuscitation goals: CI of greater than 3.0 L/minute per square metre or pHi of greater than 7.32 [17]. Although there was no difference in the primary endpoint (28-day mortality and ICU length of stay), a higher proportion of patients exhibited values below the specific target at baseline in the pHi group compared with the CI group (50% versus 10.9%). Of 32 patients with a pHi of less than 7.32 at baseline, only 22% had a pHi of greater than 7.32 after resuscitation. Areas under the ROC curves to predict mortality at baseline and at 24 and 48 hours were 0.70 versus 0.55, 0.9 versus 0.61, and 0.75 versus 0.47, respectively, demonstrating that a normalization of pHi within 24 hours of resuscitation is a strong signal of therapeutic success, and in contrast, a persistent low pHi despite treatment is associated with a very poor prognosis in septic shock patients [17]. The study, powered to detect a 20% absolute risk reduction in 28-day mortality, likely suffers from residual confounding or bias or both. For example, while there was no difference in the primary endpoint, only 22% of those in the pHi group had a pHi of greater than 7.32 after resuscitation.

Gastrointestinal mucosal perfusion can be affected by the type of vasopressor used for the initial management of septic shock. In a prospective randomized controlled trial of patients with septic shock, Morelli and colleagues [18] showed that first-line therapy with phenylephrine does not worsen hepato-splanchnic perfusion during initial haemodynamic support of patients with septic shock and that phenylephrine had effects similar to those of norepinephrine on cardiopulmonary performance and global oxygen transport and similar effects on creatinine clearance, although higher doses were required to achieve the same target of mean arterial pressure of 70 ± 5 mm Hg [18].

The rate of weaning of vasopressor drugs in patients with septic shock is usually an empirical choice made by the clinician. However, in a prospective randomised trial, Merouani and colleagues [19] applied a closed-loop control based on fuzzy logic principles to titrate intravenous norepinephrine (noradrenaline) infusion rates in septic patients in order to reduce the duration of poorly controlled haemodynamic status. Septic patients were randomly assigned to norepinephrine infused either at the clinician's discretion (control group) or under closed-loop control based on fuzzy logic (fuzzy group). The infusion rate changed automatically after analysis of mean arterial pressure in the fuzzy group. The fuzzy group had a shorter median duration of vasoactive drugs (28.5 versus 57.5 hours) and a lower total amount of norepinephrine infused during shock (0.6 versus 1.4 μg/kg); however, no difference in terms of mortality or duration of mechanical ventilation was found.

During septic shock, resistance to the haemodynamic effects of catecholamine vasopressors and inotropes is a marker of mortality risk, and the metabolic and haemodynamic responses to dobutamine may correlate with outcome in patients with septic shock. In a prospective, non-randomised, non-blinded interventional study of patients with severe sepsis or septic shock who underwent a graded dobutamine challenge (5 to 20 μg/kg per minute), Kumar and colleagues [20] showed that survival from severe sepsis or septic shock is associated with increased cardiac performance and contractility indices during dobutamine infusion.

In multivariate analysis, an increase in stroke volume (SV) index of greater than 8.5 mL/m^2 was the dominant discriminating variable for survival. The fact that both cardiac performance and contractility increases in response to dobutamine are highly associated with outcome in septic shock suggests that the inability to recruit ventricular volume during cardiovascular stress may indicate that the heart is already operating at the maximum efficacy of the Frank-Starling response and therefore has no additional reserve.

Catecholamines and inflammatory mediators play a significant role in the pathogenesis of septic cardiomyopathy, and there is growing evidence of an association between beta-adrenergic stress and the pathogenesis of septic cardiomyopathy. Beta-blockers in critically ill patients may thus attenuate cathecholamine-induced myocardial stunning and septic cardiomyopathy. In a retrospective analysis of the combined use of milrinone and enteral metoprolol therapy in 40 patients with septic shock and cardiac depression, Schmittinger and colleagues [21] show that metoprolol can reduce heart rate without detrimental effects on cardiovascular function. During the 96-hour observation period, 97.5% of patients treated with metoprolol and milrinone had a decrease in heart rate to the target of 65 to 95 beats per minute, a decrease in the central venous pressure (CVP) and an increase in SV index. Mean arterial blood pressure increased despite decreasing norepinephrine, arginine vasopressin and milrinone dosages. These changes, in association with an unchanged cardiac index and a lower heart rate, translate into an economization of cardiac work and oxygen consumption with possible beneficial effects in terms of lowering the risk of myocardial ischaemia and prevention of septic cardiomyopathy. The importance of these observations deserves to be tested prospectively.

In summary, in the management of septic shock:

1. Normalization of the gastric pHi within 24 hours of resuscitation is associated with therapeutic success.
2. Phenylephrine does not worsen hepatosplanchnic perfusion during initial haemodynamic support of patients with septic shock.
3. Titration of vasopressors using closed-loop control based on fuzzy logic principles leads to a reduction in total vasopressor dose.
4. Haemodynamic responsiveness, reflected by an increase in SV index, due to dobutamine may predict survival.
5. Metoprolol can reduce heart rate without detrimental effects on cardiovascular function in patients receiving milrinone.

Haemodynamic monitoring

Non-invasive haemodynamic monitoring

Estimation of LV filling pressure currently requires invasive measurement of PAOP via the insertion of a pulmonary artery catheter. Vignon and colleagues [22] prospectively assessed the ability of transoesophageal echocardiography (TEE) to predict an invasive PAOP of not more than 18 mm Hg in ventilated patients. TEE Doppler parameters were compared with PAOP in a group of haemodynamically stable ventilated patients in sinus rhythm. The proposed Doppler tissue imaging and colour Doppler indices were then tested prospectively in a second group of patients to determine predictive values for an invasive PAOP of not more than 18 mm Hg.

Doppler parameters that best predicted an invasive PAOP of not more than 18 mm Hg were (a) a mitral early-to-late (E/A) ratio of not more than 1.4 (ratio between the mitral E and A velocity, reflecting the atrial contribution to late diastolic LV filling), (b) pulmonary vein systolic-to-diastolic ratio of greater than 0.65 (of peak systolic-to-diastolic velocities in the pulmonary veins) and (c) a systolic filling fraction of the pulmonary vein of greater than 44% (ratio of the systolic time-velocity integral and the sum of the systolic and diastolic time-velocity integral of pulmonary vein Doppler). The relationship between Doppler indices and invasive PAOP was closer in patients with LV systolic dysfunction.

Artefact is one of the potential problems of echocardiography, particularly TTE. Karabinis and colleagues [23] conducted an ultrasound study to investigate echocardiographic artefacts in mechanically ventilated patients with lung pathology. In a total of 205 mechanically ventilated patients who had lung atelectasis or pleural effusion or both and who were undergoing transthoracic echocardiography, the authors found an intracardiac artefact, termed 'cardiac-lung mass' effect, in 8.29%. This artefact was due to a mirror image created by lung atelectasis or pleural effusion or both, giving the impression of an intracardiac mass not evident on transesophageal echocardiogram or after the lung pathology had resolved.

Critically ill patients have derangements in circulating blood volume, and accurate assessment of volume status is essential for optimal fluid management. In a prospective cohort study in patients admitted within 72 hours after aneurismal subarachnoid haemorrhage, Hoff and colleagues [24] found that clinical assessment of volume status performed by intensive care nurses using conventional haemodynamic parameters was very poor at predicting circulating blood volume when compared with pulse dye densitometry.

Predicting fluid requirement during sepsis was explored by Celi and colleagues [25]. The investigators applied artificial intelligence using a Bayesian network of physiological variables generated from a high-resolution database of information collected during the first 24 hours in ICU. With the predicted total amount of fluid given during the second 24 hours in ICU used as the outcome, the model accuracy was 77.8%, providing proof to the concept that mining empiric data using artificial intelligence can provide patient-specific and clinical scenario-specific recommendations.

Minimally invasive haemodynamic monitoring

Commercially available CO monitors use proprietary algorithms to relate arterial pressure to SV and thus CO and therefore are variably affected by factors that can affect arterial waveform. In these circumstances, algorithms that calculate the SV based on the characteristics of the arterial waveform may not accurately track changes in CO. One of those clinical circumstances is the presence of raised intra-abdominal hypertension (IAH).

Using nine haemodynamically stable, fluid-responsive pigs and bolus transcardiopulmonary thermodilution cardiac

output (CO_{TCP}) as the reference method, Gruenewald and colleagues [26] studied the ability of continuous cardiac output (CCO) methods based on arterial pressure waveform (pulse contour-derived cardiac output [PCCO] and PulseCO) and pulmonary artery catheter thermodilution (CCO_{PAC}) to detect a change in CO following a fluid challenge. CO was measured and compared during four steps of the experimental protocol: (a) at baseline, (b) after a fluid challenge, (c) after induction of IAH by pneumoperitoneum and (d) after a fluid challenge in the presence of IAH.

At baseline, all CO methods showed acceptable agreement in the increase in CO following volume loading. However, PulseCO and pre-calibration PCCO ($PCCO_{pre}$) grossly underestimated CCO following volume challenge in the presence of IAH when CO response to fluid was seen in only CCO_{PAC} and CO_{TCP}. After recalibration, PCCO was comparable to CO_{TCP}. There was also a progressive increase in bias (CO_{TCP}-PulseCO versus CO_{TCP}-$PCCO_{pre}$) during the experimental protocol in the presence of IAH.

The induction of IAH caused increases in CVP, PAOP and chest wall elastance. Arterial blood pressure increased after fluid challenge only in the absence of IAH. This finding and the mechanical effects of IAH on the arterial elastance could account for the inability of waveform-based CCO algorithms to accurately track changes in CO after fluid loading during IAH.

Two recent papers by the same investigators assessed the performance of a later FloTrac/Vigileo™ system algorithm (software version 1.07; Edwards Lifesciences LLC, Irvine, CA, USA). In both papers, the system was assessed in haemodynamically stable patients with a stable regular heart rate maintained between 80 to 90 beats per minute by fixed external pacing after elective off-pump coronary artery bypass grafting.

In the first paper, Hofer and colleagues [27] compared stroke volume variation (SVV) calculated using the new algorithm ($SVV_{FloTrac}$) with SVV calculated using the $PiCCO_{Plus}$™ system (SVV_{PiCCO}) during a blood volume shift manoeuvre, instigated by changing body positioning from a 30° head-up position to a 30° head-down position. The manoeuvre resulted in significant increases in SV, global end diastolic volume and CVP and significant decreases in $SVV_{FloTrac}$, SVV_{PiCCO} and PPV. Among the patients with an increase in SV of greater than 25% (58% of the population), $SVV_{FloTrac}$ and SVV_{PiCCO} were 16% ± 4% and 19% ± 5%, respectively. In patients with an increase in SV of less than 10%, baseline $SVV_{FloTrac}$ and SVV_{PiCCO} were 9% ± 2% and 11% ± 3%, respectively. The optimal thresholds of SVV to predict change in CO following postural change were an $SVV_{FloTrac}$ of 9.6% and an SVV_{PiCCO} of 12.1%, based on analysis of the ROC curve.

In the second paper, Senn and colleagues [28] compared the changes in CO induced by changes in body positioning using the new algorithm of the FloTrac/Vigileo™ system with (a) the previous software release (1.03), (b) the PiCCOplus™ system and (c) the intermittent transpulmonary thermodilution as a reference method. Haemodynamic measurements were performed in a supine position, a 30° head-up position, a 30° head-down position and on return to a supine position. Comparative analyses of the various algorithms showed an unacceptably large percentage error in CO between the old version of the FloTrac/Vigileo™ system and the thermodilution (percentage error of 37.5%). The new modified algorithm for the FloTrac/Vigileo™ system had a significantly better performance with a reduction of the percentage error and changes in CO that were comparable to the reference technique. Percentage error must be treated with caution, though, particularly when the reference test precision may differ from that expected. We therefore need to know the percentage error (that is, the precision) of both the new and the reference test.

Experimental studies

Prostacyclin inhalation is used to treat acute pulmonary hypertension and RV failure. To assess the haemodynamic effects of inhaled iloprost on a pig model of acute hypoxia-induced pulmonary hypertension, Rex and colleagues [29] carried out a prospective randomized placebo-controlled study in which inhalation of iloprost (compared with placebo) resulted in selective pulmonary vasodilation associated with an improvement in global haemodynamics, restoration of LV pre-load and a significant increase in CO.

A reduction in RV afterload was associated with an apparently paradoxical decrease in RV contractility, which was interpreted as being the result of an indirect mechanism ('homeometric autoregulation') caused by the immediate adaptation of RV contractility to match a drug-induced reduction in RV afterload. Parameters reflecting RV oxygen consumption normalized almost to baseline levels after iloprost treatment. Right coronary artery perfusion pressure (estimated as the difference between systolic arterial pressure and RV systolic pressure) increased, indicating a simultaneous improvement in oxygen supply to the right ventricle. There was no evidence of a direct negative inotropic effect of iloprost.

In summary:

1. Indices derived from TEE can predict an invasive PAOP of not more than 18 mm Hg in ventilated patients.
2. Clinical assessment of volume status is very poor at predicting circulating blood volume.
3. Bayesian networks of physiological variables can predict fluid requirement in ICU patients.
4. Waveform-based CCO algorithms do not accurately track changes in CO after fluid loading during IAH.
5. Version 1.07 of the FloTrac/Vigileo™ system algorithm shows better performance in haemodynamically stable patients compared with the previous software.

6. Iloprost improves global haemodynamics, LV pre-load and CO without direct negative inotropic effects.

Conclusions

This review has summarized key research papers published in the fields of cardiology and intensive care during 2008 in *Critical Care*. The papers reflect a wide range of original studies published in *Critical Care* and cover aspects of cardiovascular biomarkers in critical illness, haemodynamic management of septic shock and haemodynamic monitoring.

Competing interests

LC declares that he has no competing interests. DB acts as a consultant for LiDCO Ltd (Sawston, Cambridge, UK). MT has received research equipment from Hutchinson Technology Inc. (Hutchinson, MN, USA).

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