Review

Year in review 2007: *Critical Care* – cardiology

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Published: 14 October 2008
This article is online at http://ccforum.com/content/12/5/232

Critical Care 2008, **12:**232 (doi:10.1186/cc7007)

Abstract

This review summarises key research papers in the fields of cardiology and intensive care published during 2007 in *Critical Care*. To create a context and for comparison with the papers described in the review, we cite studies on the same subject published in other journals. The papers have been grouped into four categories: venous oximetry, cardiac surgery, perioperative fluid optimisation, and haemodynamic monitoring.

Venous oximetry

Mixed venous oxygen saturation (SvO_2) and central venous oxygen saturation ($ScvO_2$) – measured from the superior vena cava (SVC) – are used as indicators of adequacy of oxygen supply to the tissues. However, obtaining SvO_2 requires the insertion of a pulmonary artery catheter (PAC), which is invasive and is associated with an increased risk of complications [1]. $ScvO_2$ has been used as a surrogate for SvO_2, and targeting $ScvO_2$ in the treatment of patients with severe sepsis is associated with a significant survival benefit [2]. For this reason, the measurement of $ScvO_2$ is now part of the 6-hour sepsis bundle and is recommended by the Surviving Sepsis Campaign guidelines [3]. However, some questions remain: Is $ScvO_2$ an accurate reflection of SvO_2? How well do they correlate? What is the mechanism accounting for the observed differences between the two parameters [4-8]?

Generally, $ScvO_2$ is approximately 3% to 5% higher than SvO_2 as oxygen saturation (SO_2) decreases as blood travels from the SVC to the pulmonary artery (PA). The gradient varies considerably among individuals, depending on the particular disease state and on the value of SvO_2 [9]. The gradient in SO_2 and lactate [Lac] between SVC and PA (ΔSO_2 and Δ[Lac], respectively) may develop as blood from the SVC mixes with blood draining from the inferior vena cava (IVC) and/or from the heart's venous system [6].

To test this hypothesis, Gutierrez and colleagues [10] conducted a prospective observational study in nine haemodynamically stable adults without intracardiac defects or significant valvular disease who underwent right heart catheterisation for mild-to-moderate pulmonary hypertension. The authors found a significant mean ΔSO_2 of 4.4% and a Δ[Lac] of 0.16 mmol/L. The lower values in SO_2 and [Lac] measured in the PA could not be explained by the mixing of blood from the IVC with blood from the SVC, as hypothesised, since SO_2 and [Lac] were similar in the IVC and SVC. The fact that the greatest decrease in SO_2 and [Lac] occurred in the right atrium (location of the coronary sinus and the Thebesian venous system) suggests that the ΔSO_2 and Δ[Lac] are due to the mixing of SVC/IVC blood with the coronary venous blood. This finding is relevant not only because it can explain the ΔSO_2 and Δ[Lac] seen in these patients but also because, as SO_2 and [Lac] in the coronary venous blood vary in proportion to their rates of utilisation by the heart, it is conceivable that ΔSO_2 and Δ[Lac] may serve as markers of myocardial metabolism.

A low $ScvO_2$ has been associated with an increased risk of postoperative complications in high-risk surgery [11] and in severe sepsis [2]. However, the $ScvO_2$ profile of other groups of patients is unknown. Bracht and colleagues [12] showed that a low $ScvO_2$ (<60%) at admission to the intensive care unit (ICU) was associated with increased

APBCO = arterial pressure-based cardiac output; CABG = coronary artery bypass graft; CI = cardiac index; CO = cardiac output; CPB = cardiopulmonary bypass; cTnI = cardiac troponin I; CVP = central venous pressure; E = early diastolic trans-mitral velocity; E′ = early diastolic mitral annular velocity; GEDVI = global end-diastolic volume index; ICO = intermittent bolus thermodilution cardiac output; ICU = intensive care unit; IR = inflammatory response; IVC = inferior vena cava; Lac = lactate; OD = oesophageal Doppler; PA = pulmonary artery; PAC = pulmonary artery catheter; PAOP = pulmonary artery occlusion pressure; PCWP = pulmonary capillary wedge pressure; PP = pulse pressure; PPV = pulse pressure variation; ROC = receiver operating characteristic; $ScvO_2$ = central venous oxygen saturation; SO_2 = oxygen saturation; StO_2 = muscle tissue oxygenation; SVC = superior vena cava; SVI = stroke volume index; SvO_2 = mixed venous oxygen saturation; SVV = stroke volume variation; TA = tranexamic acid; TDI = tissue Doppler imaging; VS = vasoplegic shock.

mortality in an unselected group of 98 unplanned ICU admissions but that it did not impact on the ICU or hospital length of stay. Values of $ScvO_2$ in this study were not used to guide haemodynamic management. The mean $ScvO_2$ values were 70% at ICU admission and 71% six hours later. There was no overall change in $ScvO_2$ from baseline to six hours later in either the surviving or nonsurviving patients. However, there was a significant increase, but not normalisation, in $ScvO_2$ at six hours in the group of patients with a baseline $ScvO_2$ value of less than 60% (52% to 63%). Changes in $ScvO_2$ were not predictive of mortality or length of stay. Receiver operating characteristic (ROC) curve analysis revealed that, while two optimal cutoff values for the association of $ScvO_2$ with 28-day mortality could be demonstrated (60% and 69%), only patients with an $ScvO_2$ of 60% or less had a higher 28-day mortality compared with patients with an $ScvO_2$ of greater than 60% (29% versus 17%). This cutoff point may have been useful in showing an association between low $ScvO_2$ and mortality but, in view of the poor sensitivity and overall area under the ROC curve (0.53), should not guide therapy or interventions. The relationship between $ScvO_2$, lactate, and cardiac output (CO) was not addressed, as these last two parameters were not measured.

It is also interesting to note that the overall proportion of patients with an $ScvO_2$ of less than 60% on ICU admission was 21%. The $ScvO_2$ for the septic group was 68%, significantly higher than 49%, as reported by Rivers and colleagues [2]. Similarly, recent data from Dutch ICUs report that patients with severe sepsis or septic shock had a mean $ScvO_2$ of 74%. Low values of $ScvO_2$ were uncommon and only 1% of patients presenting to the ICU had an $ScvO_2$ of less than 50% [13]. These data raise concerns about the utility of $ScvO_2$ in sepsis in the ICU as supposed to emergency department and will require further studies [14]. Furthermore, SvO_2 and $ScvO_2$, though used as indirect indices of global tissue oxygenation, do not provide any insight into the state of oxygen utilisation in tissues [15]. Newer noninvasive methods have been tested as a surrogate measurement of tissue perfusion.

Podbregar and Mozina [16] investigated the relationship between SvO_2 and skeletal (thenar) muscle tissue oxygenation (StO_2) estimated noninvasively by near infrared spectroscopy (NIRS) in 65 patients with severe left heart failure (left ventricular systolic ejection fraction of less than 40% and PA occlusion pressure [PAOP] of greater than 18 mm Hg) with or without severe sepsis. The authors showed that StO_2 was higher in patients with sepsis (90% versus 84%). In nonseptic patients, there was a good correlation between StO_2 and SvO_2 and between SvO_2 and plasma lactate. StO_2 and SvO_2 tracked well with each other over time, although StO_2 overestimated SvO_2 with a bias of -2.3% and a precision 4.6%. No correlation or agreement was found between StO_2 and SvO_2 or between StO_2 and lactate in septic patients. The authors concluded that StO_2 would be able to estimate SvO_2 in patients with low CO and preserved O_2 extraction ratio (nonseptic patients), suggesting that in these circumstances, StO_2 and its temporal trends could be used as a fast, continuous, and noninvasive estimate of SvO_2. However, StO_2 is not reliable in septic patients with poor ventricular function and low O_2 extraction ratio. In these patients, StO_2 overestimates the overall oxygen delivery, as the high StO_2/low SvO_2 suggest blood flow redistribution, with a reduction in the oxygen content in the IVC and reduced cellular oxygen extraction. In the accompanying editorial, Puyana and Pinsky [15] highlight the complexities of interpreting StO_2 in relation to SvO_2 and the fact that the relationship between StO_2 and SvO_2 is not always predictable and may have different temporal kinetics in different diseases (for example, sepsis and hypovolaemia) and different stages of the same disease when mitochondrial dysfunction will impair cellular oxygen extraction.

Cardiac surgery

Cardiac biomarkers may aid the detection of patients at a higher risk of death or complications following cardiac surgery. Cardiac troponin I (cTnI) is a highly sensitive and specific biological marker of myocardial necrosis; it is an independent predictor of adverse outcome and of ICU and hospital lengths of stay in patients receiving cardiac surgery [17,18]. In a prospectively recorded database of patients who were scheduled for elective coronary artery bypass graft (CABG), valve replacement, or combined surgery with cardiopulmonary bypass (CPB) and who were deemed to be at low risk of death, Fellahi and colleagues [19] showed that the magnitude of postoperative cTnI release is related to the type of surgery. The increase in cTnI was greater in complex and prolonged surgical procedures, even in the absence of postoperative complications. Postoperative cTnI levels were higher in combined surgery (11.0 ng/mL) and valve replacement (7.8 ng/mL) compared with post CABG (5.2 ng/mL). Values of cTnI of greater than 0.6 ng/mL were considered abnormal. The study suggests that the levels of cTnI indicative of myocardial injury depend on the type of cardiac surgery performed. Thresholds of cTnI predicting severe cardiac event or death were higher in combined surgery (11.8 ng/mL) and valve surgery (9.3 ng/mL) compared with CABG (7.8 ng/mL). The specificity and negative predictive value of cTnI were greater after CABG, suggesting that an increase in postoperative cTnI after CABG surgery is more closely related to additional postoperative myocardial injury and poorer outcome. In this study, of the five variables significantly associated with severe cardiac event or death (elevated cTnI above the threshold, a left ventricular ejection fraction of less than 50%, treatment by diuretics, chronic obstructive pulmonary disease, and the duration of CPB), an elevated cTnI above the identified threshold was associated with the greatest odds of complications or death (odds ratio of 4.33). However, the authors point out that, as death was a rare event in the study, the thresholds identified may not

accurately predict death, which is probably associated with higher values of cTnI.

Extracorporeal circulation during cardiac surgery induces haemostatic alterations that lead to an inflammatory response (IR) and postoperative bleeding secondary to activation of the coagulation-fibrinolytic cascades. Jimenez and colleagues [20] show, in a case-control study on 165 patients undergoing elective CPB, that the 20.6% of patients who developed an IR had a longer lengths of stay in the ICU (7.8 versus 3.2 days) and in the hospital (17.6 versus 9.1 days). Of the patients who developed IR, 64% developed vasoplegic shock (VS). The incidence of IR was reduced by the administration of tranexamic acid (TA) (17% versus 42%), with an absolute risk reduction of 25% (numbers needed to treat = 4). Furthermore, the rates of incidence of VS were 0% in the TA group and 23% in the placebo group. Patients treated with TA had reduced inflammatory markers and required lower doses of vasopressors and a shorter duration of mechanical ventilation. The trial was interrupted early due to the higher incidence of bleeding in the placebo group.

Perioperative fluid optimisation

Traditional clinical and monitoring parameters tend to underestimate the amount of volume required for resuscitation and haemodynamic optimisation in critically ill patients. Hypovolaemia in multiple-trauma patients causes reduced oxygen delivery to the tissues and an increase in blood lactate and, even in the presence of normal physiological parameters (cryptic hypoperfusion), often leads to multiple organ dysfunction [21].

Oesophageal Doppler (OD) is a useful noninvasive tool for the management of fluid replacement in the perioperative period and in the ICU. In a randomised unblinded study on 162 multiple-trauma patients conducted in a single centre experienced with the use of OD, Chytra and colleagues [22] found that guiding fluid management with OD (aiming for a corrected flow time of greater than 0.35 seconds and a less than 10% change in stroke volume after a fluid challenge) resulted in the administration of a 2.4-fold increase in colloid in the first 12 hours in the ICU, which achieved a significant reduction in the mean blood lactate levels at 12 hours (2.92 versus 3.23 mmol/L) and 24 hours (1.99 versus 2.37 mmol/L). Fewer patients were on vasopressors and the dose of noradrenaline was lower in the OD group. However, there was no difference in organ dysfunction. There was also a significantly lower proportion of patients who developed infectious complications in the OD group (8.8% versus 34.1%, relative risk of 0.55), which may be a consequence of better tissue oxygenation and healing. Furthermore, patients had shorter stays in the ICU (median reduction of 1.5 days) and in the hospital (median reduction of 3.5 days), but there was no change in ICU and hospital mortalities. However, the study was powered to detect only a 0.6 mmol/L difference in blood lactate and a 2-day reduction in ICU length of stay; it was not powered to detect a mortality difference between the two groups. Therefore, the effect of OD-guided fluid management on mortality in this study cannot be quantified. Furthermore, OD is time-consuming and requires experienced operators, and patients need to be deeply sedated to tolerate the OD probe. The positive results of goal-directed fluid optimisation reported in the study could potentially also be achieved with the use of other relatively noninvasive devices that measure stroke volume, CO, or other derived measures.

In anaesthetised patients without cardiac arrhythmias, the variation in the arterial pulse pressure (PPV) induced by mechanical ventilation seems to be a more accurate predictor of fluid responsiveness than volumetric indices of preload (for example, CVP). PPV can be useful in determining the haemodynamic consequences of haemofiltration (that is, excessive fluid removal) or of positive end-expiratory pressure before a recruitment manoeuvre or to optimise fluid administration in acute respiratory distress syndrome, in which carefully monitored fluid management can affect lung function and duration of mechanical ventilation [23]. However, PPV is valid only if a series of conditions are met: (a) if there is a reliable arterial trace during normal sinus rhythm, (b) in the absence of spontaneous breathing, and (c) in the absence of excessively low tidal volumes. PPV is not an indicator of volume status or a marker of cardiac preload but is an indicator of the position of the cardiovascular system on the Frank-Starling curve. A series of articles published in *Critical Care* in 2007 have investigated further possible applications of PPV: intraoperative fluid optimisation of patients undergoing cardiac surgery or high-risk surgery.

Sander and colleagues [24] evaluated the suitability of central venous pressure (CVP), PAOP, global end-diastolic volume index (GEDVI), PPV, and stroke volume variation (SVV) for predicting changes in the cardiac index (CI) and stroke volume index (SVI) after sternotomy in cardiac surgery patients. This study showed that dynamic parameters such as PPV and SVV are more accurate in predicting changes in CO following sternotomy than classic static pressure measurement such as CVP and pulmonary capillary wedge pressure (PCWP). Sternotomy causes a decrease in airway pressures and hence decreases the effects of mechanical ventilation on venous return. Because PPV is directly influenced by the magnitude of cyclic changes in pleural pressure induced by mechanical ventilation, after sternotomy there was a significant decrease in PPV and SVV and increase in CI and SVI as a sole consequence of changes in airway pressure. However, unlike CVP and PCWP, changes in GEDVI, SVV, and PPV correlate with changes in CI and therefore appear to be more reliable under these conditions.

Several studies have shown that monitoring and maximising stroke volume by fluid loading during high-risk surgery (until the stroke volume remains unchanged indicating that it has reached the plateau of the Frank-Starling curve) is associated

with improved postoperative outcome. By increasing cardiac preload, volume loading induces a rightward shift on the preload/stroke volume relationship and hence a decrease in PPV. The clinical and intraoperative goal of 'maximising stroke volume by volume loading' can therefore be achieved simply by minimising PPV with the advantage of being less invasive.

In their paper, Lopes and colleagues [25] show that minimising PPV (<10%) by volume loading with hydroxyethylstarch 6% boluses during high-risk surgery decreases the proportion of patients developing postoperative complications (41% versus 75%, 1.4 versus 3.9 complications per patient), the duration of mechanical ventilation (median reduction of 4 days), and the lengths of stay in the ICU and the hospital (median reduction of 6 and 10 days, respectively). Patients in the intervention study received a significantly greater amount of fluid (4,618 versus 1,694 mL) and the PPV decreased from 22% to 9%. Unfortunately, PPV was not measured in the control group for comparison. At 24 hours, fewer patients in the treatment group required vasoactive drugs (12% versus 50%), and the mean blood lactate concentration over 24 hours was lower than that of controls (1.2 versus 2.4 mmol/L). The study was stopped after the interim analysis (33 patients enrolled) because of a significant decrease in the length of stay in the hospital (primary endpoint) in the treatment group. These results are in agreement with other fluid optimisation studies in which the use of more invasive haemodynamic parameters, such as GEDVI in patients undergoing cardiac surgery, was associated with a reduced requirement of vasoactive drugs and a shorter duration of mechanical ventilation and ICU stay [26].

Haemodynamic monitoring

CO can be assessed noninvasively from the analysis of the arterial pressure waveform. Each commercially available CO monitor uses a different proprietary algorithm to relate arterial pressure to stroke volume and thus CO. Some of these devices require calibration via a bolus dilution technique, which needs to be repeated at regular intervals or after a significant change in CO (calibrated systems). Other devices use algorithms that calculate the stroke volume based on the characteristics of the arterial waveform and individual patient demographics, without requiring calibration (uncalibrated systems).

McGee and colleagues [27], in a multicentre prospective clinical study on 84 patients, show that arterial pressure-based CO (APBCO) measurement using a Vigileo monitor/FloTrac sensor system (Edwards Lifesciences LLC, Irvine CA, USA) is comparable to the intermittent bolus thermodilution CO (ICO) technique using PAC and has the additional advantage of being noninvasive. Comparison of APBCO versus ICO showed a bias of 0.20 L/minute and a precision of ± 1.28 L/minute (limits of agreement of -2.36 to 2.75 L/minute). When changes in CO were measured by APBCO, 59% of the time the error in tracking the magnitude and the direction of the change in CO as measured by ICO was within ± 15%, 96% of the time it was within ± 30%, and 4% of the time it was greater than 30%. The limits of agreement for the difference between APBCO and ICO were 43% (significantly larger than ± 30%), which represent the value suggested for the limits of agreement between two equivalent methods [28].

Although arterial PPV has primarily been used to assess fluid volume responsiveness, Keyl and colleagues [29] investigated the effects of changes in cardiac performance/contractility after biventricular resynchronisation on PPV. The purpose of the study was to demonstrate that PPV can be modified by changes in contractility – in the absence of a significant change in heart rate, vascular tone, or intravascular volume status – in accordance with the Frank-Starling mechanism. In 19 patients undergoing the implantation of a biventricular pacing/defibrillator device for New York Heart Association class III-IV heart failure and ventricular dyssynchrony, the authors assessed dynamic blood pressure regulation during right ventricular and biventricular pacing in the frequency domain (power spectral analysis) and in the time domain (PPV is the difference between the maximal and minimal pulse pressure [PP] values, normalised by the mean value and expressed as a percentage). Respiratory PPV increased significantly during cardiac resynchronisation. PPV variation assessed in the time domain increased 1.3-fold from a median (interquartile range) of 5.3% (3.1% to 12.3%) during right ventricular pacing to 6.9% (4.7% to 16.4%) during biventricular pacing. These results highlight the influence of cardiac performance on the slope of the preload/stroke volume relationship. A reduction in ventricular contractility decreases the slope of the relationship between end-diastolic volume and stroke volume. Thus, the respiratory fluctuations of stroke volume and PPV decrease in the failing heart in mechanically ventilated patients. Conversely, an improvement in cardiac performance should create an increase in the respiratory fluctuations of PP. The study suggests that PPV can be a sensitive parameter of systolic cardiac performance in mechanically ventilated patients with stable preload and that this interaction should be considered when interpreting PPV in ICU patients who receive multiple treatments that can affect preload as well as contractility. However, the changes in contractility in this study are assumed from other studies and indices of contractility (for example, dP/dt_{max}) are not reported. Furthermore, in an accompanying editorial, Michard and colleagues [30] commented that resynchronisation can lead to changes in left ventricular size and therefore preload, making the prerequisite of a stable preload assumed in this study not completely secure [31].

In an attempt to provide an alternative method to quantify preload noninvasively, Sturgess and colleagues [32], in their retrospective study of 94 consecutive critically ill patients, investigated the distribution of tissue Doppler imaging (TDI) and its correlation with other echocardiographic indices of preload. The authors found that, in this study population,

there was a wide range of early diastolic mitral annular velocity (E′) – a preload-independent index of left ventricular relaxation – and of the ratio between peak early diastolic trans-mitral velocity (E) and E′ (E/E′) [33], an estimate of left ventricular filling pressure that corrects E velocity for the influence of myocardial relaxation [33,34]. Sixty-seven percent of the patients showed evidence of impaired myocardial relaxation (E′ of less than 9.6 cm/second) and 15% had an elevated left ventricular filling pressure (E/E′ of greater than 15). There was no difference between ventilated and nonventilated patients with regard to the values of E′ and E/E′. There was a weak correlation between E/E′ and left atrial area in the mechanically ventilated patients ($r = 0.3$, $P = 0.026$), but no correlations were demonstrated with left atrial volume, IVC diameter, or left ventricular end-diastolic volume. In the selected cohort, only an increased left ventricular end-systolic volume above 105 mL was associated with excess 28-day mortality. This study shows the complexity of interpreting tissue Doppler data when there is interplay between underlying disease and therapeutic strategies implemented in the ICU. However, it does provide potential reference ranges for TDI indices in critically ill patients, which can suggest a framework for planning future studies.

Conclusion

This review summarised key research papers published in the fields of cardiology and intensive care during 2007 in *Critical Care*. The papers reflect a wide range of original studies published in *Critical Care* covering aspects of cardiovascular physiology, intensive care, and perioperative medicine.

Competing interests

DB acts as a consultant for LiDCO plc and Deltex Medical Group plc. MT has received research equipment from Hutchinson Technology Inc.

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