Review

Year in review 2005: *Critical Care* – cardiology

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Abstract

This review summarizes key research papers published in the fields of cardiology and intensive care during 2005 in *Critical Care*. The papers have been grouped into categories: haemodynamic monitoring; goal-directed therapy; cardiac enzymes and critical care; metabolic considerations in cardiovascular performance; thrombosis prevention; physiology; and procedures and techniques.

Introduction

This review article summarizes original research papers in cardiology and critical care published in 2005 in *Critical Care*. The papers are grouped into topics for ease of reference.

Haemodynamic monitoring

The volume of distribution of intravenous glucose can be used to estimate central extracellular fluid volume and cardiac preload. Ishihara and colleagues [1] assessed the utility of standard arterial blood gas/glucose analyzers found in the intensive care unit (ICU) in accurate calculation of this volume. Previous work by the group [2] demonstrated that injection of a small bolus of glucose (5 g) followed by serial measurements of glucose concentration from arterial samples allowed calculation of the initial distribution volume of glucose (IDVG). This calculated volume was independent of pre-injection glucose concentration and concomitant infusions of glucose and/or insulin. Animal studies by the group showed a close correlation between IDVG and intrathoracic blood volume, implying clinical utility as a marker of cardiac preload [3]. Their recent study [1] used preinjectate and 3 min glucose concentrations to derive approximated IDVG. The approximated IVDG was shown to correlate well with original IDVG (the calculated volume using their original multi-sampling methodology), although the two values are not interchangeable. This paper suggests a simple way to derive cardiac preload utilizing standard techniques and equipment. Further research is needed to assess the accuracy of haemodynamic data provided by this modified technique and its practical application in the ICU.

Wiesenack and coworkers [4] examined the use of a novel pulmonary artery catheter (PAC) technique to assess fluid responsiveness. A rapid response thermistor at the tip of the modified PAC allows near continuous measurement of right ventricular ejection fraction and derivation of continuous right ventricular end-diastolic volume (CEDV). Previous studies [5-7] suggested good correlation between right ventricular end-diastolic volume and changes in stroke volume (SV), although the measurements were intermittent. This paper set out to examine the relationship between CEDV, SV and fluid responsiveness in patients undergoing coronary artery bypass grafting (CABG). A good correlation between changes in CEDV and changes in SV was observed. No similar correlation could be demonstrated for changes in central venous pressure, pulmonary capillary wedge pressure, or left ventricular end-diastolic area. Previous studies [8,9] identified a correlation between right ventricular end-diastolic volume and fluid responsiveness. However, CEDV did not predict fluid responsiveness (change in SV after fluid loading) in the study [4]. Left ventricular end-diastolic area (measured using oesophageal Doppler) was the only variable able to predict the response to fluid loading, although the correlation was weak. The authors rightly point out that aiming for set preload targets is not appropriate for all patients. Instead, the individual response to increasing preload should be assessed to guide fluid therapy specifically. However, the utility of volumetric measures of preload is strengthened by this study.

The use of pulse-contour analysis before and after cardiopulmonary bypass (CPB) in patients undergoing CABG was assessed by Sander and colleagues [10]. Pulse-contour analysis calibrated either by transpulmonary thermodilution or lithium dilution has been established as a valid alternative to

CABG = coronary artery bypass grafting; CEDV = continuous right ventricular end-diastolic volume; CI = cardiac index; CO = cardiac output; CPB = cardiopulmonary bypass; CXR = chest X-ray; GDT = goal-directed therapy; IDVG = initial distribution volume of glucose; IL = interleukin; ICU = intensive care unit; LMWH = low-molecular-weight heparin; MI = myocardial infarction; PAC = pulmonary artery catheter; PICCO = pulse contour continuous cardiac output; RCT = randomized controlled trial; RR = relative risk; SV = stroke volume; T_3 = tri-iodothyronine; T_4 = thyroxine.

haemodynamic measurements from the PAC during cardiac surgery [11,12]. However, the poor reliability in situations of significant haemodynamic instability has attracted criticism. In this paper the cardiac output (CO) data from pulse contour continuous cardiac output (PICCO) thermodilution and PAC thermodilution were compared before CPB. $CO_{PICCOtherm}$ and $CO_{PACtherm}$ were also compared with $CO_{PICCOpulse}$ following termination of CPB. Excellent correlation was seen between $CO_{PICCOtherm}$ and $CO_{PACtherm}$ before CPB (correlation coefficient 0.95, $P < 0.001$), with acceptable correlation after CPB (0.82, $P < 0.001$). Correlation of $CO_{PICCOpulse}$ with both $CO_{PICCOtherm}$ and $CO_{PACtherm}$ did not fall within acceptable limits of accuracy after CPB (0.67, $P < 0.001$ and 0.63, $P < 0.001$, respectively). The group concluded that pulse-contour analysis alone underestimates CO after the profound haemodynamic changes of CPB and cannot be relied upon to guide therapy in this situation without repeat calibration. This study has implications for the newer pulse-contour devices without calibration and their accuracy in situations of haemodynamic instability.

Goal-directed therapy

The effect of postoperative haemodynamic optimization of high-risk surgical patients was evaluated in a randomized controlled trial (RCT) conducted by Pearse and coworkers [13]. Patients in the study arm (62 people) were given fluid therapy with or without inotropic support with dopexamine to reach a target oxygen delivery of 600 ml/min per m^2. Control individuals ($n = 60$) received conventional therapy. Assessment of CO and derived oxygen delivery was done using the lithium dilution CO pulse contour system. This system has been validated as a suitable alternative to the PAC [14]. The frequency of postoperative complications was significantly reduced in the goal-directed therapy (GDT) arm (27 patients [44%] versus 40 patients [68%], $P = 0.003$; relative risk [RR] 0.63, 95% confidence interval [CI] 0.46-0.87). The number of hospital days was also reduced in the GDT group (11 days, interquartile range 7-15 days versus 14 days, interquartile range 11-27 days; $P = 0.001$). There was no significant mortality difference between the two groups. Analysis of the data revealed a greater degree of fluid loading and inotropic support in the intervention arm. This paper is the first to examine postoperative GDT in high-risk patients. Although no mortality benefit was seen, the clear difference in morbidity between the two groups suggests significant benefit to patients. Previous studies have revealed potentially important financial implications in terms of bed days for hospitals that adopt this approach [15,16]. It would be interesting to see further RCT data incorporating several centres.

The wider field of GDT research was examined in a meta-analysis conducted by Poeze and coworkers [17]. Previous meta-analyses yielded conflicting results. Heyland and colleagues [18] found no overall mortality benefit from several randomized trials. They observed that a positive mortality outcome with GDT was associated with a poor quality study. Two further reviews [19,20] suggested overall mortality benefit but did not comment on trial quality. In the review by Poeze and coworkers [17] 30 RCTs were scored for quality from 0 to 16 (incorporating randomization, blinding, selection and intervention criteria). Twenty-one trials involved perioperative optimization whereas nine trials involved sepsis and multiple organ failure. The findings were encouraging for proponents of GDT. There was an overall decreased mortality rate (RR) of 0.75 (95% CI 0.62-0.9). Closer analysis revealed that this effect was due to the significant mortality reduction in trials involving perioperative optimization (RR 0.66, 95% CI 0.54-0.81). Trials involving sepsis/multiple organ failure found no overall benefit (RR 0.92, 95% CI 0.75-1.11). The average quality of the trials was moderate but, interestingly, mortality outcome was independent of the study's quality score. This meta-analysis clearly strengthens the case for perioperative optimization of major surgical cases and compliments the RCT conducted by Pearce and coworkers [13] (see above). The role for aggressive optimization in nonsurgical patients remains unclear. The Surviving Sepsis guidelines advise early targeted fluid and inotropic therapy, following the model reported by Rivers and colleagues [21], but there is clearly a need for additional large, well designed RCTs.

Cardiac enzymes and critical care

Two studies have examined the role of troponin as a sensitive marker of myocardial injury. King and coworkers [22] conducted a prospective cohort study of 128 patients admitted to a medical ICU. Troponin I was measured on admission. A level above 0.7 ng/ml was considered significant. Follow up revealed a significantly increased mortality rate (odds ratio 7.0, 95% CI 2.44-20.5; $P < 0.001$) if the admission troponin was above 0.7 ng/ml. When adjusted for admission illness severity (measured using Acute Physiology and Chronic Health Evaluation II score), troponin was not an independent predictor of death. An elevated troponin in critically ill patients is often thought to be representative of widespread organ damage rather than coronary pathology. Sepsis is an obvious example and renal failure itself can result in abnormal troponin levels [23,24].

Lim and coworkers [25] examined the role of troponin in the diagnosis of myocardial infarction (MI) in the ICU. The study, once again, was of a prospective, cohort design. Enrolled patients were assessed by two experts for the diagnosis of MI during their admission to the ICU using international criteria [26]. This involved analysis of cardiac enzymes, electrocardiogram and transthoracic echocardiography (new cardiac wall abnormalities). Of those patients with a positive troponin T finding (>0.04 μg/l), only 56% met the agreed criteria for MI. Mortality was increased in those patients who were diagnosed with MI. In keeping with the findings presented by King and coworkers [22], an isolated troponin rise did not predict mortality when controlled for Acute Physiology and Chronic Health Evaluation II score. Troponin clearly has prognostic value in critically ill patients and aids

diagnosis of MI. However, interpretation depends on the clinical context and the results of additional investigations.

Metabolic considerations in cardiac performance

The importance of tight glycaemic control has been strengthened in recent trials of surgical and medical admissions to the intensive care unit [27,28]. Hoedemaekers and coworkers [29] performed a RCT to investigate the effect of glucose on levels of proinflammatory cytokines tumour necrosis factor-α and IL-6 and the anti-inflammatory cytokine IL-10 in patients undergoing cardiac surgery. Patients were randomized postoperatively to intensive glucose control (blood glucose between 80 and 100 mg/dl) or to standard care. The levels of cytokines tumour necrosis factor-α, IL-6 and IL-10 in mediastinal drain fluid were then measured. No significant difference could be seen between the intensive insulin therapy and control group. Amelioration of the inflammatory cascade is a proposed mechanism by which tight glycaemic control improves mortality and morbidity in postoperative patients [30]. The study by Hoedemaekers and coworkers [29] suggests that such a mechanism does not involve dynamic changes in inflammatory cytokines.

Cardiac arrest is known to affect thyroid function acutely [31]. Iltumor and coworkers [32] investigated 50 cases of cardiac arrest secondary to acute coronary syndrome and the effect on levels of tri-iodothyronine (T_3), free T_3, thyroxine (T_4), free T_4 and thyroid-stimulating hormone. The patients were compared with a group of 31 myocardial infarct patients without cardiopulmonary resuscitation and 40 healthy control individuals. Anoxic brain injury in cardiac arrest is thought to produce a sick euthyroid state by disrupting the hypothalamus-pituitary-thyroid axis. Such a state is characterized by low T_3 with impaired conversion of T_4 to T_3. It is thought that this relative thyroid deficiency has adverse prognostic implications related to poor cardiac performance [33,34]. The study demonstrated significantly reduced T_3 and free T_3 levels at 72 hours in the cardiac arrest group. This was most pronounced in patients with a longer period of resuscitation. There was no observed difference in T_4, free T_4 or thyroid-stimulating hormone. The cardiac arrest patients who survived to 2 weeks exhibited significant improvement in T_3 and free T_3 levels. These data support the concept of a sick euthyroid state following cardiac arrest. Further large trials are needed to investigate the role of T_3 replacement in this setting.

Metabolic acidosis is an almost universal feature of cardiac arrest. This is considered to relate to hyperlactataemia as a result of tissue hypoperfusion. Makino and coworkers [35] performed a quantitative analysis of acidosis in patients admitted with cardiac arrest to the emergency room of a tertiary referral centre in Japan. As predicted, cardiac arrest was associated with a significant metabolic acidosis compared with control individuals with minor injuries (standard base excess −19.1 versus −1.5, $P < 0.0001$). A major component of the acidosis was due to raised lactate (−11.8 mEq/l). The investigators later calculated the strong ion gap using the Stewart-Figge method [36,37]. This analysis takes into account weaker organic acids such as sulphate, citrate and pyruvate, which are excluded from conventional calculations such as the anion gap. The effect of a raised strong ion gap and hyperphosphataemia contributed significantly to the metabolic acidosis (−7.3 mEq/l and −2.9 mEq/l, respectively). In addition, compensatory changes, including hypochloraemia, hyperkalaemia and hypoalbuminaemia, were observed. It is apparent that the acidosis of cardiac arrest reflects far more than lactataemia alone. The clinical significance of this observation remains unclear.

Thrombosis prevention

Critically ill patients are at high risk for thromboembolic complications, including deep venous thrombosis and pulmonary embolism. Prophylactic anticoagulation with unfractionated heparin or low-molecular-weight heparin (LMWH) has therefore become standard practice in the ICU. The efficacy of LMWHs can be assessed by measurement of anti-factor Xa activity. Levels of 0.1-0.3 IU/ml are considered to indicate a satisfactory therapeutic range. Jochberger and coworkers [38] measured anti-factor Xa levels following subcutaneous injection of the LMWH certoparin in a prospective study of 62 ICU patients. At the standard once daily dose of 3000 IU, only 28% of patients reached the anti-factor Xa target of >0.1 IU/ml at 4 hours. Only 6% reached the target at 12 hours. A case of fatal pulmonary embolism forced a change in protocol to certoparin 3000 IU twice daily. Despite this, only 47% of patients hit the anti-factor Xa target at 4 hours, and again this percentage dropped at greater time intervals from injection. Failure to reach an anti-factor Xa level above 0.1 IU/ml was associated with a low pre-LMWH antithrombin level and a greater likelihood of requiring vasopressor support. The authors concluded that certoparin does not reliably achieve the required anti-factor Xa concentration for anticoagulation. There is still disagreement regarding the correlation between anti-factor Xa levels and the antithrombotic effect of LMWH [39], and this should be borne in mind when interpreting the study.

Physiology

A novel study conducted by Gutierrez and coworkers [40] examined changes in lactate concentration and oxygen saturation between the right atrium and pulmonary artery in critically ill patients with a PAC in concurrent use for haemodynamic measurements. It has previously been observed that oxygen saturation falls from the right atrium to pulmonary artery as a result of systemic venous blood mixing with highly desaturated blood from the coronary veins. Lactate is strongly absorbed by myocardium as an energy source, resulting in very low lactate concentrations in coronary venous blood. In the study, paired samples from the proximal and distal ports of the PAC were analyzed for oxygen saturation and lactate. The change in systemic oxygen

consumption between the two sites was also derived. The investigators confirmed a step down in oxygen saturation between right atrium and pulmonary artery (74.2 ± 9.1% versus 69 ± 10.4%, $P < 0.001$) and a corresponding decrease in lactate concentration (3.9 ± 3.0 mmol/l versus 3.7 ± 3.0 mmol/l, $P < 0.001$). There was a linear relationship between the change in oxygen consumption and the change in lactate concentration between the right atrium and pulmonary artery. The authors point out that the physiological relevance of these findings is not yet clear. The fact that changes in lactate between right atrium and pulmonary artery may relate in a linear manner to myocardial oxygen consumption raises interesting possibilities for the monitoring of cardiac performance.

Impaired autonomic function has been linked to an increased risk for sudden death in patients with ischaemic heart disease. Soares and coworkers [41] examined postoperative changes in autonomic function in a group undergoing CABG. Tests included heart rate variability, respiratory sinus arrhythmia, and valsalva manoeuvre. The immediate postoperative period saw a significant decline in autonomic function that improved to baseline by 60 days. The greatest impairment was seen at postoperative day 6. This study suggests that analysis of autonomic function might help to identify high-risk patients during the perioperative period. In the long term CABG may improve autonomic function via enhanced cardiac vagal modulation, suggesting a cardioprotective effect.

Procedures and techniques

Lorente and coworkers [42] undertook a detailed study of central venous catheter related infection. In all, 2595 line insertions were studied. A distinction was made between catheter-related local infection and catheter-related bloodstream infection. The latter category was defined as a positive peripheral blood culture with a corresponding culture from the offending central venous catheter tip without another obvious source for the identified organism. Subclavian, jugular and femoral insertion sites were studied. Catheter-related bloodstream infection density was significantly higher using the femoral approach compared with the jugular (8.34 versus 2.99, $P < 0.002$) and subclavian (8.34 versus 0.97, $P < 0.001$). Jugular was inferior to subclavian (2.99 versus 0.97, $P < 0.005$). The results for catheter-related local infection followed the same pattern. This study supports current clinical methodology. Subclavian and internal jugular lines are favoured over the femoral approach if possible. The authors admit that lack of randomization is a limitation of their data. However, the number of line insertions studied is favourable compared with other research in this area. It would be useful to compare haemorrhage and pneumothorax rates from the same data, because this can be a significant complication in subclavian puncture.

Graat and coworkers [43] investigated the use of the routine daily chest X-ray (CXR) in guiding therapy in the ICU. More than 2000 consecutive CXRs over a 5-month period were studied. The discovery of previously unexpected major abnormalities (large atelectasis, large infiltrates, severe pulmonary congestion, severe pleural effusion, pneumothorax and incorrect endotracheal tube position) was recorded, along with any change in management that resulted. Unexpected major findings occurred in only 5.8% of the CXRs. Of these abnormal films, fewer than half (2.2% of all CXRs) resulted in a change in ICU management. The authors concluded that the clinical value of the routine CXR in ICU, including haemodynamically labile and intubated patients, is low and have abandoned this practice. Instead, CXRs are ordered when a patient's condition changes or after CVP line or endotracheal tube insertion. Similar studies in the literature [44,45] agree with this position, but the routine CXR remains in widespread use in many units.

Conclusion

This review has encompassed key research from *Critical Care* 2005 concerning cardiology and cardiac surgery. This includes valuable additions to the contentious field of goal-directed therapy and interesting physiological observations which may prove to inspire new diagnostic and therapeutic procedures.

Competing interests

DB is a consultant for LiDCO.

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