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Cardiac complications associated with goal-directed therapy in high-risk surgical patients: a meta-analysis

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Editor's key points

- This meta-analysis tested whether or not goal-directed therapy (GDT) in high-risk surgical patients is associated with increased cardiac complications.
- Twenty-two randomized controlled trials met the criteria for inclusion.
- There was no increased incidence of pulmonary oedema, myocardial ischaemia, or both with GDT.
- Importantly, carefully conducted GDT led to decreased cardiac complications in high-risk patients.

Summary. Patients with limited cardiopulmonary reserve are at risk of mortality and morbidity after major surgery. Augmentation of oxygen delivery index (DO_2I) with i.v. fluids and inotropes (goal-directed therapy, GDT) has been shown to reduce postoperative mortality and morbidity in high-risk patients. Concerns regarding cardiac complications associated with fluid challenges and inotropes may prevent clinicians from performing GDT in patients who need it most. We hypothesized that GDT is *not* associated with an increased risk of cardiac complications in high-risk, non-cardiac surgical patients. We performed a systematic search of Medline, Embase, and CENTRAL databases for randomized controlled trials (RCTs) of GDT in high-risk surgical patients. Studies including cardiac surgery, trauma, and paediatric surgery were excluded. We reviewed the rates of all cardiac complications, arrhythmias, myocardial ischaemia, and acute pulmonary oedema. Meta-analyses were performed using RevMan software. Data are presented as odds ratios (ORs), [95% confidence intervals (CIs)], and *P*-values. Twenty-two RCTs including 2129 patients reported cardiac complications. GDT was associated with a reduction in total cardiovascular (CVS) complications [OR=0.54, (0.38–0.76), *P*=0.0005] and arrhythmias [OR=0.54, (0.35–0.85), *P*=0.007]. GDT was not associated with an increase in acute pulmonary oedema [OR=0.69, (0.43–1.10), *P*=0.12] or myocardial ischaemia [OR=0.70, (0.38–1.28), *P*=0.25]. Subgroup analysis revealed the benefit is most pronounced in patients receiving fluid and inotrope therapy to achieve a supranormal DO_2I, with the use of minimally invasive cardiac output monitors. Treatment of high-risk surgical patients GDT is not associated with an increased risk of cardiac complications; GDT with fluids and inotropes to optimize DO_2I during early GDT reduces postoperative CVS complications.

Keywords: cardiovascular complications; goal-directed; haemodynamic monitoring; high-risk surgery; perioperative

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Recent data suggest that major surgery is associated with a significant mortality risk.[1] An even higher number of patients develop postoperative complications.[2 3] The associated health and financial impact associated with postoperative complications is important, as these patients are at greater risk of long-term morbidity and mortality.[4] Identifying patients who are at greatest risk of perioperative complications enable appropriate preventive measures to be taken.[5] A limited cardiopulmonary reserve is a major risk factor for perioperative morbidity and mortality; as such, patients are less likely to meet the increased oxygen demand incurred during major surgery.[6] Perioperative goal-directed therapy (GDT) utilizes flow-based haemodynamic monitoring and therapeutic interventions as a means to augment the patients' global oxygen delivery to achieve a predetermined haemodynamic endpoint. This is with the aim of ensuring that those with poor perioperative cardiovascular (CVS) performance achieve the DO_2I seen in survivors without postoperative complications. When carried out early, in the right patient cohort, and with a clearly defined protocol, GDT has been shown to reduce postoperative mortality and morbidity.[7]

Despite this, postoperative GDT is not carried out widely. This may relate to lack of resources or doubts about its benefits. Many of the studies performed include limited patient numbers, are single-centre studies; some are considered outdated, with high mortality rates not representative of current clinical practice. Many studies to date have used the pulmonary artery catheter (PAC), the use of which has been largely superseded by less invasive CO monitoring methods because of concerns regarding the safety of the PAC.[8] A recent meta-analysis has demonstrated that although studies before 2000 demonstrate a benefit in terms of mortality and morbidity, studies conducted after 2000 demonstrate a significant reduction in complication rates, despite a smaller effect on mortality. This may, in part, be related to better patient selection and refined surgical and anaesthetic techniques. In addition, the reduction in complication rates is irrespective of the type of haemodynamic monitor used.[7]

The risk–benefit balance of GDT in high-risk surgical patients has been debated.[9] There may be risk associated with the use of fluid boluses and inotropes in patients with a known limited cardiopulmonary reserve who have arterial pressure and heart rate within the 'normal physiological range'. Treatment-related cardiopulmonary complications (total CVS complications, arrhythmias, acute pulmonary oedema, and acute myocardial ischaemia) have not been assessed previously. We hypothesized that goal-directed use of fluid and inotrope guided by haemodynamic monitoring in GDT is *not* associated with an increase in cardiopulmonary complications among high-risk surgical patients undergoing non-cardiac surgery.

Methods

Eligibility criteria

We only included randomized controlled trials (RCTs) reporting any of the following CVS outcomes: total CVS complications, arrhythmias, acute pulmonary oedema, and acute myocardial ischaemia. The analysis was limited to studies containing an adult general surgical population. GDT was defined as the use of haemodynamic monitoring and therapies aimed at manipulating haemodynamics during the perioperative period to achieve a predetermined flow-related endpoint(s). GDT must have been started pre-emptively in the perioperative period (24 h before, intraoperative, or immediately after surgery) and applied after a clear protocol. The protocol must contain predetermined step-by-step instructions for the clinicians based on data obtained from a haemodynamic monitor or surrogates (e.g. lactate, oxygen extraction ratio), and direct therapy to achieve predefined goals. Therapies included fluid administration alone or fluids and inotropes together. Studies not fulfilling these criteria, studies in cardiac surgery, and studies that did not titrate inotropes aimed at specific goals ('fixed dose' studies) were excluded from the analysis.

Information sources

Suitable studies were identified by conducting a systematic literature search of MEDLINE (via Ovid), EMBASE (via Ovid), and the Cochrane Controlled Clinical trials register (CENTRAL, Issue 4 of 2012). Only articles in the English language were considered. Date restrictions were not applied to the CENTRAL and MEDLINE searches. EMBASE was restricted to the years 2009–2012.[10] The last search update was in April 2012.

Search strategy

The following search terms were entered in the electronic databases: goal-directed therapy, optimization, haemodynamic, goal oriented, goal targeted, cardiac output, cardiac index, oxygen delivery, oxygen consumption, cardiac volume, stroke volume, fluid therapy, fluid loading, fluid administration, optimization, supranormal, lactate, and extraction ratio. Search terms were entered into the electronic databases using search strategy methods validated by the Cochrane collaboration (see Appendix for search strategies used).[11] In addition to searching electronic databases, previous review articles on the subject were hand-searched for further references.

Quality of included studies

The Jadad criteria were used for assessing methodological quality of included studies.[12] These criteria include methods of analyses used for random assignment, blinding, and flow of patients in clinical trials. The range of possible scores is 0 (lowest quality) to 5 (highest quality). Studies were not excluded based on Jadad scores.

Analysis of outcomes

Titles and abstracts were independently screened by three investigators to identify relevant studies. Pertinent full-text articles were then retrieved and analysed for eligibility against the previously outlined inclusion criteria. Information from selected studies was extracted using a standardized data collection form. Two investigators (N.A. and C.C.) independently collected data using a standardized data collection form and discrepancies were resolved by a third author (M.C.).

CVS morbidity, expressed as the number of patients suffering from overall CVS complications, was the primary outcome of our study. Secondary outcomes were defined as subsets of CVS complications; arrhythmias, acute myocardial ischaemia, and acute pulmonary oedema. Within these subgroups, studies were also analysed according to the type of monitor used, type of interventions, and therapeutic goals. 'Supranormal' DO_2I is used to describe the therapeutic goal of a $DO_2I > 600$ ml min^{-1} m^{-2}.

Statistical analysis

The meta-analysis was performed using review manager ('Revman') for MAC (Version 5.1, Cochrane collaboration, Oxford, UK). Dichotomous data outcomes were analysed using a Mantel–Haenszel random-effects model and results presented as an odds ratio (OR) with 95% confidence intervals (CIs). Statistical difference between the groups was considered to be present if the pooled 95% CI did not include 1 for the respective OR. All *P*-values were two-tailed and considered statistically significant if <0.05. I^2 methodology was used to assess statistical heterogeneity. Inconsistency and heterogeneity were considered significant when an I^2 value of $>50\%$ was present.[13]

Results

Included trials

A total of 12 398 study titles were obtained after searching electronic databases (Fig. 1). Titles and abstracts were screened and 307 references were identified as relevant to perioperative GDT. Further screening of titles and abstracts against our inclusion criteria resulted in 85 references retrieved for full-text analysis. Thirteen studies were excluded after detailed full-text evaluation, as they were not RCTs.[14–26] The remaining RCTs were analysed against inclusion criteria and the following studies were excluded: studies focusing on fluid