REVIEWS ARTICLE

Intraoperative goal directed hemodynamic therapy in noncardiac surgery: a systematic review and meta-analysis

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KEYWORDS
Goal directed fluid therapy; Meta-analysis; Hemodynamic goal; Noncardiac surgery

Abstract

Background: The goal directed hemodynamic therapy is an approach focused on the use of cardiac output and related parameters as end-points for fluids and drugs to optimize tissue perfusion and oxygen delivery. Primary aim: To determine the effects of intraoperative goal directed hemodynamic therapy on postoperative complications rates.

Methods: A meta-analysis was carried out of the effects of goal directed hemodynamic therapy in adult noncardiac surgery on postoperative complications and mortality using Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology. A systematic search was performed in Medline PubMed, Embase, and the Cochrane Library (last update, October 2014). Inclusion criteria were randomized clinical trials in which intraoperative goal directed hemodynamic therapy was compared to conventional fluid management in noncardiac surgery. Exclusion criteria were trauma and pediatric surgery studies and that using pulmonary artery catheter. End-points were postoperative complications (primary) and mortality (secondary). Those studies that fulfilled the entry criteria were examined in full and subjected to quantifiable analysis, predefined subgroup analysis (stratified by type of monitor, therapy, and hemodynamic goal), and predefined sensitivity analysis.

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PALAVRAS-CHAVE
Fluidoterapia
alvo-dirigida;
Metaanálise;
Objetivo
hemodinâmico;
Cirurgia não cardíaca

Terapia hemodinâmica alvo-dirigida no intraoperatório de cirurgia não cardíaca: revisão sistemática e meta-análise

Resumo
Justificativa: A terapia hemodinâmica alvo-dirigida (THAD) é uma abordagem focada no uso do débito cardíaco (DC) e parâmetros relacionados, como desfechos para fluidos e medicamentos para otimizar a perfusão tecidual e o fornecimento de oxigênio. Objetivo primário: determinar os efeitos da THAD sobre as taxas de complicações no pós-operatório.
Métodos: Meta-análise dos efeitos da THAD em cirurgias não cardíacas de adultos sobre as complicações pós-operatórias e mortalidade, usando a metodologia PRISMA. Uma busca sistemática foi realizada no Medline PubMed, Embase e Biblioteca Cochrane (última atualização, outubro de 2014). Os critérios de inclusão foram estudos clínicos randômicos (ECRs) nos quais a THAD no intraoperatório foi comparada com a terapia convencional de reposição de líquidos em cirurgia não cardíaca. Os critérios de exclusão foram traumatismo e estudos de cirurgia pediátrica e aqueles usando cateter de artéria pulmonar. Os desfechos, primário e secundário, foram complicações pós-operatórias e mortalidade, respectivamente. Os estudos que atenderam aos critérios de exclusão foram examinados na integra e submetidos à análise quantitativa, análise de subgrupo pré-definido (estratificada por tipo de monitor, terapia e objetivo hemodinâmico) e análise de sensibilidade pré-definida.
Resultados: 51 ECRs foram identificados inicialmente, 24 atenderam aos critérios de inclusão. Cinco ECRs foram adicionados por busca manual, resultando em 29 ECRs para análise final, incluindo 2.654 pacientes. Uma redução significativa das complicações para a THAD (RR: 0.70, IC de 95%: 0.62-0.79, p < 0.001). Nenhuma diminuição significativa na mortalidade foi observada (RR: 0.76, IC de 95%: 0.45-1.28, p = 0.30). Análises de sensibilidade qualitativa confiram os principais resultados gerais.
Conclusões: THAD no intraoperatório com monitoração minimamente invasiva diminui as complicações no pós-operatório de cirurgia não cardíaca, embora não tenha mostrado uma redução significativa da taxa de mortalidade.

Introduction

The perioperative management of high-risk surgical patients continues to be a challenge for the anesthesiologists. Despite advances in perioperative management, the incidence of serious complications after major surgery remains high. A decrease in perioperative oxygen transport is closely related to the development of organ failure and death. It has also been demonstrated that a large high-risk surgical population accounts for 12.5% of surgical procedures and for more than 80% of deaths. Surgical patients can be classified as high risk based on surgical factors or patient-related factors. Goal directed hemodynamic therapy (GDHT) is based on the optimization of preload with the use of algorithms based on fluids, inotropes and/or vasopressors to achieve a certain goal in stroke volume (SV), cardiac index (CI), or oxygen delivery (DO₂). The ultimate goal of this optimization is to avoid fluid overload, tissue hypoperfusion, and hypoxia. All the studies of perioperative hemodynamic optimization had the same starting point, fluid loading, and the same endpoint, achieving adequate DO₂. However, clinical heterogeneity between studies of GDHT cannot be...
ignored, with regard to type of surgery, patient’s characteristics, therapeutic goals, methods for achieving these goals and monitoring. The pulmonary arterial catheter (PAC) has been considered to be the "gold standard" for monitoring preload, afterload, contractility, and tissue oxygenation. The invasiveness and high rate of complications associated with this device render it as unsuitable for routine use in most cases. The use of minimally invasive monitoring has gained popularity in the past few years; these devices have been validated intraoperatively. Currently PAC is not recommended in most surgeries, and for this reason it was not analyzed in this meta-analysis. There are no data to support the practice of using central venous pressure to guide fluid therapy; therefore, central venous pressure-guided fluid therapy was not included in analysis.

Yet there are no studies in which different algorithms or different objectives are compared. The best method for assessing tissue oxygenation and intravascular volume has not yet been defined. The present review was designed to update the published evidence and determine the effectiveness of intraoperative GDHT with regard to complications and mortality with different types of algorithms and monitors used.

Material and methods

Selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology was used to identify the studies, based on the following inclusion criteria:

1. **Participants:** Adult patients (over 18 years) undergoing elective noncardiac surgery were included. The studies were not limited in terms of surgical risk.
2. **Types of intervention:** Intraoperative goal directed hemodynamic therapy: defined as hemodynamic monitoring that allows to perform a hemodynamic optimization algorithm based on the use of fluids, inotropes and/or vasopressors to achieve normal or supranormal hemodynamic values. GDHT guided by pulmonary artery catheter, transesophageal echocardiography or central venous pressure-guided GDHT were excluded.
3. **Types of comparison:** The studies that were selected for analysis included those that compared GDHT with conventional fluid management (monitoring of blood pressure, electrocardiogram, heart rate, urine output and/or central venous pressure).
4. **Results:** RCTs reporting any of the following outcomes: postoperative complications and/or mortality.
5. **Types of studies:** RCTs where intraoperative GDHT was performed in adult patients scheduled for noncardiac major surgery. Only peer-reviewed manuscripts were included.

Sources of information

Following the PRISMA protocol different search strategies (last updated in October 2014) were used to identify relevant studies that met inclusion criteria using EMBASE, MEDLINE and the Cochrane Library. There were no restrictions on the publication date or language. In addition to electronic searching, industry representatives were contacted for additional material. All identified review articles and evidence-based guidelines were hand-searched for additional references.

Search items

The search was conducted using the following key words: surgery, fluid, goal directed, end point, hemodynamic, target, goal and randomized controlled trial.

Study selection and data extraction

Two independent investigators assessed each title and abstract in order to discard any irrelevant RCTs and identify those potentially relevant. These RCTs were analyzed selecting those that met the inclusion criteria outlined above. RCT data extraction was performed by two different investigators and any discrepancy required further analysis and confirmation by a third investigator. The authors reviewed the data analysis in order to avoid errors in data transcription.

Assessment of risk of bias in included studies

Bias assessment risk was performed using the Cochrane risk of bias tool. From this tool, we used seven domains to assess the methodological quality of the studies included in the analysis.

Outcome variables

The primary outcome was the overall postoperative complications. The results were stratified according to the following variables: monitor utilized, therapy used to reach a hemodynamic goal and the hemodynamic goal. For the predefined subgroup analysis, studies were grouped:

1. **Monitor:** (a) Arterial pulse contour analysis methods (Vigileo/Flotrac®, Edwards Lifesciences Corporation, USA; ProAQT®, Pulsion medical systems SE, Germany; LiDCO Plus®, LiDCO Ltd., UK); (b) oesophageal Doppler Monitoring-ODM (CardioQ®, Deltex Medical, UK); (c) noninvasive methods (Masimo®, Masimo Corporation; CNAP® PPV, CNSystems Medizintechnik AG) and (d) measures of oxygen delivery and extraction methods.
2. **Therapy:** (a) Fluids; (b) fluids and inotropes; (c) vasopressors and fluids and (4) fluids, inotropes and vasopressors.
3. **Hemodynamic goals:** (a) SV maximization; (b) CI > 2.5 mL/min/m²; (c) preload responsiveness (including stroke volume variation, Pulse pressure variation and Pleth Variability Index®) and (d) ScvO₂.

The secondary outcome was mortality.

Statistical analysis

Review manager ("Revman") 10 for MAC (Cochrane collaboration, Oxford, UK) was used for statistical analysis. Meta-analysis was carried out using the Mantel–Haenszel
random-effects model, with results presented as risk ratio (RR) with a 95% confidence interval (CI). Forest plots were then constructed, considering $p < 0.05$ as statistically significant effect. Statistical heterogeneity was evaluated using $I^2$ statistics; $I^2$ values of less than 25% were defined as low heterogeneity, 25–50% as moderate heterogeneity and greater than 50% as high heterogeneity. A $\chi^2$ test for heterogeneity was performed, with $p < 0.100$ regarded as statistically significant. A priori sensitivity analyses were conducted on both the primary and the secondary outcomes by restricting the analysis to high quality trials: to those studies that showed no allocation bias and those without randomization/allocation bias. Publication bias was assessed using funnel plot techniques.

**Figure 1** Flow diagram illustrating search strategy.

**Figure 2** Review authors’ judgements about each risk of bias item presented as percentages across all included studies. Green, low risk of bias; white, unclear risk of bias; red, high risk of bias.
Results

Study selection

There were 14,160 references in electronic databases, of which 1003 were screened. Of those, 55 RCTs were analyzed and 24 of them were included for systematic review and meta-analysis, excluding those who did not meet the inclusion criteria. Finally a total of 29 RCTs were included; 5 RCTs were added by manual search. 2654 patients were included. Fig. 1 shows the flowchart used for item selection.

Assessment of risk of bias in individual studies

Bias risk was analyzed with the Cochrane tool. This was performed by two authors independently and we resolved any disparity by discussion and the involvement of a third person. We present the methodological quality in a summary table and a graph (Figs. 2 and 3).

Characteristics of the studies included in the analysis

The selected articles describe the results of RCTs that evaluated the use of intraoperative GDHT in noncardiac elective surgery, and that included postoperative complications and/or mortality as outcome. The characteristics of the included RCTs are shown in Table 1.

Primary results

1. Total complications
   Analyzing the 29 RCTs, 26 describe the total associated complications. GDHT was associated with a significant reduction in overall complication compared with patients treated in the control group (RR: 0.70, 95% CI: 0.62–0.79, p < 0.001) (Fig. 4).

2. Complications by monitor
   A significant decrease in complications was found in subgroup based on pulse contour analysis (RR: 0.78, 95% CI: 0.59–0.99, p = 0.04) and subgroup ODM (RR: 0.67, 95% CI: 0.53–0.85, p < 0.001). However, it was not shown in the subgroup of noninvasive monitoring (RR: 0.57, 95% CI: 0.28–1.15, p = 0.12) and was based on measures of oxygen delivery and extraction methods (RR: 0.59, 95% CI: 0.20–1.80, p = 0.36) (Fig. 5).

3. Complications by hemodynamic therapy
   A significant decrease in complications was observed in the fluids as monotherapy subgroup (RR: 0.69, 95% CI: 0.57–0.84, p < 0.001), fluids and vasopressors subgroup (RR: 0.76, 95% CI: 0.68–0.85, p < 0.001), and fluids, vasopressors and inotropes subgroup (RR: 0.54, 95% CI: 0.32–0.89, p = 0.02). However, the use of fluids and inotropes showed no decrease in complications (RR: 0.66, 95% CI: 0.34–1.28, p = 0.22) (Fig. 6).

4. Complications by hemodynamic goal
   A decrease in complications was associated with the use of GDHT in the following subgroups: Svmaximization (RR: 0.73, 95% CI: 0.61–0.89, p < 0.001), in the subgroup preload responsiveness (RR: 0.73, 95% CI: 0.59–0.95),
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinclair et al.</td>
<td>1997</td>
<td>Patients over 55 years undergoing hip replacement surgery</td>
<td>CardioQ-guided GDHT by optimizing SV and cFt with fluids</td>
<td>Standard care n 20</td>
<td>Length of stay, hemodynamic parameters</td>
<td>RCT</td>
</tr>
<tr>
<td>Conway et al.</td>
<td>2002</td>
<td>ASA I–III patients undergoing colorectal surgery</td>
<td>CardioQ-guided GDHT by optimizing SV with fluids</td>
<td>Standard care n 28</td>
<td>Hemodynamic parameters, bowel function parameters, complications</td>
<td>RCT</td>
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<tr>
<td>Gan et al.</td>
<td>2002</td>
<td>ASA I–III patients undergoing major surgery</td>
<td>CardioQ-guided GDHT by optimizing SV with fluids</td>
<td>Standard care n 50</td>
<td>Length of stay, complications</td>
<td>RCT</td>
</tr>
<tr>
<td>Venn et al.</td>
<td>2002</td>
<td>Patients undergoing hip replacement surgery</td>
<td>CardioQ-guided GDHT by optimizing SV with fluids</td>
<td>Standard care n 29</td>
<td>Length of stay, hemodynamic parameters</td>
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<tr>
<td>Walkeling et al.</td>
<td>2005</td>
<td>ASA I–III patients undergoing colorectal surgery in an ERAS protocol</td>
<td>CardioQ-guided GDHT by optimizing SV with fluids</td>
<td>Standard care n 30</td>
<td>Length of stay, oral tolerance, complications, quality of recovery</td>
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<tr>
<td>Nobblet et al.</td>
<td>2006</td>
<td>Patients undergoing colorectal surgery</td>
<td>CardioQ-guided GDHT by optimizing SV with fluids</td>
<td>Standard care n 30</td>
<td>Length of stay, complications, bowel function recovery</td>
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<tr>
<td>Donati et al.</td>
<td>2007</td>
<td>High-risk patients undergoing major abdominal surgery</td>
<td>GDHT by optimizing ERO2 with fluids and inotropes</td>
<td>Standard care n 54</td>
<td>Hemodynamic parameters, complications, length of stay</td>
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<tr>
<td>Lopes et al.</td>
<td>2007</td>
<td>High-risk patients undergoing major abdominal surgery</td>
<td>CNAP-guided GDHT by optimizing ΔPP &lt; 10%</td>
<td>Standard care n 67</td>
<td>Hemodynamic parameters, complications, length of stay</td>
<td>RCT</td>
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<tr>
<td>Buettner et al.</td>
<td>2008</td>
<td>ASA I–III patients undergoing major abdominal surgery (general, gynecological)</td>
<td>PPV-guided GTHD with fluids and vasopressors</td>
<td>Standard care n 16</td>
<td>Hemodynamic parameters, complications, ICU stay, length of stay</td>
<td>RCT</td>
</tr>
<tr>
<td>Senagore et al.</td>
<td>2009</td>
<td>Low- and moderate-risk patients undergoing laparoscopic bowel resection in an ERAS protocol</td>
<td>CardioQ-guided GDHT by optimizing SV with fluids n 21 (LR) or HES 6%</td>
<td>Standard care n 40</td>
<td>Tissue oxygenation parameters, hemodynamic parameters, length of stay</td>
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<tr>
<td>Jammer et al.</td>
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<td>Patients undergoing colorectal surgery</td>
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<td>Complications</td>
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<td>2010</td>
<td>ASA II–III patients undergoing low limb arterial by-pass</td>
<td>Flotrac-guided GDHT maintaining a CI &gt; 2.5 mL/min/m² and CVP &lt; 15 mmHg with fluids and inotropes, Sevoflurane anesthesia</td>
<td>Standard care guided by Apm and CVP n 17</td>
<td>Hemodynamic parameters, Complications, length of stay</td>
<td>RCT</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Patients</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcomes</td>
<td>Study design</td>
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<tr>
<td>Forget et al.</td>
<td>2010</td>
<td>Patients undergoing major abdominal surgery</td>
<td>Masimo-guided GDHT by optimizing PVI with fluids and vasopressors n 41</td>
<td>Standard care n 41</td>
<td>Amount of fluid administered, lactate levels, complications, length of stay, mortality</td>
<td>RCT</td>
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<tr>
<td>Mayer et al.</td>
<td>2010</td>
<td>High-risk patients undergoing major abdominal surgery</td>
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<td>Benes et al.</td>
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<td>High-risk patients (ASA III–IV) undergoing major abdominal surgery</td>
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<td>Cecconi et al.</td>
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<td>Standard care n 20</td>
<td>Amount of fluids administered, vasoactive use, complications, length of stay</td>
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<td>Challand et al.</td>
<td>2012</td>
<td>Patients undergoing colorectal surgery in an ERAS protocol. All patients</td>
<td>CardioQ-guided GDHT by optimizing SV with fluids n 89</td>
<td>Standard care n 90</td>
<td>Length of stay, readmission, complications</td>
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<td>Bartha et al.</td>
<td>2013</td>
<td>Patients over 70 years undergoing hip replacement in an ERAS protocol</td>
<td>LiDCO plus guided GDHT by optimizing SV and DOI &gt; 600 mL/min/m² with fluids and inotropes n 74</td>
<td>Standard care n 75</td>
<td>Complications, amount of fluids administered, hemodynamic response, length of stay</td>
<td>RCT</td>
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<td>Zhang et al.</td>
<td>2013</td>
<td>ASA I–II patients undergoing gastrointestinal surgery</td>
<td>PPV-guided GDHT with fluids: LR n 20; and HES 6% n 20</td>
<td>Standard care n 20</td>
<td>Length of stay, bowel function parameters, complications, hemodynamic parameters</td>
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<td>Salzwedel et al.</td>
<td>2013</td>
<td>ASA II–III patients undergoing major abdominal surgery</td>
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<td>Scheeren et al.</td>
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<td>Flotrac-guided GDHT by optimizing SV and SVV with fluids n 26</td>
<td>Standard care n 26</td>
<td>Complications, SOFA score, ICU stay, mortality</td>
<td>RCT</td>
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Table 1 (Continued)

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<th>Study</th>
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<th>Outcomes</th>
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<td>Zhang et al.</td>
<td>2013</td>
<td>ASA I–II undergoing lobectomy surgery</td>
<td>Flotrac-guided GDHT by optimizing SVV and maintaining a CI &gt; 2.5 mL/min/m² with fluids and inotropes</td>
<td>Standard care n 30</td>
<td>Length of stay, complications</td>
<td>RCT</td>
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<tr>
<td>Forget et al.</td>
<td>2013</td>
<td>Low- and moderate-risk patients undergoing colorectal surgery in an ERAS protocol</td>
<td>Masimo-guided GDHT by optimizing PVI with fluids (IPV &lt; 13)</td>
<td>Standard care n 11</td>
<td>Amount of fluids administered, complications, mortality, length of stay</td>
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<tr>
<td>Zakhaleva et al.</td>
<td>2013</td>
<td>Patients undergoing colorectal surgery in an ERAS protocol</td>
<td>CardioQ-guided GDHT by optimizing SV and cFT with fluids</td>
<td>Standard care n 40</td>
<td>Time of surgery, amount of fluids administered, bowel function recovery, complications, length of stay, mortality</td>
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<td>Srinivasa et al.</td>
<td>2013</td>
<td>ASA I–III patients undergoing colorectal surgery without an ERAS protocol</td>
<td>CardioQ-guided GDT by optimizing SV and cFT with fluids</td>
<td>Standard care n 37</td>
<td>Hemodynamic parameters, complications</td>
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<td>McKenny et al.</td>
<td>2013</td>
<td>Patients undergoing major gynecological surgery</td>
<td>CardioQ-guided GDHT by optimizing SV and cFT with fluids</td>
<td>Standard care n 50</td>
<td>Complications, length of stay</td>
<td>RCT</td>
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<td>Zheng et al.</td>
<td>2013</td>
<td>Elderly high-risk patients undergoing major abdominal surgery</td>
<td>Flotrac-guided GDHT by maintaining a CI &gt; 2.5 mL/min/m² with fluids and vasopressors</td>
<td>Standard care n 30</td>
<td>Cardiovascular complications, bowel function parameters, ICU stay, length of stay</td>
<td>RCT</td>
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<tr>
<td>Peng et al.</td>
<td>2014</td>
<td>Adult patients undergoing major orthopedic surgery</td>
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<td>Standard care n 40</td>
<td>Splanchnic organ functions, postoperative complications</td>
<td>RCT</td>
</tr>
</tbody>
</table>

GDHT, goal directed hemodynamic therapy; SV, stroke volume; Cft, corrected flow time; RCT, randomized controlled trial; ASA, American Society of Anesthesiologists; CVP, central venous pressure; ERAS, enhanced recovery after surgery; ERO2, oxygen extraction index; ΔPP, increment of pulse pressure; PPV, pressure pulse variation; LR, lactate of ringer; HES, hydroxyethyl starch; CI, cardiac index; PVI, plethysmography variation index; SVV, stroke volume variation; DOI, oxygen delivery index; SVI, indexed stroke volume; PP, pulse pressure; ScvO2, central venous oxygen saturation.

$p < 0.001$, and with a CI target, CI > 2.5 mL/min/m² (RR: 0.58, 95% CI: 0.44–0.76, $p < 0.001$), whereas in the sub-group that utilized measures of oxygen delivery and extraction methods no significant decrease was observed (Fig. 7).

Mortality

No significant differences were found with regard to mortality (RR: 0.76, 95% CI: 0.45–1.28, $p = 0.30$) (Fig. 8).

Sensitivity analysis, assessment risk of bias across studies and publication bias

No changes in the results with regard to complications ([RR: (CI 95%) 0.71 (0.61–0.82), $p < 0.01$]) or mortality ([RR: (CI 95%) 0.77 (0.42–1.40), $p = 0.39$]) were observed when restricting the analysis to those studies that had no allocation bias; or when restricting the analysis to those that had no allocation and/or randomization bias in the results with regard to complications (RR (CI 95%) 0.69 (0.59–0.81), $p < 0.01$) and mortality (RR (CI 95%) 0.95 (0.45–1.85), $p = 0.87$) On the other hand, a prespecified group analysis
Goal directed hemodynamic therapy

![Table]

<table>
<thead>
<tr>
<th>Study</th>
<th>GDHT Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>M-H</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tr>
<td>Gan et al. 2002</td>
<td>21</td>
<td>60</td>
<td>4.7%</td>
<td>0.54 [0.37, 0.81]</td>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>Venn et al. 2002</td>
<td>11</td>
<td>30</td>
<td>21</td>
<td>35%</td>
<td>0.51 [0.30, 0.85]</td>
<td>2002</td>
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<td>Conway et al. 2002</td>
<td>5</td>
<td>29</td>
<td>9</td>
<td>1.4%</td>
<td>0.54 [0.20, 1.40]</td>
<td>2002</td>
</tr>
<tr>
<td>Walkening et al. 2005</td>
<td>24</td>
<td>64</td>
<td>38</td>
<td>64%</td>
<td>0.63 [0.43, 0.92]</td>
<td>2005</td>
</tr>
<tr>
<td>Noblet et al. 2006</td>
<td>1</td>
<td>54</td>
<td>8</td>
<td>54%</td>
<td>0.13 [0.02, 0.97]</td>
<td>2006</td>
</tr>
<tr>
<td>Donati et al. 2007</td>
<td>9</td>
<td>68</td>
<td>27</td>
<td>67%</td>
<td>0.33 [0.17, 0.64]</td>
<td>2007</td>
</tr>
<tr>
<td>Lopes et al. 2007</td>
<td>7</td>
<td>17</td>
<td>12</td>
<td>16%</td>
<td>0.55 [0.29, 1.04]</td>
<td>2007</td>
</tr>
<tr>
<td>Senagore et al. 2009</td>
<td>8</td>
<td>42</td>
<td>4</td>
<td>44%</td>
<td>2.10 [0.68, 6.44]</td>
<td>2009</td>
</tr>
<tr>
<td>Mayer et al. 2010</td>
<td>6</td>
<td>30</td>
<td>15</td>
<td>30%</td>
<td>1.9%</td>
<td>2010</td>
</tr>
<tr>
<td>Forr et al. 2010</td>
<td>32</td>
<td>41</td>
<td>41</td>
<td>41%</td>
<td>0.78 [0.66, 0.93]</td>
<td>2010</td>
</tr>
<tr>
<td>Jammer et al. 2010</td>
<td>51</td>
<td>121</td>
<td>51</td>
<td>120%</td>
<td>0.99 [0.74, 1.33]</td>
<td>2010</td>
</tr>
<tr>
<td>Van der Linden et al. 2010</td>
<td>3</td>
<td>20</td>
<td>2</td>
<td>17%</td>
<td>0.51 [0.24, 1.12]</td>
<td>2010</td>
</tr>
<tr>
<td>Bartha et al. 2012</td>
<td>44</td>
<td>74</td>
<td>43</td>
<td>75%</td>
<td>1.04 [0.79, 1.36]</td>
<td>2012</td>
</tr>
<tr>
<td>Zhang et al. 2013</td>
<td>9</td>
<td>30</td>
<td>16</td>
<td>30%</td>
<td>0.56 [0.30, 1.07]</td>
<td>2013</td>
</tr>
<tr>
<td>McKenny et al. 2013</td>
<td>8</td>
<td>51</td>
<td>15</td>
<td>50%</td>
<td>0.52 [0.34, 0.81]</td>
<td>2013</td>
</tr>
<tr>
<td>Schreeren et al. 2013</td>
<td>12</td>
<td>36</td>
<td>16</td>
<td>26%</td>
<td>0.54 [0.31, 0.94]</td>
<td>2013</td>
</tr>
<tr>
<td>Salzwedel et al. 2013</td>
<td>52</td>
<td>79</td>
<td>72</td>
<td>81%</td>
<td>0.74 [0.62, 0.88]</td>
<td>2013</td>
</tr>
<tr>
<td>Forr et al. 2013</td>
<td>1</td>
<td>10</td>
<td>7</td>
<td>10%</td>
<td>0.14 [0.02, 0.96]</td>
<td>2013</td>
</tr>
<tr>
<td>Srivinasa et al. 2013</td>
<td>26</td>
<td>37</td>
<td>27</td>
<td>37%</td>
<td>0.96 [0.72, 1.28]</td>
<td>2013</td>
</tr>
<tr>
<td>Zakhaleva et al. 2013</td>
<td>7</td>
<td>32</td>
<td>19</td>
<td>40%</td>
<td>0.48 [0.22, 0.96]</td>
<td>2013</td>
</tr>
<tr>
<td>Zheng et al. 2013</td>
<td>19</td>
<td>30</td>
<td>30</td>
<td>30%</td>
<td>0.64 [0.48, 0.84]</td>
<td>2013</td>
</tr>
<tr>
<td>Peng et al. 2014</td>
<td>25</td>
<td>40</td>
<td>32</td>
<td>40%</td>
<td>0.78 [0.59, 1.04]</td>
<td>2014</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1275</td>
<td>1259</td>
<td>100%</td>
<td>0.70 [0.62, 0.79]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>460</td>
<td>645</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau²=0.04 , Chi²=54.70, df=26 (P=0.0008); I²=52%
Test for overall effect: Z=5.71 (P<0.0001)

Figure 4 Effect of GDHT in the protocol group vs control group on overall complications.

Discussion

Numerous studies have reported differences between technologies, especially in their response to typical surgical interventions such as fluid and vasoactive drug administration.26 The results obtained with one type of monitoring cannot be extrapolated to those obtained with other monitors.39 RCTs using noninvasive monitors were limited both in number of patients studied and methodological quality. How minimal invasive cardiac output monitoring techniques can be used to guide individualized fluid management40 needs to be sustained by validation studies that adhere to the proposed methodological considerations31 as well as large-scale clinical outcome studies.

There is some evidence that SV maximization strategies could be harmful in aerobically fit patients by leading to volume overload,25 and recent evidence suggests that this goal does not provide the benefits previously described.62

However, the results of our meta-analysis show that this hemodynamic goal remains valid. The use of dynamic response parameters to volume may decrease the risk of volume overload. A CI > 2.5 mL/min/m² as hemodynamic target within algorithms in which fluids, vaspressors and inotropes are used avoid the risk of hypotension due to decreased vasomotor tone. The use of inotropes increases the CO in situations where the patient is nonresponsive to the volume and does not present a reduced vasomotor tone. Inotropic support with dobutamine can result in changes in microvascular flow related to direct effects on the microcirculation as well as global CO.44 With the exception of ScvO₂, that was only evaluated in one RCT,19 and was not associated with better outcomes, this meta-analysis has not been able to detect significant differences between subgroups. Therefore it seems reasonable to adapt GDHT to risk patient, type of surgery as well as its duration44 as recommended by recent European Society of Anaesthesiology guidelines.45

A multicenter observational trial in patients with intrabdominal surgery found that low ScvO₂ was associated with an increased risk of postoperative complications in high-risk surgery. In this trial, the optimal value of mean ScvO₂ to discriminate between patients who did or did not develop complications was 73% (sensitivity 72%, specificity 61%).6 One of the major limitations of venous oximetry is that, as a global marker of demand-supply balance, it does not reflect organ-specific malperfusion. Whether ScvO₂ monitoring improves outcomes in surgical patients remains to be proven in large RCTs.

Unlike our results, a recent meta-analysis has shown a significant benefit of GDHT in patients receiving fluids and

...
Inotropes in order to achieve supraphysiological targets for oxygen delivery in high-risk patients.\(^{47}\)

This meta-analysis was unable to demonstrate a significant reduction in mortality. There are a number of reasons to explain why the control mortality may have decreased over time. These include: (1) better overall care thus decreasing mortality for similar patients; (2) clinicians’ awareness, learning from previous early published studies and therefore drifting their practice toward lower risk groups; (3) improvement in technology, that has become less invasive and therefore, gaining more credibility.\(^{48}\) Another reason for this may be that the most recent studies are not powered to assess mortality; in earlier studies, mortality was considered the most relevant endpoint, but this has changed to

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**Figure 5** Effect of GDHT in the protocol group vs control group on overall complications grouped by monitor. Pulse contour devices: Vigileo/Flotrac®, ProAQT, and LiDCO Plus®. No invasive: CNAP® PPV and Masimo®.
length of stay and morbidity endpoints with less high-risk patient group, and as a result, have very low or no mortality. However, a reduction in mortality associated with GDHT was demonstrated in groups of extremely high-risk patients (baseline mortality rate of >20%) as well as with long-term follow-up.

Unlike previous meta-analyses, we have not included those studies in which PAC was used, since these studies were published over 10 years, and do not reflect current practice. Grocott et al. meta-analysis included 31 studies with 5292 participants. The results are dominated by a single large RCT with a weight of more than 60% of the overall population in which PAC was used. The present meta-analysis confirms that the use of minimally invasive monitoring is effective and reduces postoperative complications. Postsurgical complications have a dramatic

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**Figure 6** Effect of GDHT in the protocol group vs control group on overall complications grouped by therapy.
Impact on costs. Potential costs savings resulting from GDHT are substantial\cite{1} and seem to be cost effective even with moderate clinical effect.\cite{2} Particularly, ODM technology has been considered favorably by both the NHS Center for evidence-based purchasing in the United Kingdom and United States Agency for Healthcare Research and Quality.\cite{3,4}

**Research implications**

More studies in which different types of monitoring and different types of algorithms and hemodynamic therapies are compared in patients with different risk in order to achieve optimal hemodynamic goals are needed. In addition, outcome report should be standardized. In this regard,
recommendations for the evaluation and standardization of perioperative complications have been recently published.\(^5^7\)

In summary, more studies are needed to demonstrate a significant reduction in mortality associated with GDHT.

### Weaknesses in study

The study by Mayer et al.\(^{22}\) has been under investigation for ethical reasons, the manuscript has not been withdrawn and remains part of the scientific record at the time we searched the literature. To verify potential biases in our results, both the primary and the secondary outcome were re-examined without including the Mayer et al.\(^{22}\) manuscript and no differences were found.

Many trials were single center trials and only one has investigated more than 100 patients per group.\(^1^9\) Differences in methodological quality may cause heterogeneity. Smaller studies tend to be conducted and analyzed with less methodological rigor than larger studies, and trials of lower quality also tend to show larger intervention effects.

The major limitation of our analysis is that overall complications were analyzed, regardless of the severity of these and their impact on length of stay and/or mortality. Furthermore, the use of different surgical interventions, different monitoring systems and algorithms adds more heterogeneity to the analysis. Thus, study heterogeneity may reduce the precision of treatment effect estimates and reduce the generalizability of the results of this meta-analysis.

The present meta-analysis is based on studies that describe the incidence of postoperative complications. It has to be recognized that the reporting of complications is not consistent and that the definitions used can differ in type, definition and importance between studies, limiting the applicability of some of our findings.

Furthermore, and unlike previous meta-analysis, the present meta-analysis conducted a global analysis of total

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**Figure 8** Effect of GDHT in the protocol group vs control group on mortality.

**Figure 9** Funnel plot of the published studies in relation to the primary outcome. The measure of precision used is the standard error (SE) of the logRR.
complications, without conducting an organ-specific or stratified by risk analysis. Despite these limitations, the results are consistent in most subgroups analyzed and even when the analysis is restricted to those studies with higher quality.

Conclusions

The results of this meta-analysis show that the use of intraoperative GDHT with minimally invasive monitoring decreases postoperative complications in noncardiac surgery, although it was not possible to show a significant decrease in mortality rate. ScvO₂ monitoring was not able to decrease the frequency of complications.

Conflicts of interest

The authors declare no conflicts of interest.

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Goal-directed hemodynamic therapy


56. Agency for Healthcare Research and Quality. Technology Assessment Program: esophageal Doppler ultrasound-based cardiac output monitoring for real-time therapeutic management
