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SPECIAL ARTICLE

Brazilian Consensus on perioperative hemodynamic therapy goal guided in patients undergoing noncardiac surgery: fluid management strategy – produced by the São Paulo State Society of Anesthesiology (Sociedade de Anestesiologia do Estado de São Paulo – SAESP)

Consenso Brasileiro sobre terapia hemodinâmica perioperatória guiada por objetivos em pacientes submetidos a cirurgias não cardíacas: estratégia de gerenciamento de fluidos – produzido pela Sociedade de Anestesiologia do Estado de São Paulo (SAESP)

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Introduction

The definition of the patient's physical status and current clinical condition and the emergency surgery that he will be undergoing, translated according to the American Society of Anesthesiologists (ASA), helps in the definition but does not define mortality-predictability.[1] Cardiac[2] and renal[3] risk assessment scales have been used, among other multifactorial and multidisciplinary measures,[4,5] but they tend to have no specificity and sensitivity coefficients that give the caregiver the actual predictability of the preoperative complications and death.[6]

Several retrospective, prospective and observational studies that attempted to assess perioperative mortality[7,8] demonstrated the importance of recognizing the patient's risk[9–11] as an initial measure to establish protocols and guidelines related to hemodynamic monitoring, fluid replacement (fluid and transfusion) setting goals for resuscitation (6D1), and multimodal care (ERAS/Hit project),[12–14] as well as other measures that could facilitate interactions between monitoring and intervention and support decision making using clinical guidelines.[15,16]

Moreover, several other studies have suggested that this approach may change the outcomes and significantly reduce morbidity and mortality, with significant human and social benefits interpreted from the point of view of cost-effective measures.[9]

It is estimated that about 240 million surgical procedures are performed annually around the world, where the standard mortality rate in countries and areas such as USA, Europe, and Brazil for patients under 60 years of age undergoing elective surgery and without chronic and clinically significant changes is 0.4–0.6%.[6,7,17] For patients at risk (clinical status, type of surgery, or a combination of factors), the mortality rate in noncardiac surgery can be greater than 26%.[6,7] Failure to identify patients at risk, lack of perioperative resources, and lack of intensive postoperative care are among the factors exacerbating this mortality.[6,7,11] Perioperative hemodynamic optimization has contributed, among other things, to reduce morbidity and mortality.

A retrospective study performed in the UK showed that among standard surgical patients and patients at risk, the latter group accounted for 80% of deaths of surgical patients and over 80% of total spending in the UK. In the same study, Pearse stated that if physicians do not identify the patients at risk and therefore do not offer a comprehensive standard of care, this will significantly increase morbidity and mortality in this population. Consequently, hemodynamic monitoring and fluid replacement are mandatory in patients at risk.

The base of decision making is the previous knowledge of high-risk patients, use of protocols guided by the hemodynamic monitoring of both macro- and microcirculation, and tissue perfusion evaluation and resuscitation protocols with fluids and transfusions based on oriented decisions,[18] particularly those related to fluid responsiveness.[9,16,18,19]

Fluid titration according to a hemodynamic goal is essential to improve perioperative outcomes.[20] Some studies have reported better outcomes when established guidelines of ''restrictive'' or ''limited'' fluid therapy were compared with standard care for gastrointestinal surgeries[21–23] and in patients with pulmonary dysfunction.[24,25] These studies seem to argue against the individually tailored goal-directed therapy based on intravascular volume optimization. However, studies of restrictive fluid and goal-directed therapy (GDT) essays certainly built a strong case for a priority plan of perioperative fluids. Taken as a whole, the success of both GDT and some restrictive fluid strategies suggests that perioperative fluid planning should emphasize that fluid therapy is delivered only when there is a clear indication. As for the prescription of antibiotics, analgesics and other therapeutic drugs to a specific problem, the physician should consider similar criteria for the administration of fluid. There are ''gray zones'' when it is unclear whether the patient will respond to fluid therapy or not. In these conditions, the use of functional approaches for hemodynamic monitoring and the challenges of therapeutic fluids seem justified. Hemodynamic parameters provide unique functional information on fluid responsiveness, which my help detect fluid needs and avoid unnecessary fluid loading. We should not exclude some

Preoperative risk criteria
Major criteria
Older than 70 years with some decompensated disease;
Previous severe cardiorespiratory disease (Coronary artery disease / COPD / Stroke);
Severe vascular disease involving large vessels;
Acute abdomen with hemodynamic instability;
Large blood loss (> 500 mL or > 7 mL.kg-1 younger than 12 years)
Septicemia;
Respiratory failure (need FiO2 > 40% to keep Sat >90% or mechanical ventilation time >48h;
Renal failure;
Extensive oncological surgery (e.g., gastrectomy, esophagectomy, cystectomy, etc.)
Minor criteria
Anesthetic time >2h;
Urgency/emergency surgery.

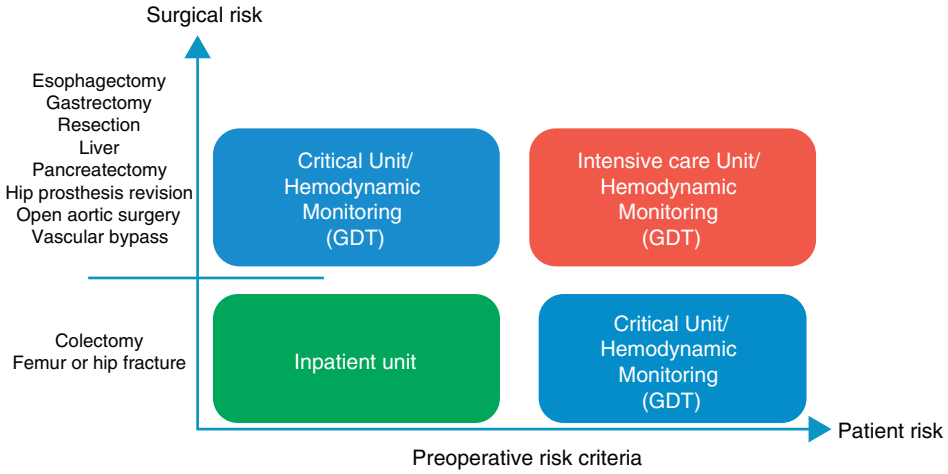

Figure 1 Matrix for the definition of high risk patients.[35]

limitations related to functional hemodynamic parameters (FHPs), such as spontaneous breathing, non-standardized tidal volume, non-standardized airway pressure/respiratory rate, non-sinus rhythm, neglected dUp (deltaUP), and right heart failure.[26,27]

Perioperative GDT aims to increase oxygen delivery (DO_2) during major surgery applying a tailored hemodynamic monitoring and therapeutic interventions. When performed early and in the right group of patients with a defined protocol, it has shown that GDT reduces postoperative mortality in the group of higher risk patients[16] and morbidity in all groups of surgical patients.[19,28]

This guideline evaluated the clinical efficacy of hemodynamic GDT in reducing morbidity and mortality in surgical patients, as well as reducing the financial and health losses associated with it. We have also proposed a set of surgical procedures and patient risk factors (i.e., age and ASA) that could benefit GDT (Fig. 1 and Table 1). Thus, the São Paulo State Society of Anesthesiology (SAESP) invited anesthesiologists and intensivists involved in perioperative care to establish a guideline for hemodynamic monitoring and fluid resuscitation in high-risk patients as a contribution to health professionals and policymakers involved in the care of patients at risk.

The use of criteria for defining patients at risk in the preoperative period is crucial. After reviewing several studies and published papers, we concluded that the creation of a table that associates high and low risks with surgical risk would increase the sensitivity and specificity of characterizing the high-risk patient.

In this context, we recommend using this table associated with this care matrix and decision making.

Guidelines and recommendations

It has been shown in several meta-analysis that the use of protocols for perioperative hemodynamic support that increases tissue perfusion reduces organ dysfunctions, mortality and hospitalization.[29] These outcomes were particularly evident when applied to more ill patients.[16] A key aspect of any perioperative protocol is the use of fluid therapy, vasopressors, and inotropes, which should also be focused on physiological hemodynamic principles (preload

Table 1 Surgical procedures to select patients who may benefit from GDT.

High surgical risk
Esophagectomy
Gastrectomy
Liver resection
Pancreatectomy
Colectomy
Rectal resection
Cystectomy
Hyperthermic Intraperitoneal Chemotherapy (HIPEC)
Femur and hip fracture
Hip revision
Abdominal Aortic Aneurysm (AAA) open repair
Shunt

and contractility) as an interaction between the autonomic response to anesthetic agents and volume status. There is no global consensus on broad guidelines of fluid therapy, thus creating local standards as necessaries. Although we are offering some guidance, the physician should definitely consider crucial aspects to identify and treat patients, associated with the following variables:

(1) Patient status (health, age, physiology status, and comorbidities): these factors are some of the characteristics that may change the autonomic response and, consequently, hemodynamic parameters; therefore, they are not necessarily related to fluids. Note that this consideration is mandatory for patients with conditions such as diabetes, liver dysfunction, advanced atherosclerosis, and preoperative volume depletion. Moreover, we may not exclude the depth of anesthesia associated with peripheral chemoreceptors (e.g., neuromuscular blockade), baroreflex (e.g., opioid), impaired cardiac contractility (e.g., general anesthetics), or sympatholysis (e.g., intravenous anesthetics).[30]
(2) Surgical risk (procedure (Fig. 1 and Table 1), approach, and surgical experience).
(3) Monitoring selection: the use of static parameters (e.g., central venous pressure and/or pulmonary artery pressure) has been associated with lower specificity and sensitivity compared to the use of the fluid responsiveness dynamic parameters (functional hemodynamics – stroke volume variation [SVV], delta PP, etc.) aiming at maintain DO_2 preoperatively. For high-risk patients undergoing medium or large surgery, the dynamic parameters associated with GDT are related to better outcomes.[31]
(4) Biomarkers for tissue perfusion adequacy (continuous monitoring of lactate, SvO_2, $ScvO_2$, $\triangle CO_2$).

Methods

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Library (2015, Issue 5), PubMed (1966 to May 2015), EMBASE (1980 to May 2015), Web of Science (1864 to May 2015), and Latin American and Caribbean Health Sciences (LILACS, 1982 to May 2015). There was no language restriction. The date of last search was May 13, 2015.

Table 1 shows the electronic databases from which the articles were extracted and the total number of returned references.

As the search was conducted both by title and single words, it was expected that all GDT studies with surgical patients were identified.

Table 2 shows the literature search strategy that was adapted for each electronic database.

Table 2 Search strategy.

((((hemodynamic goal-directed therapy OR haemodynamic goal-directed therapy OR hemodynamic goal directed therapy OR haemodynamic goal directed therapy OR goal-directed therapy OR goal directed therapy OR perioperative hemodynamic optimization OR perioperative haemodynamic optimization OR goal-directed hemodynamic OR goal-directed haemodynamic OR goal directed hemodynamic OR goal directed haemodynamic OR optimization OR haemodynamic OR hemodynamic OR haemodynamics OR TGOGDT OR hemodynamics OR goal-directed fluid therapy OR goal-directed fluid therapies OR goal directed fluid therapy OR goal directed fluid therapies OR fluid therapy OR fluid therapies OR fluid challenge OR fluid management OR perioperative hemodynamic optimization OR perioperative haemodynamic optimization OR hemodynamic stabilization OR haemodynamic stabilization OR goal oriented OR goal targeted OR cardiac output OR cardiac outputs OR cardiac index OR oxygen delivery OR DO2 OR oxygen consumption OR oxygen consumptions OR lactate OR lactates OR supranormal) AND (high risk surgical patient OR high risk surgical patients OR high-risk surgical patient OR high-risk surgical patients OR high risk surgical patient OR high risk surgical patients OR high-risk surgical patient OR high-risk surgical patients)) AND (adult OR adults)) AND (human OR humans))

Eligibility criteria

We considered including only randomized controlled trials (RCTs) or semi-randomized controlled trials (semi-RCTs), all evaluating adult patients (>18 years) undergoing noncardiac surgery and comparing GDT with standard care.

Semi-RCTs are those in which the treatment assignment was obtained by alternation, use of alternate medical records, alternate birth date or other alternate methods predictable.

GDT was defined as the use of hemodynamic optimization strategies aimed at improving tissue oxygenation through a set of protocols during the perioperative period to reduce morbidity and mortality, hospitalization stay and major complications. One of the requirements for GDT consists of specific parameters to guide fluid therapy.

We included studies that applied GDT at the following times: preoperatively, intraoperatively, and 0–12 h after surgery.

The GDT interventions analyzed in these guidelines are as follows:

1. Fluid administration alone; and
2. Combination of fluid and vasopressor/inotropes.

We consider any doses of the interventions described above. The control group received standard care or a conventional strategy during goal-directed therapy.

We considered analyzing the following types of outcomes: mortality; morbidities (e.g., infections; cardiovascular, pulmonary, and renal complications; anastomotic leak; nausea; vomiting); duration of hospital stay and duration of intensive care unit (ICU) stay; duration of mechanical ventilation (calculated when the mean and standard deviation were reported by the authors); and costs (as a narrative description).

Study selection

Two authors independently selected the potential studies, assessed the trial quality, and extracted data.

Strength of evidence and system of classification and recommendation

To create this guideline, the studies found in the literature were classified according to the GRADE system of the strength of evidence and strength of recommendation classification.[32–34]

The grading system classifies recommendations as strong (Grade 1) or weak (Grade 2) according to the balance between benefits, risks, burden and costs, and the degree of confidence in estimates of benefits, risks, and burden. The system classifies quality of evidence (as reflected in confidence in estimates of effects) as high (Grade A), moderate (Grade B), or low (Grade C) according to factors that include the risk of bias, precision of estimates, the consistency of the results, and the directness of the evidence.[32–34]

To help readers, GRADE results of evidence were represented using a color system in which green indicates strong recommendation (i.e., 1), red indicates weak recommendation (i.e., 2), and yellow indicates studies with high probability recommendation based on evidences, but this recommendation was downgraded due to some problem in its internal and/or external validity (Grade 1 B/C or 2, regardless if A, B, or C).

Methods used for evidence analysis

An evidence table was developed for GDT based on a current literature review and expert panel consensus (Tables 3–7). Whenever possible, we calculated the relative risk (RR) for mortality and morbidity, as well as the mean difference (MD) between duration of hospital and ICU stay and its confidence intervals (CI) of 95%. Furthermore, the number of patients who required treatment to prevent further poor outcome (e.g., the number of patients that needed to be treated for one to benefit compared to a control in a clinical trial) was calculated to obtain statistically significant results.

The average age calculated in this study was based on the average age of both groups (i.e., intervention and control arms) of each study included in this guideline.

Results

Tables 3–7.

Table 3 Treatment options for GDT in surgical patients according to level of evidence and grade of recommendation.

Intervention		Period	GRADE	Clinical condition
Crystalloid and colloid (not specified)[15]	Inotropic drugs (dopexamin)	Intraoperative and 0–12 h after surgery	1A	Elective and non elective
Colloids (hidroxietilamide)[42]	–	Intraoperative	1A	Non elective
Colloids (gelatin)[3,37]	Inotroic (dopexamin)	0–12 h after surgery	1B	Elective
Colloids (hydroxyethyl starch)[32,46]	Inotropic (dobutamin) and vasoactive drugs	Intraoperative and 0–12 h after surgery	1B	Elective
Colloids (hydroxyethyl starch)[34,40]	Inotropic (dobutamin)	Preoperative	1B	Elective
Fluid[42,48]	–	Intraoperative	1B	Elective
Crystalloid and colloid[39]	With or without inotropic agents (dobutamine)	0–12 h after surgery	2A	Elective
Colloid (hydroxyethyl starch)[46]	Inotropic agents (dobutamine) and vasoactive drugs	Intraoperative and 0–12 h after surgery	2A	Elective
Fluid (colloid)[45]	Inotropic agents (dobutamine)	Intraoperative	2B	Non elective
Colloid[47]	Inotropic agents (dobutamine)	0–12 h after surgery	2B	Elective
Fluid[43]	Inotropic agents (dobutamine) and vasoactive drugs (dopamine)	Intraoperative and 0–12 h after surgery	2B	Elective
Fluid[44]	–	Intraoperative	2B	Elective

GRADE, degree of recommendation.

Table 4 Relative risk and the number needed to treat mortality in GDT surgical patients according to the degree of recommendation.

Period and intervention	Follow-up	Relative risk (RR) (CI 95%)	NNT	Reference
Intraoperative: fluid (colloids)	30 days	0.50 (0.05–5.37)	[a]	Benes 2010[12]
Intraoperative and 0–12 h after surgery: fluid (colloid and inotropic [dopexamine])	30 days	1.08 (0.48–2.43)	[a]	Pearse 2014[15]
Intraoperative: fluid and inotropic	30 days	Not estimable	[a]	Cecconi 2011[40]
Intraoperative: fluid (colloids)	At hospital	0.50 (0.05–5.08)	[a]	Sinclair 1997[42]
Intraoperative: fluid (starches)	30 days	0.38 (0.08–1.67)	[a]	Lopes 2007[44]
Intraoperative: fluid	30 days	0.20 (0.01–3.97)	[a]	Scheeren 2013[48]
0–12 h after surgery: fluid (gelofusine) and inotropic (dopexamine)	28 and 60 days	0.83 (0.30–2.33) and 0.75 (0.30–1.89)	[a]	Pearse 2005[37]
0–12 h after the surgery: fluid and inotropic	30 days	1.73 (1.24–2.40)	6.2	Donati 2007[47]
Intraoperative and 0–12 h after surgery: fluid, inotropic and vasoactive drugs	30 days 60 days	0.47 (0.14–1.62) 0.32 (0.10 to 0.98)	[a] 2.8	Lobo 2000[43]

[a] The number needed to treat (NNT) was not calculated because there was no significant difference between groups. When there is no treatment effect, the absolute risk reduction is zero and the NNT is infinite.

Study selection

We identified a total of 12,165 records, after removing duplicates, through database searches for original review (Fig. 2). After sorting by title and, subsequently, by abstract, we found full copies of 600 records that were potentially eligible for inclusion in the guideline. We excluded 584 studies for the following reasons: off-topic; editorials or letters; narrative reviews; case study; cardiac studies; duplicates; published protocols; and cohort and case–control studies. Therefore, 15 RCTs and semi-RCTs met the inclusion criteria for this guideline (Table 8).

How to select patients who may benefit from GDT?
GRADE: 1C

Response: We recommend using GDT according to patient's risk and surgical risk because these factors can improve the following outcomes: mortality, morbidity (e.g., infection; cardiovascular, pulmonary and renal complications; anastomotic leaks; nausea; vomiting); length of hospital and ICU stay; and duration of mechanical ventilation[35] (Fig. 2). We recommend the use of GDT in patients aged over 65 years and ASA $\geq$ II and patients undergoing $\geq$2 h of surgery or with expected blood loss over 500 mL or urgent/emergency surgery or one of the surgical procedures listed in Table 1.[36]

Is GDT more effective and safer than standard care to reduce mortality and morbidity in high-risk surgical patients?
GRADE: 1A

Response: Yes. The use of GDT reduces morbidity in different age group patients, while it reduces mortality only in very high-risk patients.[15,37–42]

Arguments: Reduction in mortality with GDT in high-risk patients was seen in patients with early mortality rates > 20%.[41,43] This high mortality rate is consistent with mortality rates of patients undergoing high-risk surgery, previously reported in Brazil.[43,44] The use of protocols with

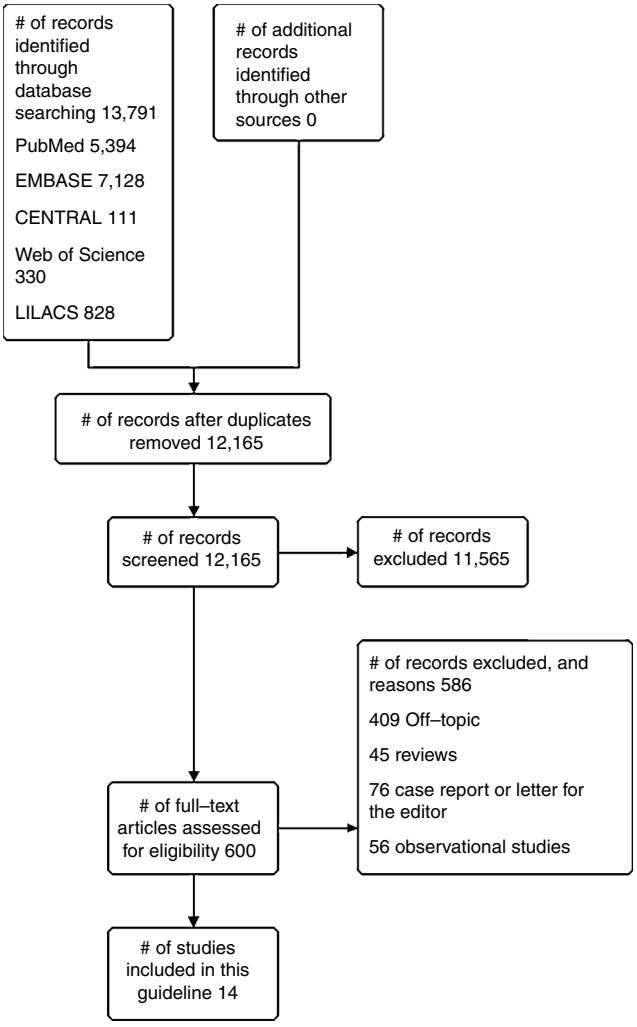

Figure 2 Flowchart of the assessed studies for these guidelines.

Table 5 Trends for lower and higher morbidity in GDT surgical patients according to the degree of recommendation: relative risk and number needed to harm occurrence.

Period	Intervention	Outcome	Relative risk (RR) (CI 95%)	NNT	Reference
0–12 h after surgery	Fluid (crystalloid and colloid), and inotropic drugs (with or without dobutamine)	Morbidity defined in POMS (postoperative morbidities Survey)	1.04 (0.96–1.11)	[b]	Ackland 2015[39]
		Pulmonary	1.11 (0.96–1.29)		
		Renal	1.03 (0.91–1.17)		
		Gastrointestinal	1.11 (0.89–1.38)		
		Cardiovascular	1.09 (0.68–1.74)		
		Hematologic	1.33 (0.56–3.16)		
		Pain	1.14 (0.98–1.33)		
Intraoperative and 0–12 h after surgery	Fluid (colloid and inotropic (dopexamine)	Compound outcomes (postoperative mortality within 30 days and predefined serious postoperative complications[a])	0.84 (0.71–1.01)	[b]	Pearse 2014[15]
	Fluid (colloid and inotropic (dopamine)	Ischemia or myocardial infarction	1.24 (0.50–3.11)		
		Cardiac or respiratory arrest	1.14 (0.56–2.29)		
		Gastrointestinal bleeding	1.62 (0.68–3.85)		
	Fluid (crystalloid, colloid) and inotropic (dobutamine)	Complications	1.13 (0.69–1.85)		Bisgaard 2013[a,38]
Intraoperative and 0–12 h after surgery	Fluid (crystalloids and colloids), and inotropic drugs (with or without dobutamine)	Infection	0.97 (0.66–1.41)	[b]	Ackland 2015[39]
		Neurologic	0.51 (0.24–1.09)		
		Wound	0.97 (0.20–4.68)		
	Fluid (colloids) and inotropic (dobutamine)	Complications	0.99 (0.26–3.78)	[b]	Donati 2007[47]
		Cardiocirculatory failure	0.20 (0.02–1.64)		
		Respiratory failure	0.99 (0.26–3.78)		
		Renal failure	0.28 (90.6–1.31)		
		Liver failure	0.25 (0.05–1.12)		
		Hematological failure	0.14 (0.01–2.67)		
	Fluid (gelofusine) and inotropic (dopamine)	Complications (infection, respiratory, cardiovascular, abdominal, and massive postoperative bleeding)	0.64 (0.46–0.89)	4	Pearse 2005[37]
	Fluid and inotropic	Total and major complications	Total: 0.13 (0.02–0.91) Important: 0.80 (0.64–1.02)	2.8	Cecconi 2011[40]
	Fluid, inotropic and vasoactive drugs	Arrhythmia	0.14 (0.01–2.46)	[b]	Lobo 2000[43]
		Shock	0.14 (0.01–2.46)		
		Stroke	0.32 (0.01–7.30)		
		Bronchopneumonia	0.63 (0.21–1.88)		
		Wound infection	0.19 (0.01–3.71)		
		Fistula	0.71 (0.18–2.74)		

Table 5 (*Continued*)

Period	Intervention	Outcome	Relative risk (RR) (CI 95%)	NNT	Reference
Intraoperative	Fluid (starches)	Respiratory complications	0.38 (0.23–0.95)	2.5	Lopes 2007[44]
		Renal complications	0.09 (0.01–0.59)	1.5	
		Arrhythmia	0.47 (0.14–1.57)		
		Infection	0.47 (0.21–1.08)	[b]	
		Acute pulmonary edema	0.19 (0.01–3.66)		
		Abdominal	0.31 (0.01–7.21)		
	Fluid and inotropic	Survivors with complications	0.80 (0.54–1.19)	[b]	Bartha 2013[45]
	Fluid (colloids)	Serious complications	0.32 (0.15–0.69)	4	Benes 2010[12]
		Complications	0.51 (0.33–0.80)	3.6	
	Fluid	Wound infection	0.07 (0.00–1.11)	[b]	Scheeren 2013[48]
	Inotropic (dobutamine) and vasoactive drugs	Complications	0.40 (0.20–0.82)	2.22	Bisgaard 2013b[46]

[a] Pulmonary embolism, ischemia or myocardial infarction, arrhythmia, cardiac or respiratory arrest, limb or finger ischemia, cardiogenic pulmonary edema, respiratory acute stress syndrome, gastrointestinal bleeding, intestinal infarction, anastomosis breakdown, paralytic ileus, acute psychosis, stroke, acute kidney injury, infection (source uncertain), urinary tract infection, surgical site infection, organ or space infection, blood infection, nosocomial pneumonia, and postoperative bleeding.
[b] The number needed to treat (NNT) was not calculated because there was no significant difference between groups. When there is no treatment effect, the absolute risk reduction is zero and the NNT is infinite.

supranormal physiological targets decreased morbidity in high-risk patients.[16] A careful hemodynamic monitoring before, during, and after surgery to adjust fluid therapy facilitates the recognition and early correction of tissue hypoperfusion. The reduction in complication rates was deeper in high-risk patients, protocols with supranormal physiological targets, and cases receiving inotropic agents in addition to fluid. Although the use of inotropic agents has not been recommended in the study OPTIMISE, when the study was later added to the systematic review and meta-analysis of the study group, the intervention was associated with a reduction in complication rates.[15]

Is GDT effective and safe when applied intraoperatively to reduce mortality and morbidity in high-risk surgical patients?

GRADE: 1B

Response: Yes, GDT is safe and effective when applied intraoperatively to reduce postoperative complications in high-risk surgical patients.[12,15,38,40,42,43,45–48]

Arguments: Several studies have suggested that GDT applied upon increased blood flow may reduce postoperative complications. Most of these studies were conducted during the intraoperative period.[49–51] All these studies shared the need for enhanced monitoring with a gavage[49,52] arterial catheter,[43,50,51] or pulmonary artery catheter (PAC).[12] These studies concluded that hemodynamic optimization during surgery improves the surgical outcomes in high-risk patients, and all forms of monitoring appear to be effective. Goal-directed therapy typically uses a monitoring tool for assessing cardiac function continuously and via a set of protocol instructions, administration of fluid and vasoactive agents is titrated to optimize cardiac performance. Central to these studies is that the GDT should not be defined by the presence or absence of a monitoring device but by explicit treatment objectives, such as maintenance of cardiac index and blood volume dynamic parameters. Generally, in these surgical patients, GDT should be provided during all procedures, from induction to 6–24 h in the ICU. Recently, Pearse et al.[15] reported the OPTIMISE results, a pragmatic multicenter trial performed in 17 hospitals with 734 randomly chosen high-risk patients undergoing gastrointestinal surgery to receive standard care or GDT intraoperatively and for 6 h after surgery. The intervention tested in this study consisted of a dopexamine infusion + bolus administration of colloid (250 mL) to maintain maximum stroke volume (SV) during the study period. SV was determined using an advanced monitor. The primary endpoint incidence

Table 6 Mean difference in length of hospital and ICU stay in GDT surgical patients according to the degree of recommendation.

Intervention	Type of outcome	Mean difference (ND) (95% CI)	Reference
Intraoperative: fluid	ICU	−12.00 (−34.89–10.89)	Scheeren 2013[48]
0–12 h after surgery: fluid and inotropic	Hospital	−2.10 (−3.82 to −0.38)	Donati 2007[47]

Table 7 Intervention characteristics of the included studies by period of time.

Elective or non-elective surgery	Surgery type	Mean age	Intervention	Monitor Type	Technique	Main target	Calibrated	GRADE	Reference
Preoperative and intraoperative									
Non-elective	Orthopedic	74.7	Fluid (colloid)	Doppler	Minimally invasive	Systolic volume; correct flow of time; CO	Yes	1B	Sinclair 1997[42]
Elective	Total hip arthroplasty	66	Fluid and inotropic	Vigileo/ FloTrac system	Minimally invasive	DO_2 > 600 mL/ min/m^2	No	1A	Cecconi 2011[40]
Elective	Retroperitoneal, aortic major open surgery, major renal, bladder surgery, and hysterectomy and oophorectomy for cancer	No report	Fluid	Not applied	Not applied	Not applied	Not applied	2B	Cuthbertson 2011[56]
Intraoperatory									
Elective	Abdominal important and radical cystectomy	70.5	Fluid (colloid)	Vigileo/ FloTrac system	Minimally invasive	Variation in stroke volume	No	1B	Scheeren 2013[48]
Elective	Intra-abdominal	66.5	Fluid (colloid)	Sistema Vigileo/ FloTrac system	Minimally invasive	Variation in stroke volume	Not reported	1B	Benes 2010[12]
Non-elective	Orthopedic	85.5	Fluid (colloid) and inotropic (dobutamine)	Lidco	Minimally invasive	Oxygen delivery	Yes	2B	Bartha 2012[62]
Elective	Upper and lower gastrointestinal, hepatobiliary, urological	62.5	Fluid (starch)	Pulse pressure variation	Minimally invasive	Delta PP $\leq$ 10%	Not applied	2B	Lopes 2007[44]
Intraoperative and 0–12 h after surgery									
Both	Upper and lower gastrointestinal, small intestine with or without pancreas, urologic, gynecologic.	71.7	Fluid (colloid) and inotropic (dopamine)	Lidco rapid	Minimally invasive	Systolic volume	No	2B	Pearse 2014[15]
Elective	Aortic	68	Fluid (hydroxyethyl starch) and inotropic (dopamine) and vasopressors	Lidco plus	Minimally invasive	DO_2	Yes	2B	Bisgaard 2013a[38]
Elective	Upper and lower gastrointestinal and vascular.	72.5	Fluids (crystalloids, colloids), inotropic (dobutamine) and vasopressors	Lidco plus	Minimally invasive	DO_2	Yes	1B	Bisgaard 2013b[46]
Elective	Total esophagectomy, gastrectomy, pancreatectomy, bowel resection, abdominal aortic aneurysm	62.7	Fluid, inotropic (dobutamine) and vasopressors (dopamina)	Pulmonary artery catheter	Invasive	DO_2	No	2B	Lobo 2000[43]
0–12 h after surgery									
Elective	Vascular, upper and lower gastrointestinal, hepatobiliary, urological	61	Fluid (gelofusine) and inotropic (dopexamine)	Lidco plus	Minimally invasive	Oxygen delivery index; systolic volume	Yes	1B	Pearse 2005[37]

Table 7 (*Continued*)

Elective or non-elective surgery	Surgery type	Mean age	Intervention	Monitor Type	Technique	Main target	Calibrated	GRADE	Reference
Elective	Abdominal aortic aneurysm, intestinal resection for cancer, pancreaticoduodenectomy, aortoiliac bypass	66	Fluid (colloids) and inotropic (dobutamine)	Not applied	CVC	O_2Ext ($SaO_2 - ScvO_2 / SaO_2$) < 27%	Not applied	1B	Donati 2007[47]
Elective	Upper gastrointestinal, liver and hepatobiliary resection, lower gastrointestinal and vascular	68	Fluid (crystalloids and colloids) and inotropic (dobutamine)	Lidco plus	Minimally invasive	Cardiac output	Yes	2A	Ackland 2015[39]

(a composite of pre specified postoperative complications within 30 days of the surgery) was lower in GDT group (36.6% vs. 43.4% [relative risk (RR) 0.84; (95% CI, 0.71–1.01)]; absolute risk reduction, 6.8% [95% CI, −0.3% to 13.9%]). This reduction, consistent with the benefits observed in many previous trials,[12,38,40,42,43,44–48] was still significant after adjustment for initial risk factors or after deleting the first 10 patients.

The authors performed an additional analysis, including the OPTIMISE results in an updated systematic review.[15] These results further strengthened the general conclusion that GDT of some sort is likely to be beneficial to high-risk patients and has few adverse effects documented. Findings of a meta-analysis of 38 trials, including data from OPTIMISE study suggest that the intervention is associated with a lower incidence of complications (intervention, 488/1548 [31.5%] vs. control, 614/1476 [41.6%]; RR, 0.77 [95% CI, 0.71–0.83]) and non-significant reductions in mortality within 28 days and 30 days (intervention, 159/3215 deaths [4.9%] vs. control, 206/3160 deaths [6.5%]; RR, 0.82 [95% CI, 0.67–1.01]) and mortality in the longer follow-up period (intervention, 267/3215 deaths [8.3%] vs. control, 327/3160 deaths [10.3%]; RR, 0.86 [95% CI, 0.74–1.00]). These findings are consistent with reports from Centers for Medicare & Medicaid Services[53] and National Institute for Health and Care Excellence,[54] which recommended the use of hemodynamic therapy algorithms.

Table 8 Electronic databases, date of last search, and number of returned references.

Electronic databases	Date of last search	Number of returned references
PubMed	1966 to May 2015	5394
CENTRAL	Issue 05, 2015	111
EMBASE	1980 to May 2015	7128
Web of Science	1864 to May 2015	330
LILACS	1982 to May 2015	828

Is GDT effective and safe when applied postoperatively to reduce mortality and morbidity in high-risk surgical patients?
GRADE: 1A

Response: Yes. We recommend applying GDT after surgery in high-risk surgical patients.

Arguments: Studies have shown that this strategy may contribute to reduce morbidity[15,37] GDT should be applied in the first 8 h postoperatively and requires hemodynamic monitoring to guide fluid replacement, inotropes, vasopressors, and vasodilators. In a cost-benefit analysis, Ebm et al.[55] reported that GDT could reduce costs by £ 2631.77/patient and £ 2134.86/in-hospital survival, indicating that it is effective both clinically and in terms of cost. Additional costs of implementation can be offset by savings from cost reduction due to reduction in complication rates and hospital stay. In addition, this study showed that GDT not only prolonged quality-adjusted life expectancy (0.83 years and 9.8 months), but also led to a cost reduction projection during life of £ 1285.77, resulting in a negative incremental cost-benefit rate of £ 1542.16/quality-adjusted life-year.[55]

Should we hemodynamically monitor patients to apply GDT in high-risk surgical patients?
GRADE: 1A[15,40,43,44]

Response: Yes, every patient who will undergo GDT should be hemodynamically monitored. We recommend any monitor that is available to estimate the cardiac output (CO) or different tools associated with pulse oximeter (plethysmograph variability index – PVI), bedside monitors (pulse pressure variation – PPV) and CO monitors (stroke volume variation – SVV, SV, oxygen supply – DO_2). In addition, other tools have been used to guide GDT, such as PAC, esophageal Doppler, and methods for pulse curve analysis. It is noteworthy that no invasive monitoring, such as pulse oximetry with plethysmographic analysis or methods associated with leg elevation maneuvers should be used as a functional hemodynamic parameters (FHP).[12,15,37–40,42,43,45–48,56,57] However, some of the perioperative goal-directed strategies failed because they are based on maximizing CO/SV without considering fluid responsivity.[58] Still, Cannesson[59] reported

that ''(...) feedback from anesthesiology providers was that this protocol [NICE NHS protocol suggesting fluid to maximize SV] forced them to give more fluids than thought should be given, and team leaders decided to include the stroke volume variation (SVV) as the trigger to fluid administration to increase physicians' adherence.[59]

Arguments: All studies used some type of device to monitor hemodynamic parameters. To apply GDT, it is necessary first to establish a protocol for delivery of oxygen and prevent tissue hypoperfusion, and many protocols have been published in the literature. In general, fluid and inotropes are used. Fluid should be administered when patients require increased perfusion and are also responsive to volume.[60]

Fluid responsiveness may be assessed by PPV, SVV, PVI or by the superior vena cava compressibility. It is important to adjust and make sure that patients' parameters are eligible for the assessment of the fluid responsiveness variables, without respiratory triggers, arrhythmias or open chest surgery, and tidal volume of at least 8 mL/kg estimated by height. Postoperatively, if the patient is breathing spontaneously, a strategy called ''passive elevation of the legs'' may be used as a means to change the ventricular preload associated with the measurement of the change in stroke volume, which provides an accurate means to guide the therapy providing fluid rates in high-risk patients. Patients are considered responsive if the cardiac output increases from 10% to 15% of baseline values. When dynamic parameters (PPV, SVV, PVI) may not be used, a CO monitor is required to quantify changes in stroke volume or DO_2. An important aspect to be avoided while applying GDT is fluid overload; that is, when patients do not derive benefit from the fluid administration; otherwise, there is no increase in cardiac output.

What tools should be used for GDT?
GRADE: 1A

Response: We recommend any monitor that is available to estimate the cardiac output or different tools associated with pulse oximeter (PVI), bedside monitors (PPV), and CO monitors (SVV, SV, DO_2). To apply GDT properly, the doctor must rely on SV optimization based on DO_2 or PPV optimization (the first requires a CO monitor, but not the latter). In addition, other tools have been used to guide GDT, such as PAC, esophageal Doppler, and methods of pulse curve analysis. Therefore, all these methods may be used as they have been associated with reductions in morbidity and/or hospital stay.[12,15,37–40,42,43,45–48,56]

Arguments: Studies have been based on protocols and not on specific devices; no monitoring technique by itself can improve outcomes. Some devices offer more advantages, such as being less invasive or minimally invasive. For example, pulse curve analysis, transpulmonary thermodilution, and esophageal Doppler feature parameters to apply GDT. However, these methods are generally more expensive and are not offered by the Unified Health System (SUS) – Ministry of Health. In this scenario, pulmonary artery catheters may be used to replace minimally invasive techniques. Monitoring requirements may vary with time and depend on the local availability of equipment and training. It is very important to emphasize that the entire team should be familiar and trained to insert devices, manage and interpret data, and apply strategies. This recommendation is for all types of monitoring, even if it is a minimally invasive technique. It is important to monitor the hemodynamic changes over short periods of time, and interventions should be made when necessary. A continuous measurement of all hemodynamic variables is preferable because one does not want to waste time to correct any instability or achieve a goal. Monitors for continuous monitoring of cardiac output are preferred, although there are no data to support the superiority of cardiac output continuous measurement over intermittent monitoring. These measures could be justified, however, if sudden changes could be detected early and intervention could readily be provided.[14]

What comorbidities are reduced associated with the use of GDT?
GRADE: 1B

Response: Perioperative GDT reduces the following complications after surgery: infections; wounds; gastrointestinal bleeding and cardiocirculatory failure; and pulmonar, neurological, renal and hematological insufficiencies (Table 5).

Arguments: Surgical procedures in high-risk patients are associated with high incidence of postoperative complications. It was proved that GDT significantly reduces the number of surgical patients with postoperative complications. Thirty-one studies with 5292 participants were enrolled in a Cochrane publication of 2012[61] to describe the effects of increased perioperative blood flow using fluid with or without inotropic or vasoactive drugs. The number of patients with complications has been reduced through the intervention, with a RR of 0.68 (95% CI 0.58–0.80). Hospital stay was reduced in the treatment group, on averaged, by 16.1 days (95% CI 0.43–1.89; $p = 0.002$). In addition, three morbidity rates were reduced by increasing the overall blood flow: kidney failure, with a RR of 0.71 (95% CI 0.57–0.90); respiratory failure, with a RR of 0.51 (95% CI 0.28–0.93); and wound infections, with a RR of 0.65 (95% CI 0.51–0.84). These data indicate that in 100 patients exposed to treatment, it can be expected that 13/100 avoid a complication, 2/100 prevent renal impairment, 5/100 prevent respiratory failure, and 4/100 prevent postoperative wound infection.

An updated literature search, recently published by Pearse,[15] identified 38 trials that included 6595 participants, with 23 trials including 3024 participants and providing data on postoperative morbidities. Complications were less frequent in patients treated according to a hemodynamic therapy algorithm (intervention 488/1548 [31.5%] vs. control 614/1476 [41.6%]; RR 0.77 [95% CI, 0.71–0.83]). The intervention was also associated with a reduced incidence of postoperative infection (intervention, 182/836 [21.8%] vs. control, 201/790 [25.4%]; RR, 0.81 [95% CI, 0.69–0.95]) and a reduced hospital stay (average reduction of 0.79 days [95% CI, 0.96–0.62]). There was no significant reduction in mortality within 28 days and 30 days (intervention, 159/3215 [4.9%] vs. control, 206/3160 [6.5%]; RR, 0.82 [95% CI, 0.67–1.01]) and mortality in the longer follow-up period (intervention, 267/3215 deaths [8.3%] vs. control, 327/3160 deaths [10.3%]; RR, 0.86 [95% CI, 0.74–1.00]) (Table 5).

Is there a good cost-benefit in the use of GDT compared to standard treatment to reduce mortality and morbidity in high-risk surgical patients?
GRADE: 1C

Response: GDT implementation in high-risk surgical patients undergoing major elective surgery is effective both clinically and in terms of cost compared to standard treatment. The implementation of additional costs may be offset by savings from cost reduction due to the reduction complication rates and hospital stay.[62]

Arguments: Several studies have shown that GDT implementation in high-risk surgical patients was effective both clinically and in terms of cost. Fenwick[63] compared methods to optimize oxygen delivery (using adrenaline or dopexamine) to reduce the risks associated with major elective surgery in high-risk patients and to compare the costs and cost-effectiveness of these approaches. The cost-benefit analysis related the difference in cost to the difference in year of life gained for a follow-up period of two years. Ebm[55] suggested that GDT in high-risk surgical patients should be thoroughly explored to curb the increase in costs associated with medical care.[62,64]

Discussion

The fluid challenge

A fluid challenge is one of the best tools that the anesthetist has to assess fluid responsiveness. For such, a change in preload (fluid bolus) should be induced when monitoring subsequent changes in stroke volume, cardiac output, and dynamic indices, such as PPV, SVV and PVI.[65]

The use of a fluid bolus offers two advantages:

(1) A way of assessing the response of a patient to fluid using changes in dynamic and static volume indices, flow and oxygenation; and
(2) A change in the increase of intravascular volume and often a necessary increase in the flow (cardiac output).

A fluid bolus is a provocative test of the circulation, similar to the use of a step function engineering to define a system. A ''test'' using a small amount of fluid (bolus) to assess the volume responsiveness can reduce the risk of an excessively liberal fluid strategy and the possible effects of fluid overload. These tools help determine the requirements for further fluid therapy, preventing deleterious effects of fluid overload through the administration of small volumes.

Noteworthy, the fluid challenge technique is a test of the cardiovascular system; it allows clinicians to assess whether a patient has a preload reserve sufficient to increase stroke volume with more fluid. Fluid therapy should be considered (Rahbari)[66] after a positive response to a fluid challenge. In contrast to a single fluid challenge, fluid may also be administered in a controlled manner based on an algorithm, repeating the fluid challenge as long as there is a positive response. This controlled approach is called ''maximizing stroke volume'' and is the cornerstone of most goal-directed therapy protocols (Noblett).[67] Thus, the only reason to perform a fluid challenge is to increase the stroke volume of a patient; if this increase does not occur; it is likely that an additional administration of fluid is harmful. The only excess fluid that can be administered in a fluid challenge is the amount used to which the patient does not respond.

A fluid challenge should comprise four separate orders: type of fluid to be administered; volume of fluid to be administered; infusion rate; and stopping rules if adverse effects are seen before the full amount of the bolus is administered. For rapid infusions of very small fluid bolus (e.g., 250 mL of crystalloid for 1–2 min), stopping rules are probably not necessary. However, if larger amounts of fluid or longer infusion times are used, it is important to have clear stopping rules to prevent right heart failure or pulmonary edema.

Although there is no consensus on type or exact dosage of fluid administration, boluses are delivered faster at a rapid rate (5–10 min) with a quick evaluation of the physiological response. The magnitude of this response helps determine the fluid challenge effectiveness, as well as the requirements for additional fluid therapies. Considering all these aspects, this approach avoids the deleterious consequences of fluid overload. The peak and maintenance of the dynamic and static variables improvement after a fluid bolus depend both on physiological state and fluid composition. Furthermore, the response maintenance after the bolus may be reduced in the presence of continued bleeding.

We recommend bolus therapy rather than continuous infusion when the aim is to improve the pressure, perfusion, and oxygen delivery. There should be a standard for fluid bolus in relation to the composition and fluid volume, infusion rate, and post-bolus evaluation time. Variables used to evaluate the fluid bolus efficacy should include appropriate changes in cardiac output or stroke volume and, if appropriate, dynamic indices of fluid responsiveness.

Limitations of dynamic indices

Fluid responsiveness measurements cannot be used in all patients and, in many it cannot be used at all times. Dynamic indices have a high predictive value in determining the responsiveness to fluid; however, specific criteria must be met to use these indices to assess fluid responsiveness. Intraoperative movements, electrosurgical equipment, and physiological artifacts (noise) can interfere with the accurate interpretation of the dynamic indexes. Four primary limitations may exist in the use of dynamic indexes.

First, arrhythmias (e.g., atrial fibrillation) prevent the use of PVI, PPV, SVV, and pulse wave velocity (PWV) for predicting the fluid responsiveness, as the variability of the inferior and superior vena cava remains accurate. The same limitation of PVI, PPV, SVV, and PWV is observed in subjects that show varying levels of spontaneous respiratory efforts. Again, the diameter variability of the inferior and superior vena cava is still predictive of responsiveness to fluid during spontaneous breathing. Second, if the current volume is less than 8 mL/kg, the negative predictive value of the PVI, PPV, SVV and PWV is reduced, while threshold range values >13% retain their positive predictive value. Third, marked decreases in chest wall compliance decrease the positive predictive values of all indices, while the intra-abdominal pressure can mask hypovolemia, but will not change the predictive value of responsiveness to the volume of these indices. Fourth, in acute cor pulmonale with high ventricular

interdependence, it will be observed a paradoxical positive value of PVI, PPV, SVV or PWV, which will be further increased upon fluid resuscitation. This increase is due to positive pressure inspiration decreasing the end-diastolic volume in the right ventricle, allowing increased left ventricular filling and thus a greater stroke volume. However, the largest pulse pressure and stroke volume occur during inspiration, while in patients responsive to volume, greater pulse pressure and stroke volume will occur during exhalation.

As few clinicians control changes in flow and pressure on the breathing phase, and it is known that the patient has pulmonary hypertension and cor pulmonale, it is better not to use dynamic indices alone to assess responsiveness to volume. Recent studies have demonstrated that the intraoperative use of PPV/SVV was inconclusive in identifying 25% of patients requiring fluid to undergo general anesthesia.[68] The use of these indices in ICU patients to assess fluid responsiveness is even more problematic, with only 2% of ICU patients meeting the criteria.[69] Therefore, when dynamic indices are used to guide fluid therapy, some measures of increased perfusion effectiveness should be considered. In such cases, and with the limitations of all dynamic indices listed above, it is indicated to perform a fluid challenge or a passive leg elevation test to identify the fluid responsiveness.

Specifically, when any of the above limitations prevent the use of these parameters, one can consider performing a passive leg elevation maneuver (LEM).[70] In contrast to mechanical breathing, which usually reduces CO, LEM cause an endogenous fluid challenge, which will increase the CO in ''responsive'' patients. LEM maneuver have a sensitivity of 89.4% and a specificity of 91.4% for predicting fluid responsiveness and is best combined with minimally invasive cardiac output monitors that can control changes in stroke volume and cardiac output, dynamically in real time, regardless of ventilation mode.[71,72] LEM execution, however, requires a major change of position, which often makes it impracticable for intraoperative use.

However, there are cases in the operating room (OR) in which postural changes can induce hemodynamic response that may serve as a diagnostic maneuver for fluid responsiveness.

Implications

We recommend that hemodynamic parameters are used as an integral part of GDT protocols. However, the limitations of each dynamic index must be considered. The presence of fluid responsiveness is not an indication for fluid administration; the final decision to give fluid must be supported by the clear need for hemodynamic improvement, presence of fluid responsiveness, and absence of associated risks.

Conflicts of interest

The authors declare no conflicts of interest.

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