Poor Adoption of Hemodynamic Optimization During Major Surgery: Are We Practicing Substandard Care?

Timothy E. Miller, MB ChB, FRCA, Anthony M. Roche, MB ChB, FRCA, MMed (Anaes), and Tong J. Gan, MD, MHS, FRCA

Hemodynamic optimization of surgical patients during the perioperative period aims to improve outcomes. This is frequently referred to as goal-directed therapy (GDT), a term that has been used for nearly 30 years to describe methods of optimizing fluid and hemodynamic status. Unfortunately, the term has never been standardized, and therefore can mean different things to different people, causing a significant amount of confusion. It can refer to supramaximal oxygen delivery using a pulmonary artery catheter (PAC),[1] early treatment of sepsis in the emergency department,[2] or perioperative optimization of fluid status,[3] all different goals directing different therapies.

It could be said that we all practice a form of GDT intraoperatively every day, except that our goals are normally related to arterial blood pressure (BP), heart rate, and occasionally central venous pressure (CVP). These are all known to be poor indicators of intravascular volume and cardiac output (CO). In healthy volunteers, heart rate and BP remain relatively unchanged despite a 25% hemorrhage of blood volume.[4] One systematic review showed that CVP is unable to identify which patients need more fluid, and concluded that CVP should no longer be routinely measured in the intensive care unit, operating room, or emergency department.[5] This leads to a key question: Can monitoring of stroke volume (SV) and CO improve our ability to optimize fluid and hemodynamic status?

This issue of *Anesthesia & Analgesia* includes 2 excellent systematic reviews by Hamilton et al.[6] and Gurgel and do Nascimento[7] on hemodynamic optimization of patients undergoing major surgery. The authors avoided the term GDT, and instead described the techniques as "preemptive hemodynamic intervention" and "optimizing tissue perfusion." It is clear that the reviews examined the same subject, with 26 studies (of 29 and 31, respectively) common to both articles.

From the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina.

Accepted for publication February 28, 2011.

Conflict of Interest: See Disclosures at the end of the article.

Reprints will not be available from the authors.

Address correspondence to Tong J. Gan, MD, MHS, FRCA, Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710. Address e-mail to tjgan@duke.edu.

DOI: 10.1213/ANE.0b013e318218cc4f

Perioperative hemodynamic optimization was first described in the 1980s, when the PAC was used to guide fluid and inotrope administration.[8] This enabled clinicians to augment tissue oxygen delivery to supranormal levels (DO_2 >600 mL/min/m^2) in high-risk surgery patients, the target being based on earlier work by Shoemaker et al.[9] observing survivors after high-risk surgery. As both systematic reviews have shown, oxygen-targeted approaches were generally successful, and when mortality in high-risk surgery was approaching 20%, most studies were able to show a survival benefit.[1,10–12]

Despite these promising results, the technique was not widely adopted. Oxygen-targeted approaches required significant resources, were very labor intensive, and most importantly were reliant on information from the PAC. Catheterization of the right heart began falling out of favor in intensive care units in the 1990s after the publication of several observational studies showing increased mortality.[13] Because early GDT was linked so closely with the use of PACs, it became embroiled in this controversy.

The last 20 years have seen the arrival of a number of minimally invasive CO technologies such as esophageal Doppler, arterial pressure waveform analysis devices providing SV variation (SVV) and pulse pressure variation (PPV), and monitors based on bioimpedance and bioreactance technology.[14] This has enabled clinicians to monitor and optimize SV, SVV, CO, and other hemodynamic variables without the need for a PAC.

These monitors are easy to operate and minimally invasive, so they have gained wider use than PAC optimization in high-risk patients. They are also frequently used in patients undergoing major but not necessarily high-risk surgery, for example, elective abdominal surgery, extensive cancer surgery, hip arthroplasty, or major spinal surgery. Hemodynamic optimization in this patient population can usually be obtained by optimization of preload alone. The change in SV, SVV, or CO in response to a fluid challenge is used to assess volume responsiveness. When a patient is hypovolemic, an IV fluid challenge will typically result in a >10% increase in SV or CO, or a reduction in SVV. This patient has "recruitable" SV and is in a fluid-responsive state. In the perioperative setting, fluid challenges should be considered until the SV no longer increases by 10% and preload has been optimized. SVV and PPV alone have also been shown to be superior to static indices in predicting

volume responsiveness in controlled mechanically ventilated patients.[15] However, special care should be taken in applying fluid challenges in patients with severely compromised cardiac function. In right heart dysfunction, SVV and PPV may misleadingly suggest volume responsiveness, although further volume may be harmful.[16] Earlier PAC optimization concepts used predetermined supraphysiologic goals, whereas a key difference in the present approach is individualized optimization within each patient's cardiac capacity.

Despite what many believe to be conflicting bodies of evidence, volume optimization is in fact complementary to a "restrictive" fluid approach, particularly with regard to crystalloids.[17] Our use of crystalloids has been greatly exaggerated over the last 50 years. An excellent review claimed that the so-called third space does not exist, and that intraoperative evaporative losses are probably no more than 100 mL/h.[18] Hence, a background infusion of balanced crystalloid (e.g., lactated Ringer solution) of 1 to 2 mL/kg/h for maintenance requirements can be combined with colloid boluses of 250 mL for volume optimization.

A number of studies have demonstrated that perioperative volume optimization is beneficial, and that it results in improved outcomes with lower complication rates and shorter hospital lengths of stay. Admittedly, most are single-center trials.[19] In modern major elective surgery, mortality is much less than previous optimization of high-risk patients with the PAC; therefore, these small studies are underpowered to detect a mortality difference.

So the pertinent question remains: Why is modern hemodynamic optimization not performed routinely for high-risk surgery? One possible factor is that anesthesiologists like to see immediate results. Benefits from optimization will not be obvious during the intraoperative and early postoperative periods. Lack of user-friendly equipment and skepticism with regard to the concept may also have a role. Furthermore, the absence of large-scale randomized controlled trials is almost certainly a significant factor. Systematic reviews, despite their inherent limitations, are therefore a valuable way of analyzing the literature.

The 2 systematic reviews published in *Anesthesia & Analgesia* this month are the largest yet published on hemodynamic optimization in major surgery. Hamilton et al.[6] specifically investigated hemodynamic intervention, and showed a significant reduction in complications with modern minimally invasive devices that are comparable with PAC optimization. This is an important finding, because the growing availability of minimally invasive devices is the future of perioperative optimization.

Gurgel and do Nascimento[7] focus more on tissue perfusion, and include negative studies such as one by Takala et al.,[20] which added an intervention in the study group (in this case dopexamine) without a clear optimization goal. Although this reduces the significance of their overall results, nevertheless they again showed a clear benefit with optimization. The lack of a reliable marker of tissue perfusion is highlighted, with lactate and central venous oxygen saturation the best available. Monitoring "adequacy" of tissue perfusion remains controversial, but until such time as the ideal tissue perfusion monitor is available, our present focus should remain on optimization of CO and DO_2.

So what does the future hold? Interest in perioperative hemodynamic optimization continues to grow. It is easy to accomplish for all major surgery, makes physiologic sense, and has a growing evidence base. A reduction in complication rates and shorter hospital stays have been widely demonstrated across surgical types. There is emerging evidence that optimization during the perioperative period may be associated with a long-term (15 years) survival benefit in high-risk patients.[21] Furthermore, Enhanced Recovery After Surgery programs are currently driving increased interest in hemodynamic optimization.[22] This is common practice in our hospital for selected procedures.

There are effectively 2 main groups of patients in which the clinician should carefully consider monitoring and optimization. First, we believe that a minimally invasive CO monitor should be considered in all major surgery to optimize preload. If CO and/or BP are still inadequate after volume optimization, the physiologic variables should guide the addition of an inotrope or vasopressor. This should be individualized to meet the patient's needs, and is currently based on measurements of CO and DO_2, with the future hope of advanced monitoring of tissue perfusion.

The second group of patients is those at increased risk of significant perioperative morbidity and mortality. Should we aim for supraphysiologic targets or not? These meta-analyses make a strong point for aiming "high," especially in the sickest of this second group of perioperative patients. Although the target DO_2 of 600 mL/min/m^2 suggested by Shoemaker et al.[8] could still be ideal, it seems prudent to individualize each patient's target based on their specific physiologic profile. Our challenge: Do we believe that supramaximal targets are necessary in these patients, are we brave enough to implement them, and what will we use to accomplish these goals?

As the population ages, the number of patients requiring major noncardiac surgery is only going to increase. Hemodynamic optimization using a variety of invasive and minimally invasive technologies may be a key step in improving short-, intermediate-, and long-term outcomes in these patients.

DISCLOSURES

Name: Timothy E. Miller, MB ChB, FRCA.
Conflicts of Interest: This author has received honoraria from Covidien and Edwards Lifesciences, and research support from Cheetah Medical.
Name: Anthony M. Roche, MB ChB, FRCA, MMed (Anaes).
Conflicts of Interest: This author has received honoraria from Covidien, Masimo, Hospira, and Fresenius.
Name: Tong J. Gan, MD, MHS, FRCA.
Conflicts of Interest: This author has received honoraria from Baxter, Eisai, and Fresenius, and research support from Eisai, Durect, and NICOM.

REFERENCES

1. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993;270:2699–707
2. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77

3. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PSA. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002;97:820–6
4. Hamilton-Davies C, Mythen MG, Salmon JB, Jacobson D, Shukla A, Webb AR. Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. Intensive Care Med 1997;23:276–81
5. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 2008;134:172–8
6. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate- and high-risk surgical patients. Anesth Analg 2011;112:1392–402
7. Gurgel ST, do Nascimento P Jr. Maintaining tissue perfusion in high-risk surgical patients: a systematic review of randomized clinical trials. Anesth Analg 2011;112:1384–91
8. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988;94:1176–86
9. Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic patterns in surviving and nonsurviving shock patients: use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. Arch Surg 1973;106:630–6
10. Lobo SM, Salgado PF, Castillo VG, Borim AA, Polachini CA, Palchetti JC, Brienzi SL, de Oliveira GG. Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. Crit Care Med 2000;28:3396–404
11. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 2000;90:1052–9
12. Wilson J, Woods I, Fawcett J, Whall R, Dibb W, Morris C, McManus E. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. BMJ 1999;318:1099–103
13. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJ Jr, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA 1996;276:889–97
14. Funk DJ, Moretti EW, Gan TJ. Minimally invasive cardiac output monitoring in the perioperative setting. Anesth Analg 2009;108:887–97
15. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 2009;37:2642–7
16. Wyler von Ballmoos M, Takala J, Roeck M, Porta F, Tueller D, Bracht H, Baenziger B, Jakob SM. Pulse pressure variation and hemodynamic response in patients with elevated pulmonary artery pressure: a clinical study. Crit Care 2010;14:R111
17. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Riis J, Jeppesen IS, Teilum D, Christensen AM, Graungaard B, Pott F. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens—a randomized assessor-blinded multicenter trial. Ann Surg 2003;238:641–8
18. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. Anesthesiology 2008;109:723–40
19. Giglio MT, Marucci M, Testini M, Brienza N. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. Br J Anaesth 2009;103:637–46
20. Takala J, Meier-Hellmann A, Eddleston J, Hulstaert P, Sramek V. Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. European Multicenter Study Group on Dopexamine in Major Abdominal Surgery. Crit Care Med 2000;28:3417–23
21. Rhodes A, Cecconi M, Hamilton M, Poloniecki J, Woods J, Boyd O, Bennett D, Grounds RM. Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study. Intensive Care Med 2010;36:1327–32
22. Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, von Meyenfeldt MF, Fearon KC, Revhaug A, Norderval S, Ljungqvist O, Lobo DN, Dejong CH. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg 2009;144:961–9

A Systematic Review and Meta-Analysis on the Use of Preemptive Hemodynamic Intervention to Improve Postoperative Outcomes in Moderate and High-Risk Surgical Patients

Mark A. Hamilton, MRCP, FRCA, Maurizio Cecconi, MD, and Andrew Rhodes, FRCP, FRCA

BACKGROUND: Complications from major surgery are undesirable, common, and potentially avoidable. The long-term consequences of short-term surgical complications have recently been recognized to have a profound influence on longevity and quality of life in survivors. In the past 30 years, there have been a number of studies conducted attempting to reduce surgical mortality and morbidity by deliberately and preemptively manipulating perioperative hemodynamics. Early studies had a high control-group mortality rate and were criticized for this as being unrepresentative of current practice and raised opposition to its implementation as routine care. We performed this review to update this body of literature and to examine the effect of changes in current practice and quality of care to see whether the conclusions from previous quantitative analyses of this field remain valid.

METHODS: Randomized clinical trials evaluating the use of preemptive hemodynamic intervention to improve surgical outcome were identified using multiple methods. Electronic databases (MEDLINE, EMBASE, and the Cochrane Controlled Clinical Trials register) were screened for potential trials, reference lists of identified trials were examined, and additional sources were sought from experts and industry representatives. Identified studies that fulfilled the entry criteria were examined in full and subjected to quantifiable analysis, subgroup analysis, and sensitivity analysis where possible.

RESULTS: There were 29 studies identified, 23 of which reported surgical complications. In total, the 29 trials involved 4805 patients with an overall mortality of 7.6%. The use of preemptive hemodynamic intervention significantly reduced mortality (pooled odds ratio [95% confidence interval] of 0.48 [0.33–0.78]; $P = 0.0002$) and surgical complications (odds ratio 0.43 [0.34–0.53]; $P < 0.0001$). Subgroup analysis showed significant reductions in mortality for studies using a pulmonary artery catheter, supranormal resuscitation targets, studies using cardiac index or oxygen delivery as goals, and the use of fluids and inotropes as opposed to fluids alone. By contrast, there was a significant reduction in morbidity for each of the 4 subgroups analyzed.

CONCLUSION: The use of a preemptive strategy of hemodynamic monitoring and coupled therapy reduces surgical mortality and morbidity. (Anesth Analg 2011;112:1392–402)

Major surgery is associated with a significant and quantifiable rate of both morbidity and mortality.[1,2] This risk of adverse events is increased in groups of patients with certain clinical criteria, for instance, emergency surgery or surgery in a patient with limited cardiovascular or respiratory reserve. The mitigation of these risks is important both for the individual patient who then has a better outcome and for health care planners and managers who are able to provide a higher quality of care for a reduced overall cost.[1,3]

Over the last 30 years, many authors have described how the use of flow-based hemodynamic monitoring combined with hemodynamic manipulations in the perioperative period can reduce the incidence of both morbidity, and in some studies, mortality.[4–32] For a variety of reasons, this practice has not been developed as a routine standard of care and includes the fact that many of these studies have been performed on small sample sizes from single centers. Very few studies have been conducted in a multicentric manner. Previous systematic reviews and meta-analyses have demonstrated benefits with this approach for major surgical patients[33–36]; however, there is a need for these to be updated given the recent plethora of studies published since the generation of newer and less-invasive hemodynamic monitors and improvement in the overall quality of care delivered.

This systematic review and meta-analysis was designed to explore whether a preemptive strategy of hemodynamic monitoring and manipulation in the perioperative period for moderate- and high-risk surgical patients can improve postoperative outcome.

METHODS

Search Strategy

Three electronic databases (MEDLINE, EMBASE, and the Cochrane Controlled Clinical Trials register) were searched with the following keywords: hemodynamic

From the Department of Intensive Care Medicine, St. George's Healthcare NHS Trust, London, United Kingdom.

Accepted for publication June 10, 2010.

Conflict of Interest: See Disclosure at the end of the article.

Address correspondence and reprint requests to Dr. Andrew Rhodes, Department of Intensive Care Medicine, St. George's Healthcare NHS Trust, London, SW17 0QT, UK. Address e-mail to andyr@sgul.ac.uk.

DOI: 10.1213/ANE.0b013e3181eeaae5

monitoring, cardiac output, stroke volume, oxygen delivery, goal-directed therapy, dobutamine, dopexamine, surgery, and randomized controlled trial. The search strategy was run from 1985 and closed on January 24, 2010. Articles were restricted to English language and human studies only. In addition to electronic searching, industry representatives were contacted for additional material, and personal archives and communications were searched. All identified review articles and evidence-based guidelines were hand-searched for additional references, and reference lists for identified studies were snowballed for additional articles. The title and abstracts identified from the search strategy were then screened for potential articles by 2 investigators. After this primary exclusion, full articles were obtained and examined for suitability.

Study Inclusion Criteria

All randomized controlled clinical trials evaluating a preemptive hemodynamic monitored approach to cardiovascular management were considered and reviewed. All studies had to be properly randomized to control for selection bias and had to report hospital mortality as an outcome on an intention-to-treat basis. Studies were excluded from the analysis if the hemodynamic monitoring was only used differently between the control and protocol groups before randomization, because these studies tended to be fixed-dose drug studies that did not fit our selection criteria.[24,37,38] Only peer-reviewed papers were included. Abstracts from scientific meetings were not screened; previous studies in this field have shown only low yield to this process, despite attempting to counter for potential reporting bias.

We defined a hemodynamic intervention as the proactive use of hemodynamic monitoring and therapies to manipulate hemodynamics in the perioperative period. Therapies could be classified as IV fluids and/or additional inotropic support. The hemodynamic intervention had to be preemptively started in the perioperative period, which was defined as 24 hours preoperatively, intraoperatively, or up to 24 hours into the postoperative period. Previous meta-analyses have included heterogeneous groups of patients that were not restricted to moderate- and high-risk groups of surgical patients. We therefore aimed only to assess studies that were assessing the impact of these interventions on a moderate- to high-risk group of patients. We defined this group according to criteria previously published by Shoemaker et al.[11] and later modified by Pearse et al.[15]

Methodological Quality of Included Studies

Eligible studies were graded using the systems described by Jadad et al.[39] Nonrandomized studies were excluded. This scale is used to describe study quality by scoring 5 elements of randomization, application, and blinding with a score range of 1 to 5.

Analysis of Outcomes

The primary outcome was hospital mortality. As an outcome measure, it is discrete, well defined, and reported in the majority of articles. Our secondary outcome measure

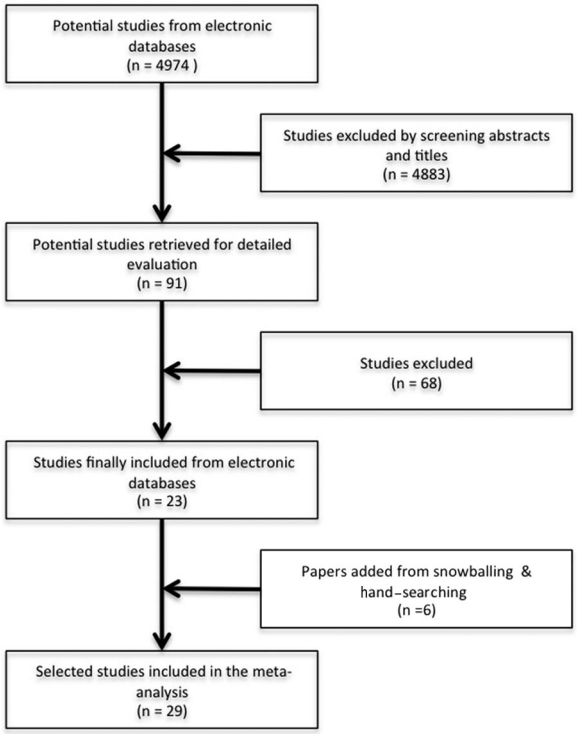

Figure 1. Flow chart showing the number of abstracts and articles identified and evaluated during the review process.

was the number of patients with complications after surgery. Although this outcome measure is less easy to define, it is frequently reported and provides a description of what is happening to the patient population. We chose not to report length of stay because it is often used as a marker of process and reported differently across institutions and countries. A number of a priori subgroup and sensitivity analyses were planned: (a) the type of monitoring used, (b) therapy used (fluids versus fluids and inotropes), (c) therapeutic goals, and (d) resuscitation target (normal versus supranormal). Supranormal was defined as any study that aimed to achieve an oxygen delivery index of $\geq$600 mL/min/m^2 in 1 of the trial arms. Data were extracted from each original article by 2 authors and cross-checked for reliability; disputed data were resolved by the third author by a majority decision on reference to the original text.

A sensitivity analysis was performed on both the primary and secondary outcomes. This consisted of a correction for quality using the Jadad score, with a score >3 classified as a higher quality study.[39] In addition, a time-dependent analysis was performed to examine the influence of change in care and underlying event rates in the last 35 years by decade.

Statistical Analysis

The meta-analysis was performed using the Review Manager, version 5 software (The Cochrane Collaboration, Oxford, UK), with a random effects model. The results are presented as an odds ratio (OR) for dichotomous data with its 95% confidence intervals (CIs). All results were checked

Table 1. Randomized Clinical Trials of Preemptive Hemodynamic Intervention to Improve Postoperative Outcome

Trial/author	Year	Type of intervention	Goals of optimization	Control group
Bender et al.[32]	1997	Fluids and inotropes	CI ≥2.8 L/min/m^2, SVR ≤1100 dynes-s/cm^5, PAOP 8–14	Standard care
Berlauk et al.[31]	1991	Fluids and inotropes	CI ≥2.8 L/min/m^2, SVR ≤1100 dynes-s/cm^5, PAOP 8–14	Standard care
Bishop et al.[30]	1995	Fluids and inotropes	Do_2I ≥670 mL/min/m^2, $\dot{V}o_2I$ ≥166 mL/min/m^2, and CI ≥4.5 L/min/m^2 within 24 h of admission and at least 48 h thereafter	Systolic pressure ≥120, HR ≤110, Hb ≥10, UO >30–50 mL/h, CVP 8–12, PAOP 8–12
Bonazzi et al.[29]	2002	Fluids and inotropes	CI >3 L/min/m^2, SVR ≤1450 dynes-s/cm^5, PAOP >10 and <18, Do_2 >600 mL/min/m^2	Standard care
Boyd et al.[28]	1993	Fluids and inotropes	Do_2 >600 mL/min/m^2	MAP 80–110, PAP 12–14, Sao_2 >94%, Hb >12, UO >0.5 mL/kg/h
Buettner et al.[27]	2008	Fluids	SPV <10%, Hct <23% = blood, clotting abnormal = product	
Chytra et al.[26]	2007	Fluids and inotropes	FTc >0.35, SV	CVP 12–15, MAP >65, Spo_2 >95%, HR <100 beats/min, UO >1 mL/kg/h, temperature 37°C, Hb >8.5
Conway et al.[25]	2002	Fluids	FTc >0.35, SV	Standard care
Donati et al.[24]	2007	Fluids and inotropes	Maintain O_2ER <27%,CVP from 8 to 12 cm H_2O, mean arterial blood pressure >80 mm Hg, urinary output >0.5 mL/kg/h	CVP 8–12 cm H_2O, MAP >80 mm Hg, urinary output >0.5 mL/kg/h
Gan et al.[23]	2002	Fluids	FTc >0.35, SV	If UO <0.5 mL/kg/h, heart rate ≥20% above baseline/>110 beats/min, mean SBP <20% below baseline or <90 mm Hg, or CVP <20% of baseline; 200-mL fluid bolus administered until the above target was restored
Lobo et al.[22]	2000	Fluids and inotropes	Do_2 intentionally increased to levels >600 mL/min/m^2	Do_2 between 520 and 600 mL/min/m^2
Lobo et al.[21]	2006	Fluids and inotropes	Do_2 >600 (fluids and dobutamine)	Do_2 >600 (fluids alone)
Lopes et al.[20]	2007	Fluids	PPV = <10%	Standard care
Kapoor et al.[19]	2008	Fluids and inotropes	CI >2.5 mL/min/m^2, CVP >6 mm Hg, SVV <10%, $Sc\dot{V}o_2$ >70%, SVI >30 mL/bet/m^2, SVRI >1500 dynes-s/cm^5/m^2, Do_2I >450 mL/min/m^2, CVP 6–8 mm Hg, MAP 90–105 mm Hg, Hct ≥30%, pH >7.35–7.45, Pao_2 >100 mm Hg, $Paco_2$ 35–45 mm Hg, Spo_2 >95%, UO >1 mL/kg/h	CVP 6–8 mm Hg, MAP 90–105 mm Hg, Hct ≥30%, pH >7.35–7.45, Pao_2 >100 mm Hg, $Paco_2$ 35–45 mm Hg, Spo_2 >95%, UO >1 mL/kg/h
McKendry et al.[18]	2004	Fluids and inotropes	Maintain stroke index >35 mL/m^2	Standard care
Mythen,[17]	1995	Fluids	CVP increase <3 mm Hg and 10% increase in SV	Standard care
Noblett et al.[16]	2006	Fluids	FTc > 0.35, SV	Standard care
Pearse et al.[15]	2005	Fluids and inotropes	Do_2I >600 mL/min/m^2	Common goals, Sao_2 ≥94%, Hb >8 g dL, temperature 37°C, HR <100 beats/min or <20% above baseline, MAP 60–100 mm Hg, CI ≥2.5 mL/min/m^2
Pölönen et al.[14]	2000	Fluids and inotropes	$S\dot{V}o_2$ >70% and lactate <2	Standard care
Sandham et al.[13]	2003	Fluids and inotropes	Do_2I 550–600 mL/min/m^2, CI 3.5–4.5, MAP >70 mm Hg, PAOP 18 mm Hg, HR <120 beats/min, Hct >27%	Standard care
Schultz et al.[12]	1985	Fluids and inotropes	Normalization of abnormalities	Standard care
Shoemaker et al.[11]	1988	Fluids and inotropes	CO >4.5 L/min, Do_2 >600 mL/min/m^2, $\dot{V}o_2$ >170 mL/min/m^2	Standard care
Sinclair et al.[10]	1997	Fluids	FTc >0.35, SV 10%	Standard care
Ueno et al.[9]	1998	Fluids	First 12 h, dopamine, Spo_2% >95%, Hb >10, LVSWI, PAOP, CI >4.5 L/min/m^2, Do_2 >600 mL/min/m^2, and $\dot{V}o_2I$ >175 mL/min/m^2	Spo_2% >95%, Hb >10, LVSWI, PAOP

(*Continued*)

Table 1. *(Continued)*

Trial/author	Year	Type of intervention	Goals of optimization	Control group
Valentine et al.[8]	1998	Fluids and inotropes	CI ≥2.8 L/min/m^2, SVR ≤1100 dynes-s/cm^5, PCWP ≥8 and <15, other parameters same as Berlauk et al.31	Standard care
Venn et al.[7]	2002	Fluids	FTc >0.35, SV 10%	Standard care
Wakeling et al.[6]	2005	Fluids	SV increase of 10%, CVP increase of >3 mm Hg	CVP 12–15, standard care
Wilson et al.[5]	1999	Fluids and inotropes	Do_2I >600 mL/min/m^2, PAOP 12, Hb ≥11, Sao_2 >94%	Standard care
Ziegler et al.[4]	1997	Fluids and inotropes	$S\dot{V}o_2$ >65%, PAOP ≥12, Hb ≥10	Standard care (IV fluids only)

CI = cardiac index; SVR = systemic vascular resistance; SVRI = systemic vascular resistance index; PAOP= pulmonary artery occlusion pressure; Do_2I = oxygen delivery index; $\dot{V}o_2I$ = oxygen consumption index; MAP = mean arterial blood pressure; HR = heart rate; Hb = hemoglobin concentration; CVP = central venous pressure; Hct = hematocrit; $S\dot{V}o_2$ = arterial saturation of oxygen; UO = urine output; FTc = corrected flow time; SVV = stroke volume variation; SVI = stroke volume index; $S\dot{V}o_2$ ($Scvo_2$) = mixed (central) venous oxygen saturation; SPV = systolic pressure variation; O_2ER = oxygen extraction ratio; PPV = pulse pressure variation; LVSWI = left ventricular stroke work index; PAP = pulmonary arterial pressure.

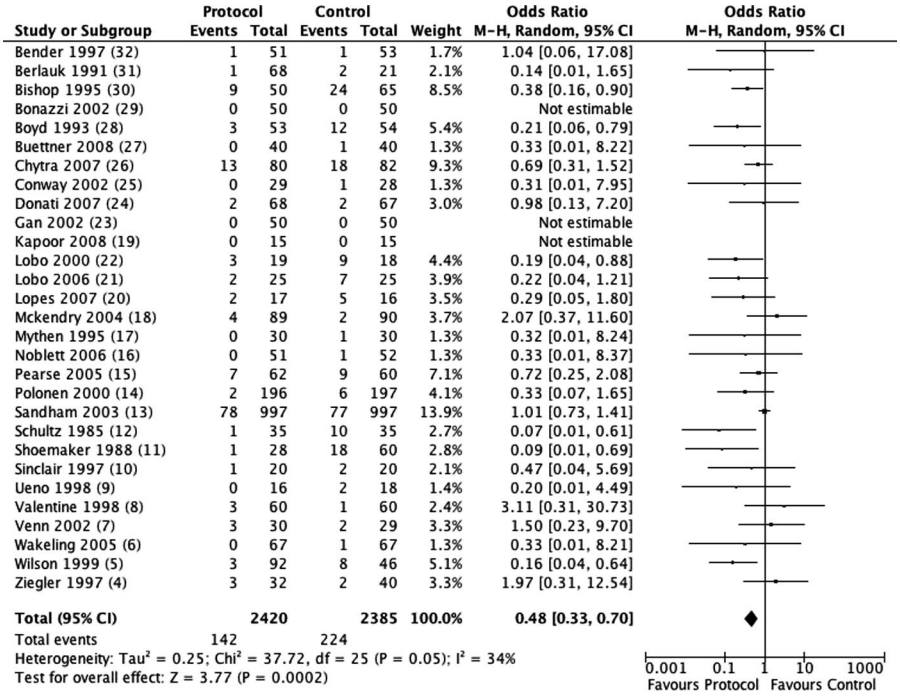

Figure 2. Effects of preemptive hemodynamic intervention in protocol group versus control on mortality rate. M-H = Mantel-Haenszel.

for statistical heterogeneity using the I^2 methodology. Significance was set at a P value <0.05.

RESULTS

Included Trials

Our search strategy retrieved 4974 titles suitable for further review. Screening of these titles and abstracts produced 91 potential articles that were examined in detail against the predefined eligibility criteria. Further examination led to the exclusion of 68 studies from the analysis because they did not meet high-risk criteria, lacked randomization or nonprospective study design, or did not fulfill our moderate- and high-risk inclusion criteria (Fig. 1). This resulted in 23 articles that were included from electronic databases. Through snowballing of references, handsearching, and contacting experts and industry representatives, 6 more articles were added. Therefore, 29 articles were included in the final analysis.

Description of Studies

The 29 identified studies are described in detail in Table 1. All reported mortality as an end point. Three studies had a zero rate of mortality in both protocol and control groups. These 3 studies were reexamined to ensure that they met moderate- to high-risk criteria. Twenty-three studies reported the number of patients in whom complications developed during the course of their stay. The reporting of complications was variable across the studies as were the definitions of complications in use. Two studies did use standardized methods of outcome reporting such as the postoperative morbidity survey, but the majority were diffuse.[6,40]

Mortality

All 29 studies reported mortality as an end point. The overall effect when combining the studies was a significant reduction in mortality for the intervention group (pooled

Table 2. Subgroup Analysis for Mortality

Subgroup	No. of studies	No. of patients	Control group mortality	Odds ratio (95% CI)
Monitor				
ODM	9	894	28/448 (6%)	0.75 (0.41–1.37)
PAFC	15	3511	179/1739 (10%)	0.35 (0.19–0.65)*
Other[a]	5	400	17/198 (9%)	0.61 (0.27–1.35)
Therapy				
Fluids	10	700	16/350 (5%)	0.44 (0.19–1.06)
Fluids and inotropes	19	4105	208/2035 (10%)	0.47 (0.29–0.76)*
Goals				
CI/Do_2	17	3350	183/1657 (11%)	0.38 (0.21–0.68)*
FTc/SV	9	894	28/448 (6%)	0.75 (0.41–1.37)
Other[b]	3	561	13/280 (5%)	0.43 (0.15–1.19)
Resuscitation target				
Supranormal	8	0.29 (0.18–0.47)	89/346 (26%)	0.29 (0.18–0.47)*
Normal	21	0.86 (0.66–1.13)	135/2039 (7%)	0.86 (0.66–1.13)

ODM = esophageal Doppler monitoring; PAFC = pulmonary artery flotation catheter; CI = cardiac index; Do_2 = oxygen delivery; FTc = corrected flow time; SV = stroke volume.

[a] PiCCOplus, CVP/A line, DX2020, FloTrac, LidCO*plus*.

[b] Oxygen extraction ratio, pulse pressure variation, SVo_2, and lactate.

*Statistically significant.

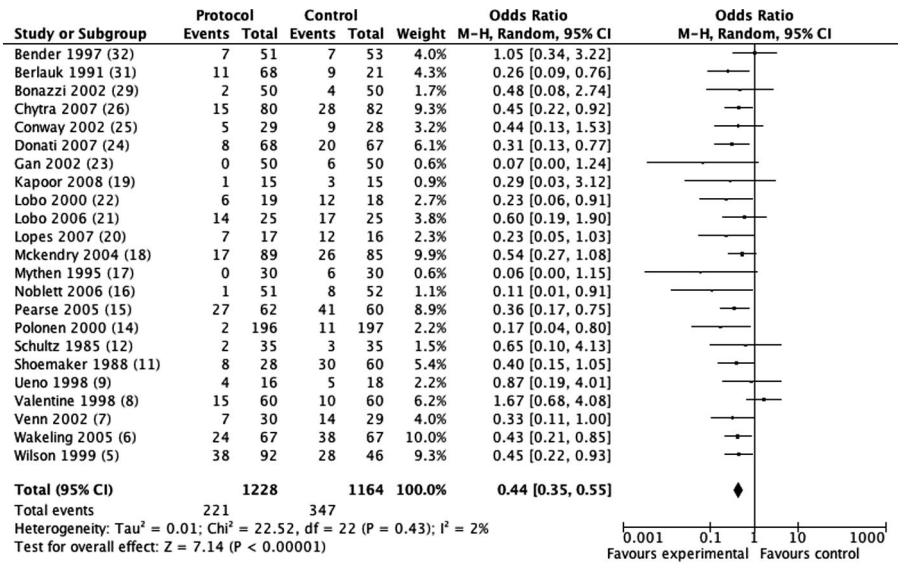

Figure 3. Effects of preemptive hemodynamic intervention in protocol group versus control on complication rate. M-H = Mantel-Haenszel.

OR of 0.48 [0.33–0.78]; $P = 0.0002$) (Fig. 2). Subgroup analysis of the mortality end point revealed that mortality was reduced in those studies using a pulmonary artery catheter (OR 0.35 [0.19–0.65]; $P = 0.001$), for fluids and inotropes as opposed to IV fluids alone (OR 0.47 [0.29–0.76]; $P = 0.002$), cardiac index or oxygen delivery as the end point (OR 0.38 [0.21–0.68]; $P = 0.001$), and studies using a supranormal resuscitation target (OR 0.29 [0.18–0.47]; $P = 0.00001$) (Table 2).

Morbidity

Twenty-three of the 29 studies reported the number of patients with complications as an end point. Meta-analysis of these studies (Fig. 3) demonstrated a significant reduction in the overall complication rate (OR 0.43 [0.34–0.53]; $P < 0.00,001$) and a significant reduction across all of the 4 subgroups assessed (Table 3).

Trial Quality

The quality of the individual studies as assessed by the Jadad score is presented in Table 4. It is apparent that very few of the studies were performed in a double-blind manner and nearly all were done in a single center. Figure 4 shows an OR plot of mortality split by quality. The higher quality studies (with a Jadad score ≥3) fail to show a significant reduction in mortality, as opposed to lower quality studies that do. The effect of quality on morbidity is shown in Figure 5. In contrast to mortality, there is a significant reduction in morbidity irrespective of trial quality. The point estimate of effect is similar for the 2 groups but the CI for the lower quality studies is wider.

Time-Dependent Analysis

Figure 6 shows a graph of the apparent decline in control-group mortality over time, with recent studies demonstrating lower mortality rates. Figure 7 shows an approximate

Table 3. Subgroup Analysis for Number of Patients with Complications

Subgroup	No. of studies	No. of patients	No. of patients with complications in control group	Odds ratio (95% CI)
Monitor				
ODM	9	987	163/469 (35%)	0.41 (0.30–0.57)*
PAFC	10	1085	108/537 (20%)	0.54 (0.33–0.88)*
Other[a]	4	320	76/158 (48%)	0.32 (0.19–0.54)*
Therapy				
Fluids	9	742	126/372 (34%)	0.38 (0.26–0.55)*
Fluids and inotropes	14	1650	221/792 (28%)	0.47 (0.35–0.64)*
Goals				
CI/Do_2	12	982	169/461 (37%)	0.52 (0.37–0.74)*
FTc/SV	8	849	135/423 (32%)	0.41 (0.28–0.58)*
Other[b]	3	561	43/280 (15%)	0.26 (0.13–0.52)*
Resuscitation target				
Supranormal	6	469	133/227 (59%)	0.42 (0.29–0.63)*
Normal	17	1923	214/937 (23%)	0.43 (0.31–0.60)*

ODM = esophageal Doppler monitoring; PAFC = pulmonary artery flotation catheter; CI = cardiac index; Do_2 = oxygen delivery; FTc = corrected flow time; SV = stroke volume.

[a] CVP/arterial line, DX2020, FloTrac, LidCO*plus*.

[b] Oxygen extraction ratio, pulse pressure variation, $S\dot{V}o_2$, and lactate.

* Significant difference.

Table 4. Quality Assessment of Included Randomized Clinical Trials

Author and year	Jadad score
Bender et al.,[32] 1997	1
Berlauk et al.,[31] 1991	2
Buettner et al.,[27] 2008	2
Bishop et al.,[30] 1995	1
Bonazzi et al.,[29] 2002	2
Boyd et al.,[28] 1993	1
Chytra et al.,[26] 2007	3
Conway et al.,[25] 2002	2
Donati et al.,[24] 2007	3
Gan et al.,[23] 2002	5
Lobo et al.,[22] 2000	3
Lobo et al.,[21] 2006	3
Lopes et al.,[20] 2007	2
Kapoor et al.,[19] 2008	2
McKendry et al.,[18] 2004	3
Mythen and Webb,[17] 1995	2
Noblett et al.,[16] 2006	5
Pearse et al.,[15] 2005	3
Pölönen et al.,[14] 2000	3
Sandham et al.,[13] 2003	3
Schultz et al.,[12] 1985	1
Shoemaker et al.,[11] 1988	2
Sinclair et al.,[10] 1997	2
Ueno et al.,[9] 1998	2
Valentine et al.,[8] 1998	3
Venn et al.,[7] 2002	3
Wakeling et al.,[6] 2005	3
Wilson et al.,[5] 1999	4
Ziegler et al.,[4] 1997	2

halving of mortality rates in the control group every decade (29.5%, 13.5%, 7%). It can be seen, however, that although the mortality is reduced over time, the complication rate remains consistent, with approximately one-third of patients experiencing complications (Fig. 8).

DISCUSSION

This systematic review and meta-analysis has demonstrated that preemptive hemodynamically targeted therapy in the perioperative period can reduce both morbidity and mortality after surgery. Although over time the control-group mortality decreased, suggesting a lowering of the threshold for the performance of these techniques, the impact of this therapy remains even for the lower risk categories of patients. Although mortality was not proven to be reduced in the lower risk group, the effects on reducing morbidity were still valid, confirming the assumption that the technique of targeted hemodynamic intervention is beneficial across risk profile groups and across monitoring technologies.

There are a number of reasons why the control mortality may have decreased over time. These include the possibilities of better overall care thus decreasing mortality for similar patients, clinicians learning from previous early published studies and therefore drifting their practice toward lower risk groups, and also the likelihood that as technology has improved and become less invasive, the technique has gained more credibility. This can be seen especially in the way the pulmonary artery catheter, with all of its incumbent controversies,[41,42] has now been largely superseded by less-invasive hemodynamic monitoring techniques such as esophageal Doppler-based systems and arterial pressure analysis.[43] It is of note that, although the debate surrounding the pulmonary artery catheter focused on an inability to prove a significant beneficial effect to patients,[44–46] this study has demonstrated a highly significant reduction in both morbidity and mortality with the use of this technique for these patients. The same is also true for the newer generation of monitoring modalities.

The burden of complications and mortality for surgical patients is becoming increasingly understood.[1,3] Many authors have now demonstrated that the rate of complications is related to a number of factors that include the type of surgery performed, the skill of the operating team, the overall "fitness" of the patient, and also the provision of a number of techniques that have shown to reduce the risk.[47–50]

This study confirms that hemodynamic targeted therapy can reduce this risk. Khuri et al.[1] demonstr-

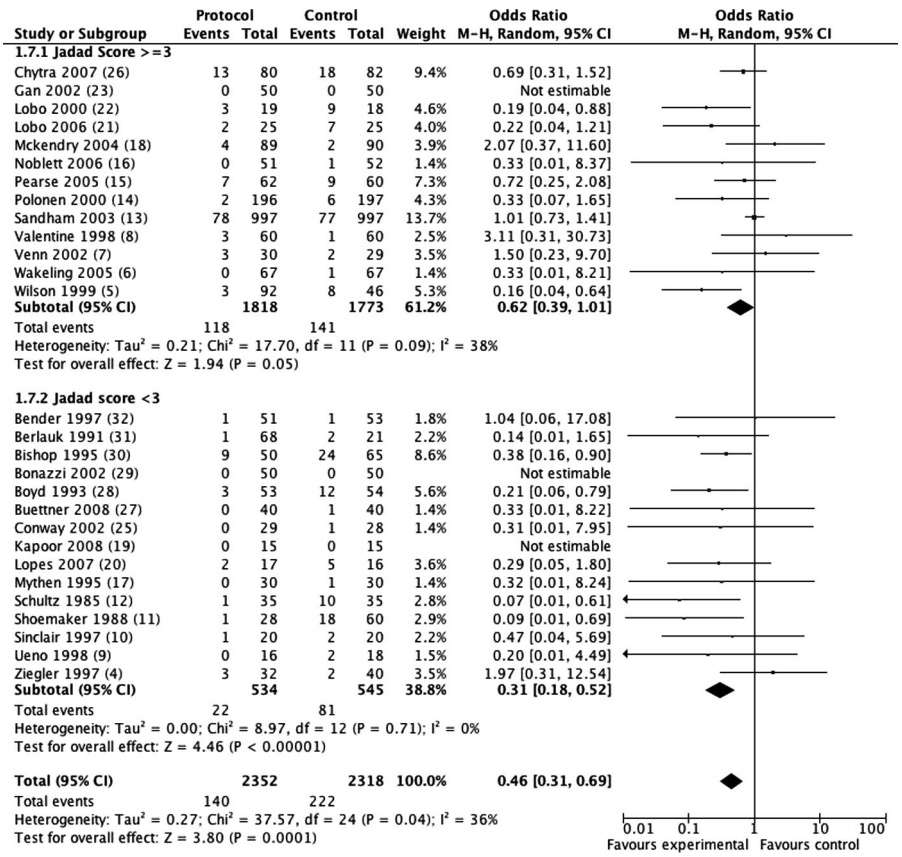

Figure 4. Effects of preemptive hemodynamic intervention in protocol group versus control on mortality rate, grouped by quality of the study as assessed by a Jadad score of more than or less than 3. M-H = Mantel-Haenszel.

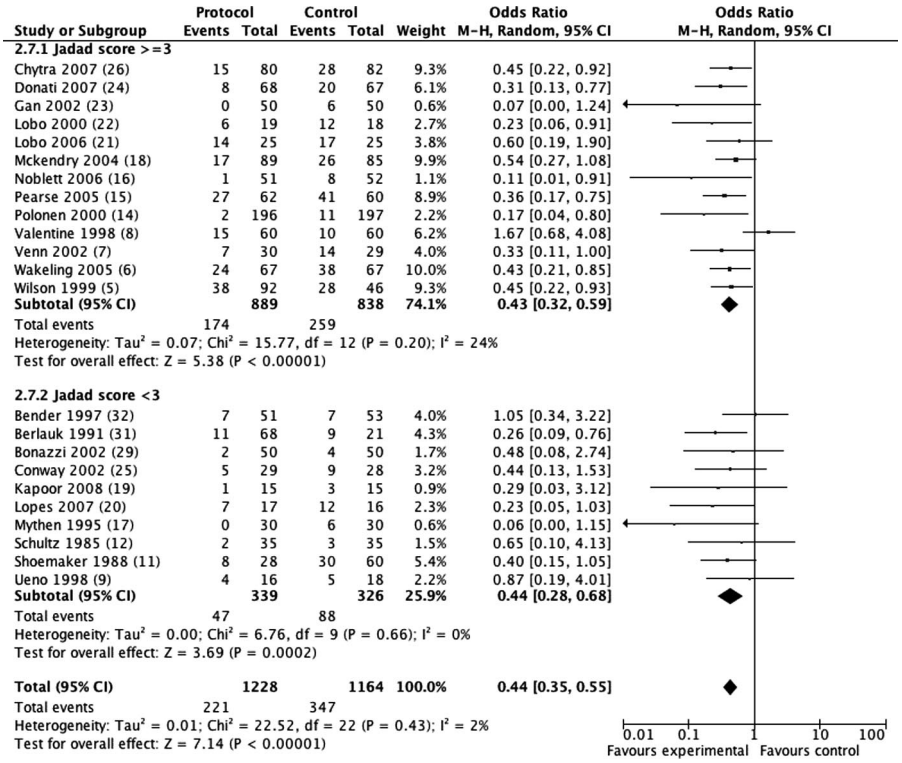

Figure 5. Effects of preemptive hemodynamic intervention in protocol group versus control on complication rate, grouped by quality of the study as assessed by a Jadad score of more than or less than 3. M-H = Mantel-Haenszel.

ated that this reduction in postoperative complications can have long-lasting effects on the survival of these patients, outside of the remit of a short-term follow-up period in these studies. If this hypothesis is correct, then the upfront costs of this relatively inexpensive technique are easily outweighed by the longer-term benefits. Irrespective of this, the prevention of complications is in itself a mechanism for saving significant amounts of

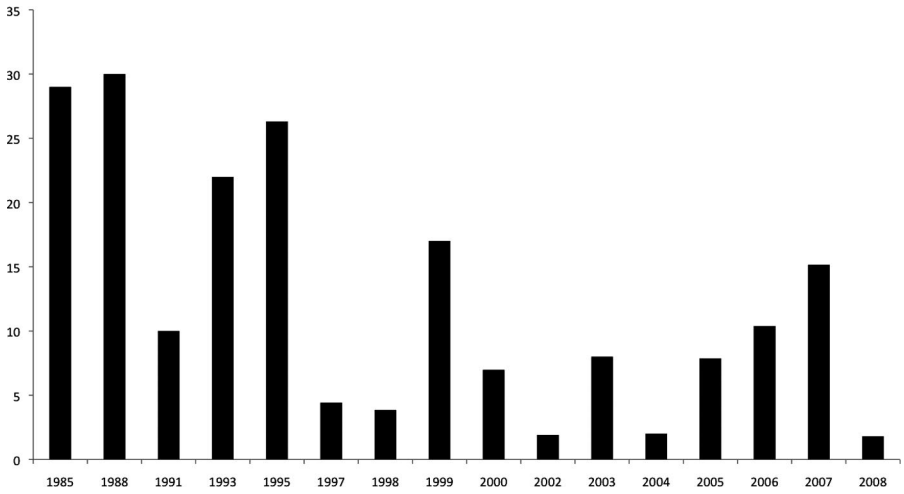

Figure 6. Graphical representation of control-group mortality in identified trials over time.

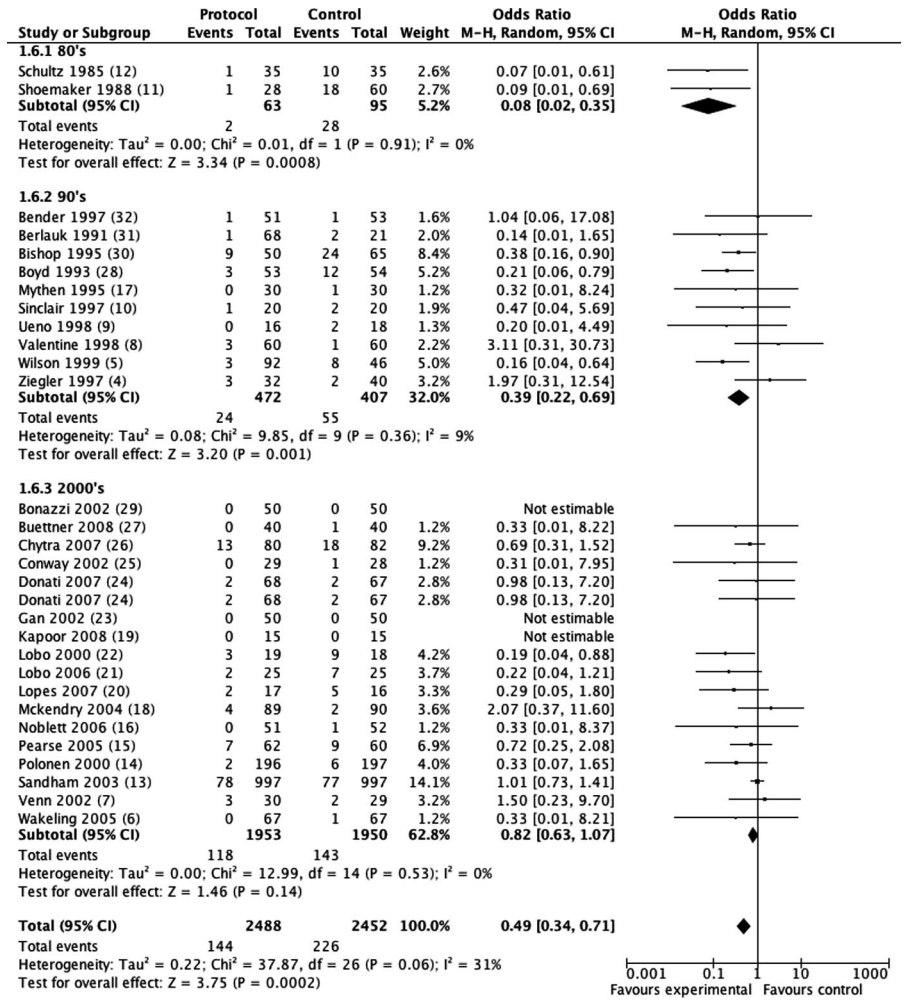

Figure 7. Effects of preemptive hemodynamic intervention in protocol group versus control on mortality rate, grouped by the decade the study was performed. M-H = Mantel-Haenszel.

health care resources, because it is often these complications that prolong hospital length of stay and result in multiple costly interventions. Recent work published in the *New England Journal of Medicine* has also raised the possibility that survival is related to the identification and then immediate and appropriate management of these complications.[3] It remains a possibility that patients being studied in trials such as ours have a lower than normal complication and mortality rate for this very reason. By participating in a study, they are frequently assessed and probably offered a quality of care that is above the standard approach.

This study has a number of limitations. We made no attempt to correct for the type or quantity of fluids or inotropes given, because they are inconsistently reported in the literature and have a demonstrable wide variability in

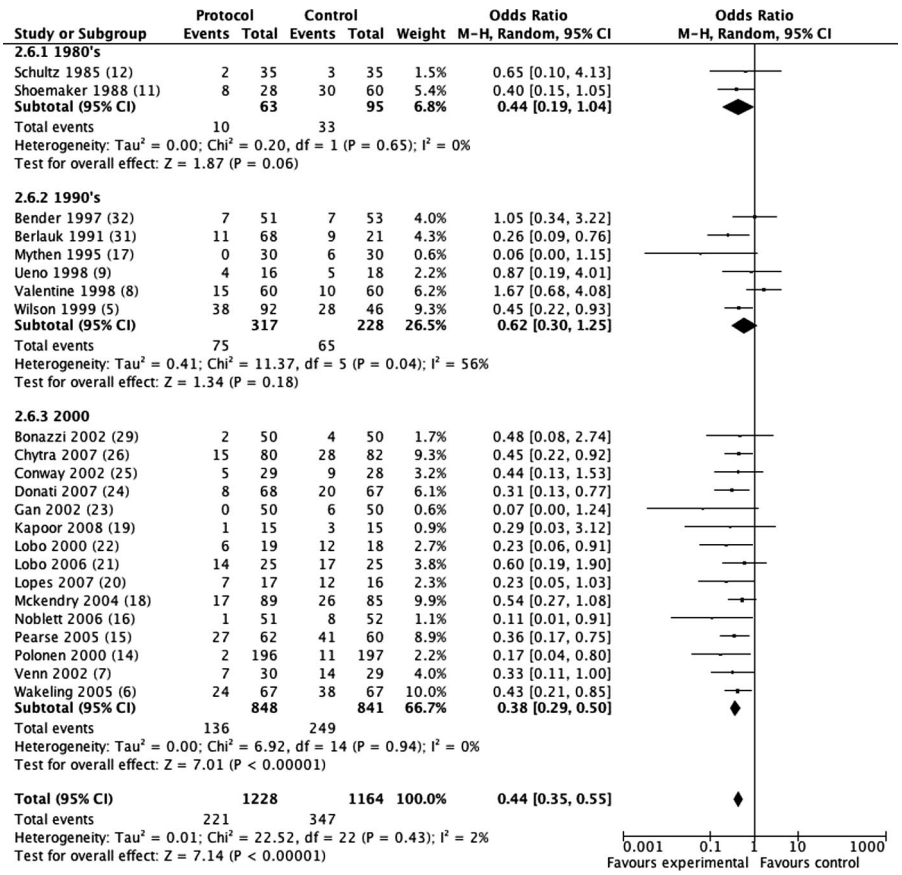

Figure 8. Effects of preemptive hemodynamic intervention in protocol group versus control on complication rate, grouped by the decade the study was performed. M-H = Mantel-Haenszel.

their dosing across studies. Also, a number of grouped studies rather than individual patient data were meta-analyzed. Some authors would suggest that this would be a more robust methodology, although obtaining the original data is often not possible, especially over such a long period such as this. It also has to be recognized that very few of the studies that we identified were performed in a high-quality design. It is almost impossible to have a properly double-blind study when the 2 groups need to have therapy targeted to different protocols. It is also of note that the majority of the trials were single-centered and performed on a limited sample size. The heterogeneity of this analysis is therefore relatively high, although the results remain consistent across a number of subgroups and sensitivity analyses, thereby helping to affirm our assumptions. We have also reported 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, limiting the applicability of some of our findings.

CONCLUSIONS

This meta-analysis suggests that a preemptive targeted approach to the management of hemodynamics in the perioperative period may reduce morbidity and mortality for high-risk surgical patients.

AUTHOR CONTRIBUTIONS

All authors were involved and helped in the design, execution, analysis, and writing of the manuscript.

DISCLOSURE

Andrew Rhodes, LiDCO (lecturing fees and grant), Edwards Lifesciences (lecturing fees), Hutchinson Medical (research support), PulseCor (research support), Cheetah (research support), and Abbott (consulting fees); Mark A. Hamilton, Deltex Medical (lecturing fees), Edwards Lifesciences (lecturing fees), and Hutchinson Medical (research support); and Maurizio Cecconi, LiDCO (lecturing fees and grant), Edwards Lifesciences (lecturing fees), Hutchinson Medical (research support), PulseCor (research support), and Chhetah (research support).

REFERENCES

1. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ; Participants in the VA National Surgical Quality Improvement Program. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005;242:326–41
2. Pearse RM, Harrison DA, James P, Watson D, Hinds C, Rhodes A, Grounds RM, Bennett ED. Identification and characterisation of the high-risk surgical population in the United Kingdom. Crit Care 2006;10:R81
3. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009;361:1368–75
4. Ziegler DW, Wright JG, Choban PS, Flancbaum L. A prospective randomized trial of preoperative "optimization" of cardiac function in patients undergoing elective peripheral vascular surgery. Surgery 1997;122:584–92
5. Wilson J, Woods I, Fawcett J, Whall R, Dibb W, Morris C, McManus E. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. BMJ 1999;318:1099–103

6. Wakeling HG, McFall MR, Jenkins CS, Woods WGA, Miles WFA, Barclay GR, Fleming SC. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. Br J Anaesth 2005;95:634–42
7. Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P. Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. Br J Anaesth 2002;88:65–71
8. Valentine RJ, Duke ML, Inman MH, Grayburn PA, Hagino RT, Kakish HB, Clagett GP. Effectiveness of pulmonary artery catheters in aortic surgery: a randomized trial. J Vasc Surg 1998;27:203–11
9. Ueno S, Tanabe G, Yamada H, Kusano C, Yoshidome S, Nuruki K, Yamamoto S, Aikou T. Response of patients with cirrhosis who have undergone partial hepatectomy to treatment aimed at achieving supranormal oxygen delivery and consumption. Surgery 1998;123:278–86
10. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. BMJ 1997;315:909–12
11. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988;94:1176–86
12. Schultz RJ, Whitfield GF, LaMura JJ, Raciti A, Krishnamurthy S. The role of physiologic monitoring in patients with fractures of the hip. J Trauma 1985;25:309–16
13. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ, Laporta DP, Viner S, Passerini L, Devitt H, Kirby A, Jacka M; Canadian Critical Care Clinical Trials Group. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003;348:5–14
14. Pölönen P, Ruokonen E, Hippeläinen M, Pöyhönen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 2000;90:1052–9
15. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Crit Care 2005;9:R687–93
16. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. Br J Surg 2006;93:1069–76
17. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg 1995;130:423–9
18. McKendry M, McGloin H, Saberi D, Caudwell L, Brady AR, Singer M. Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery. BMJ 2004;329:258
19. Kapoor PM, Kakani M, Chowdhury U, Choudhury M, Lakshmy, Kiran U. Early goal-directed therapy in moderate to high-risk cardiac surgery patients. Ann Card Anaesth 2008;11:27–34
20. Lopes MR, Oliveira MA, Pereira VOS, Lemos IPB, Auler JOC, Michard F. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. Crit Care 2007;11:R100
21. Lobo SM, Lobo FR, Polachini CA, Patini DS, Yamamoto AE, de Oliveira NE, Serrano P, Sanches HS, Spegiorin MA, Queiroz MM, Christiano AC, Savieiro EF, Alvarez PA, Teixeira SP, Cunrath GS. Prospective, randomized trial comparing fluids and dobutamine optimization of oxygen delivery in high-risk surgical patients [ISRCTN42445141]. Crit Care 2006;10:R72
22. Lobo SM, Salgado PF, Castillo VG, Borim AA, Polachini CA, Palchetti JC, Brienzi SL, de Oliveira GG. Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. Crit Care Med 2000;28:3396–404
23. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PSA. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002;97:820–6
24. Donati A, Loggi S, Preiser J-C, Orsetti G, Münch C, Gabbanelli V, Pelaia P, Pietropaoli P. Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. Chest 2007;132:1817–24
25. Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C. Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. Anaesthesia 2002;57:845–9
26. Chytra I, Pradl R, Bosman R, Pelnár P, Kasal E, Zidková A. Esophageal Doppler-guided fluid management decreases blood lactate levels in multiple-trauma patients: a randomized controlled trial. Crit Care 2007;11:R24
27. Buettner M, Schummer W, Huettemann E, Schenke S, van Hout N, Sakka SG. Influence of systolic-pressure-variation-guided intraoperative fluid management on organ function and oxygen transport. Br J Anaesth 2008;101:194–9
28. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993;270:2699–707
29. Bonazzi M, Gentile F, Biasi GM, Migliavacca S, Esposti D, Cipolla M, Marsicano M, Prampolini F, Ornaghi M, Sternjakob S, Tshomba Y. Impact of perioperative haemodynamic monitoring on cardiac morbidity after major vascular surgery in low risk patients: a randomised pilot trial. Eur J Vasc Endovasc Surg 2002;23:445–51
30. Bishop MH, Shoemaker WC, Appel PL, Meade P, Ordog GJ, Wasserberger J, Wo CJ, Rimle DA, Kram HB, Umali R. Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. J Trauma 1995;38:780–7
31. Berlauk JF, Abrams JH, Gilmour IJ, O'Connor SR, Knighton DR, Cerra FB. Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery: a prospective, randomized clinical trial. Ann Surg 1991;214:289–97
32. Bender JS, Smith-Meek MA, Jones CE. Routine pulmonary artery catheterization does not reduce morbidity and mortality of elective vascular surgery: results of a prospective, randomized trial. Ann Surg 1997;226:229–36
33. Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care Med 2002;30:1686–92
34. Poeze M, Greve JWM, Ramsay G. Meta-analysis of hemodynamic optimization: relationship to methodological quality. Crit Care 2005;9:R771–9
35. Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Crit Care Med 2009;37:2079–90
36. Giglio MT, Marucci M, Testini M, Brienza N. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. Br J Anaesth 2009;103:637–46
37. Takala J, Meier-Hellmann A, Eddleston J, Hulstaert P, Sramek V. Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. European Multicenter Study Group on Dopexamine in Major Abdominal Surgery. Crit Care Med 2000;28:3417–23
38. Stone MD, Wilson RJT, Cross J, Williams BT. Effect of adding dopexamine to intraoperative volume expansion in patients undergoing major elective abdominal surgery. Br J Anaesth 2003;91:619–24
39. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12

40. Bennett-Guerrero E, Feierman D, Barclay G, Parides M, Sheiner P, Mythen M, Levine D, Parker T, Carroll S, White M. Preoperative and intraoperative predictors of postoperative morbidity, poor graft function, and early rejection in 190 patients undergoing liver transplantation. Arch Surg 2001;136:1177
41. Finfer S, Delaney A. Pulmonary artery catheters. BMJ 2006;333:930–1
42. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJ Jr, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA 1996;276:889–97
43. Hofer CK, Cecconi M, Marx G, della Rocca G. Minimally invasive haemodynamic monitoring. Eur J Anaesthesiol 2009;26:996–1002
44. Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, Singer M, Rowan K. An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial. Health Technol Assess 2006;10:iii–iv, ix–xi, 1–133
45. Richard C, Warszawski J, Anguel N, Deye N, Combes A, Barnoud D, Boulain T, Lefort Y, Fartoukh M, Baud F, Boyer A, Brochard L, Teboul JL. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2003;290:2713–20
46. Rhodes A, Cusack RJ, Newman PJ, Grounds RM, Bennett ED. A randomised, controlled trial of the pulmonary artery catheter in critically ill patients. Intensive Care Med 2002;28:256–64
47. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med 2002;137:511–20
48. Dudley RA, Johansen KL, Brand R, Rennie DJ, Milstein A. Selective referral to high-volume hospitals: estimating potentially avoidable deaths. JAMA 2000;283:1159–66
49. Silber JH, Rosenbaum PR. A spurious correlation between hospital mortality and complication rates: the importance of severity adjustment. Med Care 1997;35:OS77–92
50. Silber JH, Rosenbaum PR, Schwartz JS, Ross RN, Williams SV. Evaluation of the complication rate as a measure of quality of care in coronary artery bypass graft surgery. JAMA 1995;274:317–23

Section Editor: **Michael J. Murray**

Maintaining Tissue Perfusion in High-Risk Surgical Patients: A Systematic Review of Randomized Clinical Trials

Sanderland T. Gurgel, MD, and Paulo do Nascimento, Jr., MD, PhD

BACKGROUND: Surgical patients with limited organic reserve are considered high-risk patients and have an increased perioperative mortality. For this reason, they need a more rigorous perioperative protocol of hemodynamic control to prevent tissue hypoperfusion. In this study, we systematically reviewed the randomized controlled clinical trials that used a hemodynamic protocol to maintain adequate tissue perfusion in the high-risk surgical patient.

METHODS: We searched MEDLINE, Embase, LILACS, and Cochrane databases to identify randomized controlled clinical studies of surgical patients studied using a perioperative hemodynamic protocol of tissue perfusion aiming to reduce mortality and morbidity; the latter characterized at least one dysfunctional organ in the postoperative period. Pooled odds ratio (POR) and 95% confidence interval (CI) were calculated for categorical outcomes.

RESULTS: Thirty-two clinical trials were selected, comprising 5056 high-risk surgical patients. Global meta-analysis showed a significant reduction in mortality rate (POR: 0.67; 95% CI: 0.55–0.82; $P < 0.001$) and in postoperative organ dysfunction incidence (POR: 0.62; 95% CI: 0.55–0.70; $P < 0.00{,}001$) when a hemodynamic protocol was used to maintain tissue perfusion. When the mortality rate was >20% in the control group, the use of a hemodynamic protocol to maintain tissue optimization resulted in a further reduction in mortality (POR: 0.32; 95% CI: 0.21–0.47; $P < 0.00{,}001$). Monitoring cardiac output with a pulmonary artery catheter and increasing oxygen transport and/or decreasing consumption also significantly reduced mortality (POR: 0.67; 95% CI: 0.54–0.84; $P < 0.001$ and POR: 0.71; 95% CI: 0.57–0.88; $P < 0.05$, respectively). Therapy directed at increasing mixed or central venous oxygen saturation did not significantly reduce mortality (POR: 0.68; 95% CI: 0.22–2.10; $P > 0.05$). The only study using lactate as a marker of tissue perfusion failed to demonstrate a statistically significant reduction in mortality (OR: 0.33; 95% CI: 0.07–1.65; $P > 0.05$).

CONCLUSIONS: In high-risk surgical patients, the use of a hemodynamic protocol to maintain tissue perfusion decreased mortality and postoperative organ failure. Monitoring cardiac output calculating oxygen transport and consumption helped to guide therapy. Additional randomized controlled clinical studies are necessary to analyze the value of monitoring mixed or central venous oxygen saturation and lactate in high-risk surgical patients. (Anesth Analg 2011;112:1384–91)

The mortality rate in some subgroups of surgical patients is much higher than expected for most surgical procedures.[1] Despite the multifactorial causes of death and organ failure in these patients, a persistent inadequacy of tissue perfusion seems to be the pivotal factor for the development of perioperative organ failure.[2] With respect to risk identification, there seems to be a tendency toward the occurrence of a postoperative cardiac event in the surgical patient, but for most high-risk patients, the main cause of death is more often related to tissue perfusion dysfunction than to a cardiac problem.[3]

From the Department of Anesthesiology, Universidade Estadual Paulista, Botucatu, São Paulo, Brazil.

Accepted for publication October 4, 2010.

Conflict of Interest: See Disclosures at the end of the article.

Reprints will not be available from the authors.

Address correspondence to Dr. Paulo do Nascimento, Jr., Department of Anesthesiology, Universidade Estadual Paulista, UNESP, Distrito de Rubião Jr, s/n, PO Box 530, Botucatu, SP, Brazil, 18.618-970. Address e-mail to pnasc@fmb.unesp.br.

DOI: 10.1213/ANE.0b013e3182055384

Thus, even if it seems obvious that surgical patients with a risk of tissue hypoperfusion should be monitored and treated during a perioperative period with fluids, blood, and drugs, there are some unanswered questions about this approach. Who, when, and how to maintain tissue perfusion, but mainly, what is the best goal to guide tissue perfusion? In this systematic review, we analyzed the methodological quality of randomized controlled clinical trials of high-risk surgical patients whose tissue perfusion was monitored and maintained perioperatively, and evaluated the influence of treatment on postoperative organ failure and mortality. Furthermore, the role of individual markers of tissue perfusion as the goal for treatment in the perioperative period to establish information for clinical practice and guidelines for the future was also analyzed.

METHODS

This article is a systematic review of randomized controlled clinical trials of surgical patients with a limited physiological organic reserve who were submitted to a hemodynamic protocol to maintain adequate tissue perfusion compared with patients who had standard care in the perioperative

Table 1. Criteria to Define High-Risk Surgical Patients

1. Previous severe cardiorespiratory illness (acute myocardial infarct, chronic obstructive pulmonary disease, stroke)
2. Extensive ablative surgery planned for carcinoma, e.g., esophagectomy and total gastrectomy, prolonged surgery (>8 h)
3. Severe multiple trauma, e.g., >3 organs or >2 systems, or opening 2 body cavities
4. Massive acute blood loss, blood volume <1.5 L · m^{-2}, hematocrit <20%
5. Age >70 y and evidence of limited physiological reserve of ≥1 vital organ
6. Shock, mean arterial blood pressure <60 mm Hg, central venous pressure <15 cm H_2O, and urine output <20 mL · h^{-1}
7. Acute abdominal event with hemodynamic instability, e.g., pancreatitis, gangrenous bowel, peritonitis, perforated viscus, gastrointestinal bleeding
8. Late-stage vascular disease involving aortic disease

period. The impact of the treatment on postoperative organ failure and mortality was analyzed. MEDLINE, Embase, LILACS, and Cochrane databases were searched up to November 2009 with the following terms: end point, optimization, goal-directed therapy, hemodynamic optimization, global tissue hypoxia, multiple organ failure, multiple organ dysfunction, surgery, high-risk patients, postoperative period, perioperative period, trauma, shock, burns, critical care, intensive care, oxygen delivery, oxygen transport, oxygen consumption, cardiac output, dobutamine, fluid therapy, blood lactate, central venous oxygen saturation ($Scvo_2$), mixed venous oxygen saturation ($S\bar{v}o_2$), and oximetry.

The criteria of inclusion were as follows: randomized controlled clinical studies, blinded or not; patients older than 18 years submitted to major surgery with high likelihood of development of complications in the postoperative period, according to the presence of ≥1 high-risk criteria defined by Shoemaker et al.[4] in 1988 (Table 1); presence of a well-defined hemodynamic protocol to maintain tissue perfusion with either/both fluids or/and vasoactive and inotropic drugs with therapeutic goals well defined (primary end points for treatment involving variables of tissue perfusion: cardiac output, oxygen delivery/consumption, $Scvo_2$/$S\bar{v}o_2$, lactate); presence of a control group with patients treated according to standard of care; and reduction of mortality rate (defined as the total mortality rate within the first 28 postoperative days or in-hospital mortality, if postoperative days were not reported in the articles), and/or postoperative organ dysfunction, as defined by Donati et al.[5] (Table 2), as the main outcomes. The measured variables as the result of hemodynamic control, i.e., death and organ dysfunction, were validated and categorized as postoperative complications by Dindo et al.[6] in a cohort study of 6336 patients.

Studies of patients with sepsis or septic shock or with patients presenting evidence of organ dysfunction or failure before surgery were excluded from the analysis. Analysis of the outcome of postoperative organ dysfunction was conducted in the form of a dichotomous variable, that is, the number of patients who had at least 1 organ dysfunction versus the number of patients without any organ dysfunction.

Selected studies were analyzed according to their methodological quality, using a scoring system previously evaluated (Table 3).[7] Considering possible differences in clinical outcomes according to the scientific rigor of the trials, we chose to separate the trials in 2 distinct analyses according to the

Table 2. Criteria to Define Postoperative Organ Failure

1. Cardiocirculatory: mean arterial blood pressure <80 mm Hg, central venous pressure >18 mm Hg, and urinary output <0.5 mL · kg^{-1} · h^{-1}; acute myocardial infarction; myocardial ischemia defined as an ST-segment depression or increase of 1 mm
2. Respiratory: mechanical ventilation or requirement for continuous positive airway pressure for >24 h
3. Renal: serum creatinine concentration >2 mg · dL^{-1} or need for renal replacement therapy
4. Hepatic: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >80 IU and total bilirubin >2 mg · dL^{-1} or AST and ALT >200 IU or total bilirubin >3 mg · dL^{-1}
5. Hematology: platelets <50,000 × $10^3/\mu L$; leukocytosis <2500 or >30,000 × $10^3/\mu L$; disseminated intravascular coagulation, defined as decrease of platelet count >50% with increase of prothrombin time ≥50% or increase of partial thromboplastin time >20% and increase of D-dimer >500 ng · mL^{-1}
6. Glasgow coma scale score <7

Table 3. Criteria to Define Methodological Quality of the Trials

	Score		
	0	1	2
Methodology			
Randomization	Nonrandomized		Randomized
Blinding	Nonblinded		Blinded
Analysis	Other		Treatment intention
Primary outcome	Other than mortality	Mortality as secondary outcome	Mortality as primary outcome
Population			
Selection	Nonevident or elected nonconsecutive patients	Consecutive elected patients	
Patients at baseline	Noncompared or no evidence	Compared	
Follow-up	Incomplete	Complete	
Intervention			
Protocol	Nonevident	Reproducible	
Cointerventions	Nondescribed	Nonidentical or nonevident	Well described and defined
Group crossover	Nondescribed	>10% of patients	<10% of patients

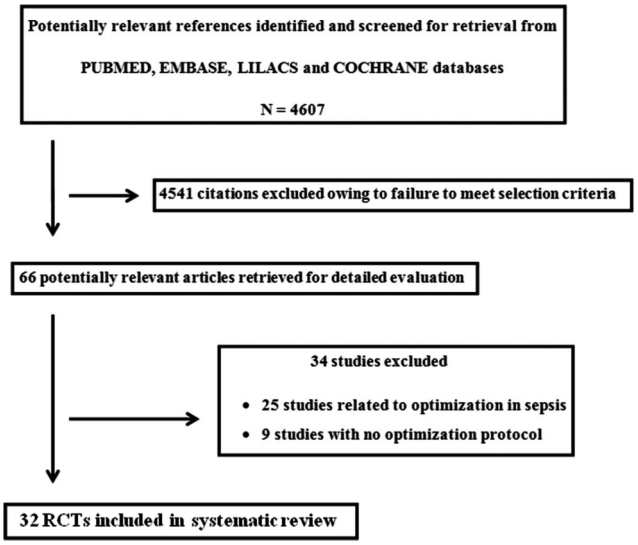

Figure 1. Number of articles identified and evaluated during the review process. RCTs = randomized controlled trials.

methodological quality score, one with the score between 0 and 9 and another with a score between 10 and 16.

Based on the possible influence of patients' clinical conditions on mortality, the selected clinical trials were also divided in 3 subgroups according to the mortality rate of the control group: 0% to 10%, 11% to 20%, and >20%.

For statistical evaluation, the MetaView module of Review Manager 5.0 (RevMan) computer software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) was used. Odds ratio (OR) and 95% confidence interval (CI) with a model of fixed effect for dichotomy variables were calculated with the Mantel-Haenszel method. χ^2 with $P > 0.05$ for homogeneity was used, and I^2 was calculated for a heterogeneity test, considering values between 0% and 30% of little importance, values between 31% and 50% of moderate importance, values between 51% and 75% of high importance, and values ≥76% of extreme importance.

RESULTS

A total of 4607 potentially relevant references were identified and screened for retrieval. Sixty-six studies were selected, and 32 randomized controlled trials with 5056 patients met the eligibility criteria (Fig. 1).

The average methodological system score was 9.5 from a range of 0 to 16, corresponding to 59.3% of the top score. The average score was close to the median (equal 9) and the mode (equal 10), suggesting a normal distribution.

Figures 2 through 4 show pooled ORs for mortality according to the control group mortality rate. Table 4 shows characteristics of selected clinical trials, including intervention, methodological quality score, and treatment goals to maintain tissue perfusion. Table 5 shows ORs and 95% CIs, level of heterogeneity, and overall effect for mortality and organ failure incidence according to the methodological score of the studies, mortality rate of control groups, use of pulmonary artery catheter, and variables used for hemodynamic control.

DISCUSSION

There is a subgroup of patients during some surgical procedures that have a high potential for complications during the perioperative period. To explore the possible interventions that might reduce the incidence of complications in these patients, a substantial number of randomized controlled clinical trials on perioperative hemodynamic stabilization are necessary. A systematic review of these clinical trials would be considered the highest level of evidence and guide for interventions that improve outcome.[8] There is still a need to explore perioperative hemodynamic control in high-risk surgical patients, considering not only the diverse markers of tissue perfusion, but also

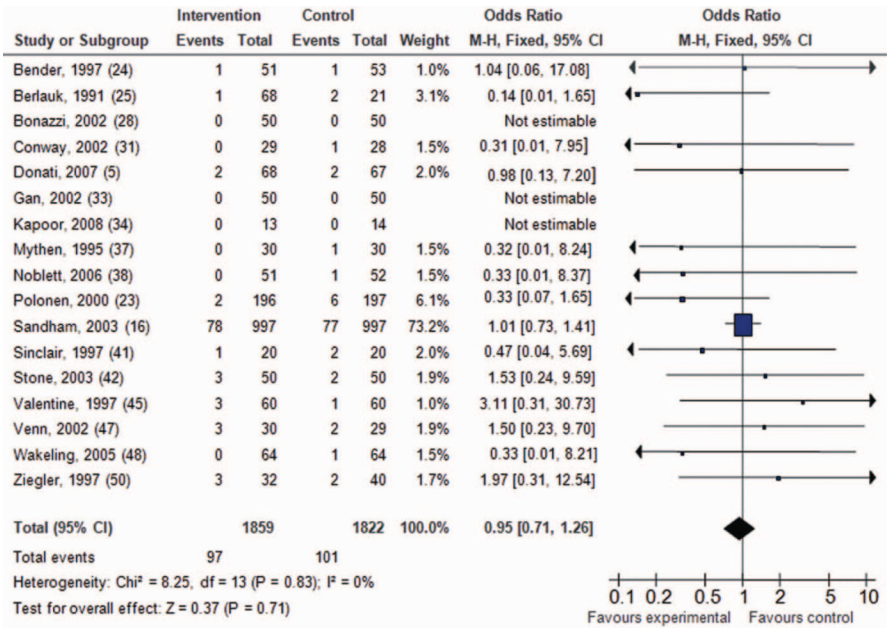

Figure 2. Studies with mortality in the control group ranging from 0% to 10%. The pooled odds ratio (OR) and 95% confidence interval (CI) are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamond represents the point estimate of the pooled OR, and the length of the diamond is proportional to the CI.

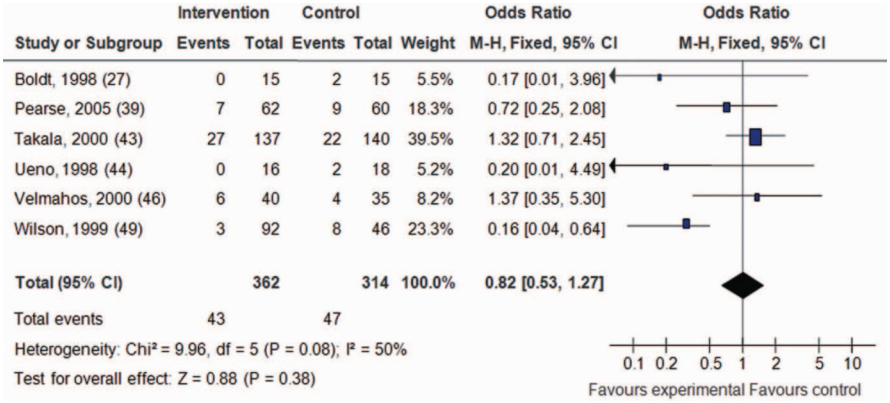

Figure 3. Studies with mortality in the control group ranging from 11% to 20%. The pooled odds ratio (OR) and 95% confidence interval (CI) are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamond represents the point estimate of the pooled OR, and the length of the diamond is proportional to the CI.

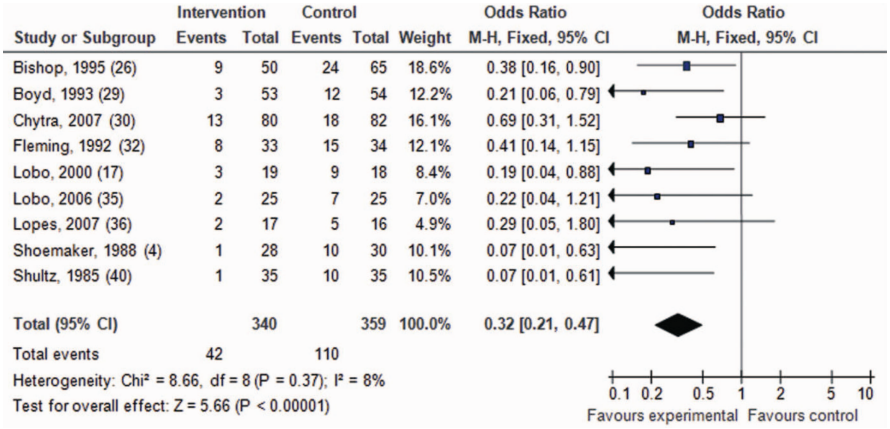

Figure 4. Studies with mortality in the control group >20%. The pooled odds ratio (OR) and 95% confidence interval (CI) are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamond represents the point estimate of the pooled OR, and the length of the diamond is proportional to the CI.

the targets for treatment. We focused on those trials comprising high-risk surgical patients with no evident organ dysfunction before surgery and submitted to an early protocol of hemodynamic treatment, trying to prevent occult tissue hypoperfusion.

There are several previous systematic reviews on high-risk surgical patients studied using a hemodynamic protocol to maintain adequate tissue perfusion during the perioperative period.

Boyd[1] identified 17 randomized controlled clinical trials that had investigated perioperative therapies designed to increase tissue perfusion in surgical patients, many of them with limited cardiovascular reserve. A total of 1974 patients were enrolled in the studies and the OR for reduction in mortality was 0.45, with 95% CIs ranging from 0.33 to 0.60. The author suggested that outcome could be improved preoperatively by increasing tissue oxygen delivery in such patients.

Heyland et al.[9] may have been the first to systematically review randomized clinical trials designed to achieve supranormal values of cardiac, oxygen delivery, and consumption indexes in critically ill patients. They rigorously selected 7 articles of 64 potentially identified, and did not find a significant reduction in mortality rate (relative risk 0.86, 95% CI from 0.62 to 1.20). Nonetheless, their analysis of 2 studies with preoperative increase of tissue perfusion showed significant reduction in mortality rate, suggesting that hemodynamic preoperative control could benefit the high-risk surgical patient.

Kern and Shoemaker[10] reviewed 21 randomized controlled studies with hemodynamic protocols for acutely ill, high-risk elective surgery, trauma, and septic patients, using either normal or supranormal values for therapy, the latter described as cardiac index >4.5 $L \cdot min^{-1} \cdot m^{-2}$, oxygen transport index (Do_2I) >600 $mL \cdot min^{-1} \cdot m^{-2}$, and oxygen consumption ($\dot{V}o_2I$) >170 $mL \cdot min^{-1} \cdot m^{-2}$. They found that in severely ill patients (control group mortality >20%), 6 studies showed a significant (23%) mortality difference between the control and protocol groups with early treatment. However, in 7 studies in which hemodynamic stabilization was performed after the development of organ failure, there was not a significant reduction in mortality rate.

Poeze et al.[11] selected 30 randomized clinical trials of high-risk clinical and surgical patients hemodynamically treated and analyzed the methodological quality of the studies. The methodological quality of the studies was considered moderate and the outcomes of the randomized clinical trials were not related to their quality. In the studies that included patients with sepsis or organ dysfunction, no benefits were seen in outcome with hemodynamic control, but those with perioperative interventions aimed at maintaining tissue perfusion of high-risk surgical patients significantly reduced mortality.

Three recent reviews involving a few series of randomized controlled studies explored different aspects of hemodynamic stabilization. Bundgaard-Nielsen et al.[12] identified 9 studies in which a goal-directed therapeutic strategy was

Table 4. Characteristics, Intervention, Methodological Quality Score, and Treatment Goals of Included Studies

Studies	Type of surgery	Intervention	Methodological score	Treatment goals
Bender et al.,[24] 1997	Vascular	Fluid, blood, drugs.	8	PCWP 8–14; CI>2.8; SVR <1100
Berlauk et al.,[25] 1991	Peripheral vascular	Fluid, drugs	9	PCWP 8–15; CI>2.8; SVR <1100
Bishop et al.,[26] 1995	General surgery	Fluid, drugs	10	PCWP <18; CI >4.5; Do_2I >670; $\dot{V}o_2I$ >166
Boldt et al.,[27] 1998	Pancreatic surgery	Drugs	8	PCWP 12–14; CI >2.5; MAP >70
Bonazzi et al.,[28] 2002	Infrarenal aortic	Fluid, drugs	10	PCWP <18; CI >3; Do_2I >600; SVR <1450
Boyd et al.,[29] 1993	General surgery	Fluid, drugs	10	Do_2I >600
Chytra et al.,[30] 2007	Trauma	Fluid, blood, drugs	10	Esophageal Doppler: FTc 0.35–0.40
Conway et al.,[31] 2002	Gastrointestinal	Fluid	8	CI optimized
Donati et al.,[5] 2007	Gastrointestinal	Fluid, blood, drugs	10	O_2ER <27
Fleming et al.,[32] 1992	Trauma	Fluid, blood, drugs	7	CI >4.5; Do_2I >670; $\dot{V}o_2I$ >166
Gan et al.,[33] 2002	General surgery	Fluid	10	Esophageal Doppler: SV optimized
Kapoor et al.,[34] 2008	Cardiac surgery	Fluid, drugs	9	CI 2.5; Do_2I 450–600; SVV <10; $Scvo_2$ >70; SVRI 1500–2500
Lobo et al.,[17] 2000	General surgery	Fluid, drugs	11	Do_2I >600
Lobo et al.,[35] 2006	General surgery	Fluid, drugs	11	Do_2I >600
Lopes et al.,[36] 2007	General surgery	Fluid	8	ΔPP <10
Mythen and Webb,[37] 1995	Cardiac surgery	Fluid	8	Esophageal Doppler: SV optimized
Noblett et al.,[38] 2006	Gastrointestinal	Fluid	13	Esophageal Doppler: FTc >0.35; SV optimized
Pearse et al.,[39] 2005	General surgery	Fluid, blood, drugs	11	Do_2I >600
Polonen et al.,[23] 2000	Cardiac surgery	Fluid, blood, drugs	7	$S\bar{v}o_2$ >70; lactate<2
Sandham et al.,[16] 2003	General surgery	Fluid, blood, drugs	11	Do_2I 550–600; CI 3.5–4.5
Shoemaker et al.,[4] 1988	General surgery	Fluid, drugs	5	CI >4.5; Do_2I >600; $\dot{V}o_2I$ >170
Schultz et al.,[40] 1985	Femoral fractures	Fluid, drugs	8	LVSW/PCWP optimized
Sinclair et al.,[41] 1997	Femoral fractures	Fluid	8	Esophageal Doppler: FTc 0.35–0.40
Stone et al.,[42] 2003	Major abdominal	Fluid, drugs	13	Esophageal Doppler: SV optimized
Takala et al.,[43] 2000	Major abdominal	Fluid, blood, drugs	13	CI >2.5
Ueno et al.,[44] 1998	Hepatic surgery	Fluid, drugs	7	CI >4.5; Do_2I >600; $\dot{V}o_2I$ >170
Valentine et al.,[45] 1998	Aorta	Fluid, blood, drugs	10	PCWP <15; CI >2.8; SVR <1100
Velmahos et al.,[46] 2000	Trauma	Fluid, blood, drugs	11	CI >4.5; Do_2I >600; $\dot{V}o_2I$ >170; Spo_2/Fio_2 >200
Venn et al.,[47] 2002	Femoral fracture	Fluid	10	Esophageal Doppler: SV optimized
Wakeling et al.,[48] 2005	Major abdominal	Fluid	12	Esophageal Doppler: SV optimized
Wilson et al.,[49] 1999	General surgery	Drugs	12	Do_2I >600
Ziegler et al.,[50] 1997	Vascular	Fluid, blood, drugs	9	$S\bar{v}o_2$ >65; PCWP >12; Hb >10

PCWP = pulmonary capillary wedge pressure (mm Hg); CI = cardiac index ($L \cdot min^{-1} \cdot m^{-2}$); SVR = systemic vascular resistance (dynes · s · cm^{-5}); Do_2I = oxygen transport index ($mL \cdot min^{-1} \cdot m^{-2}$); Vo_2I = oxygen consumption index ($mL \cdot min^{-1} \cdot m^{-2}$); MAP = mean arterial blood pressure (mm Hg); FTc = corrected flow time (s); O_2ER = extraction rate of oxygen (%); SV = stroke volume (mL); SVV = stroke volume variation (%); $Scvo_2$ = central venous oxygen saturation (%); SVRI = systemic vascular resistance index (dynes · s · $cm^{-5} \cdot m^{-2}$); ΔPP = pulse pressure variation (%); $S\bar{v}o_2$ = mixed venous oxygen saturation (%); lactate ($mmol \cdot L^{-1}$); LVSW = left ventricular stroke work ($g \cdot m$); Spo_2/Fio_2 = ratio of oxygen saturation as measured by pulse oximetry and inspired oxygen fraction; Hb = hemoglobin ($g \cdot dL^{-1}$).

Table 5. Pooled Odds Ratio and 95% CI, Level of Heterogeneity, and Overall Effect for Mortality and Organ Failure Incidence According to the Methodological Score of the Studies, Mortality Rate of Control Group, Use of Pulmonary Artery Catheter, and Variables Used for Hemodynamic Control

	Pooled odds ratio (95% CI); level of heterogeneity; *P* value for overall effect	
Category (no. of trials included)	Mortality	Organ dysfunction
All the 32 RCTs	0.67 (0.55–0.82); moderate; $P < 0.001$	0.62 (0.55–0.70); high; $P < 0.00001$
Methodological score 0–9 ($n = 14$)	0.27 (0.16–0.46); little; $P < 0.0001$	0.46 (0.31–0.69); little; $P < 0.0001$
Methodological score 10–16 ($n = 18$)	0.79 (0.64–0.99); moderate; $P > 0.05$	0.66 (0.58–0.75); high; $P < 0.00001$
Control group mortality 0%–10% ($n = 17$)	0.95 (0.71–1.26); little; $P > 0.05$	0.74 (0.64–0.85); high; $P < 0.0001$
Control group mortality 11%–20% ($n = 6$)	0.82 (0.53–1.27); moderate; $P > 0.05$	0.61 (0.44–0.85); high; $P < 0.001$
Control group mortality >20% ($n = 9$)	0.32 (0.21–0.47); little; $P < 0.00001$	0.38 (0.26–0.56); little; $P < 0.00001$
PAC for hemodynamic control ($n = 19$)	0.67 (0.54–0.84); high; $P < 0.001$	Insufficient information
$CI/Do_2I/\dot{V}o_2I$ for hemodynamic control ($n = 18$)	0.71 (0.57–0.88); moderate; $P < 0.05$	0.69 (0.60–0.79); extreme; $P < 0.00001$
$S\bar{v}o_2/Scvo_2$ for hemodynamic control ($n = 3$)	0.68 (0.22–2.10); high; $P > 0.05$	0.49 (0.23–1.06); moderate; $P > 0.05$
Lactate for hemodynamic control ($n = 1$)	0.33 (0.07–1.65); nonapplicable; $P > 0.05$	0.17 (0.04–0.80); nonapplicable; $P < 0.05$

CI = confidence interval; RCTs = randomized controlled trials; PAC = pulmonary artery catheter; CI = cardiac index; Do_2I = oxygen transport index; $\dot{V}o_2I$ = oxygen consumption index; $S\bar{v}o_2$ = mixed venous oxygen saturation; $Scvo_2$ = central venous oxygen saturation.

used to maximize flow-related hemodynamic variables in surgical patients, intra- and postoperatively. They verified that the treatment strategy reduced gastrointestinal complications and hospital length of stay. Abbas and Hill[13] analyzed the use of esophageal Doppler on hemodynamic control with fluids in major abdominal surgery, selecting 5 studies comprising 420 patients, and demonstrated that there was a reduction in hospital stay in the intervention group. Giglio et al.[14] selected 16 studies involving perioperative monitoring and manipulation of hemodynamic variables to reach normal or supranormal values and also concluded that goal-directed hemodynamic therapy reduces gastrointestinal

complications after major surgery, as tissue perfusion is maintained.

This review differs from previously published reviews on hemodynamic monitoring and control because it focuses on surgical patients with no organ failure before surgery, with a high risk of complications and death, and submitted to a specific protocol to maintain tissue perfusion involving cardiac output, oxygen delivery/consumption, and its derived variables, such as $S\bar{v}o_2$. With these filters, 32 randomized clinical trials were recovered with >5000 patients, the largest number of individuals in a review on this topic.

In the present review, we found that in high-risk surgical patients with no evident organ dysfunction before surgery, the use of a protocol to maintain adequate hemodynamic status and tissue perfusion reduced the mortality rate and the possibility of organ failure in the postoperative period (Table 5). Therefore, strategies to ensure adequate perioperative tissue perfusion should be adopted. It is surprising that in a recent publication, Pearse et al.[15] showed a different outcome in the United Kingdom, where the high-risk surgical population accounted for 12.5% of surgical procedures but for >80% of deaths. Despite the high mortality rates, fewer than 15% of these patients were admitted to intensive care. It could be that the care providers did not focus on tissue perfusion management for many of those patients.

When analyzing the methodological quality of the trials, we found that a significant percentage of the randomized controlled clinical studies involving therapeutic interventions that aimed at hemodynamic control had some methodological deficiency. Our results showed that, independent of the methodological quality score, perioperative hemodynamic control significantly reduced the incidence of organ failure. However, the methodological score influenced mortality in overall effect. Studies classified as 10 to 16 according to Chalmers score[7] did not result in a significant reduction in mortality, even though there was a tendency toward a reduction (OR: 0.79; 95% CI: 0.64–0.99; moderate heterogeneity; $P > 0.05$) (Table 5). Additional well-designed randomized controlled studies are necessary to clarify this discrepancy and ultimately to determine whether mortality can be reduced through the maintenance of perioperative tissue perfusion in high-risk surgical patients.

The analysis of the subgroup whose control group had a higher mortality rate (>20%) showed that perioperative hemodynamic control significantly reduced mortality (Table 5). From this finding, we understand that the higher the risk involved, the more benefit patients have with a protocol to maintain tissue perfusion. In this highest-risk subgroup, there were probably more patients submitted to more complex operations, more elderly patients, and probably more patients with some limitation in physiological reserves. In the other 2 subgroups whose control groups had mortality rates of <20%, specific hemodynamic control protocols did not significantly reduce mortality. A lower mortality rate in the control group probably indicates selection of individuals with better clinical conditions having less-complex elective operations. The probability of a state of tissue hypoperfusion in these patients then seems to be greatly reduced. However, maintaining tissue perfusion perioperatively significantly reduced the incidence of organ dysfunction in all groups of patients (Table 5).

Even though the work of Sandham et al.,[16] involving a considerable number of patients, has met the criteria for inclusion in this meta-analysis, the study's therapeutic intervention did not necessarily cause an increase in tissue perfusion compared with the control group. Most likely, the protocol used for the intervention did not allow uniform hemodynamic management among the randomized patients. A meta-analysis conducted without the inclusion of this study would decrease the OR and 95% CI for the event mortality from 0.67 (0.55–0.82) to 0.53 (0.41–0.68).

A well-defined protocol with explicit goals is important for the results, which tend to be better than in studies comparing the use of a pulmonary artery catheter with standard care (Sandham et al.[16]). For example, Lobo et al.[17] randomized high-risk surgical patients, and with a defined goal (Do_2I >600 mL · min^{-1} · m^{-2}) and a specific algorithm for treatment (fluids, drugs) were capable of considerably and significantly reducing the mortality rate (OR: 0.19; 95% CI: 0.04–0.88), as compared with Sandham et al. (OR: 1.01; 95% CI: 0.73–1.41).

In addition, we found that the use of a pulmonary artery catheter as a guide for hemodynamic treatment in the high-risk surgical patient significantly reduced the mortality rate (Table 5), contradicting those who found an increase in mortality rate with its use.[18] High-risk surgical patients with no evident signs of preoperative tissue hypoperfusion and those without any kind of organ failure may benefit from pulmonary artery catheterization and hemodynamic control, which differs from many critically ill patients, some with multiple organ failure, who have progressive and nonreversible tissue damage and will not benefit from any kind of monitoring and treatment.

Studies for analysis were selected in which perioperative hemodynamic control was guided by cardiac index, Do_2I, and $\dot{V}o_2I$, where we found a significant reduction in the incidence of both mortality and organ failure (Table 5). The literature has shown the insensitivity of using clinical variables such as arterial blood pressure, heart rate, consciousness level, urinary volume, and perfusion of extremities to determine the presence of tissue hypoperfusion in both clinical and stable surgical patients.[19] We recommend use of tools that clearly help to recognize and maintain tissue perfusion and can significantly contribute to the final result: reduction in mortality rate and organ failure incidence. In the present review, 18 of the 31 selected studies had hemodynamic control guided by cardiac index, Do_2I, and $\dot{V}o_2I$ and a significantly reduced incidence of postoperative complications.

However, in the 3 studies that used $S\bar{v}o_2$ or $Scvo_2$ as goals to hemodynamically treat high-risk surgical patients, there was no significant reduction in either mortality or organ failure. In other specific conditions such as cardiac failure,[20] respiratory insufficiency,[21] sepsis,[22] and cardiac surgery,[23] low values of $S\bar{v}o_2$ or $Scvo_2$ were significantly related to increased mortality. Additional studies are necessary to gain a better understanding of the role of these markers in the perioperative period, because anesthesia

and reduction of metabolism may make it difficult to interpret variations in $S\bar{v}o_2$ or $Scvo_2$.

In this meta-analysis, we found just one study in which lactate was used as a specific marker for perioperative hemodynamic control. There was no significant reduction in mortality, but organ dysfunction was significantly reduced. Similar to $S\bar{v}o_2$ and $Scvo_2$, in high-risk surgical patients, additional studies will be necessary to better understand the role of lactate as a guide for perioperative hemodynamic management.

In summary, the present meta-analysis suggests that, in high-risk surgical patients with no evident organ dysfunction before surgery, maintaining tissue perfusion perioperatively according to a specific protocol reduces postoperative mortality and morbidity. Furthermore, the higher the risk, the more benefit there is from hemodynamic control. The use of the pulmonary artery catheter, and cardiac index, Do_2I, and $\dot{V}o_2I$ as targets for hemodynamic control reduces postoperative mortality and organ dysfunction in this group of patients. Additional studies with $S\bar{v}o_2$, $Scvo_2$, and lactate as markers of tissue perfusion in the high-risk surgical patient should be performed to clarify their potential as goals for perioperative hemodynamic control and reduction of postoperative complications and mortality. Finally, methodological trial quality seems to influence mortality analysis in perioperative patients more than in other subsets of patients, such as those with sepsis and organ failure.

DISCLOSURES

Name: Sanderland T. Gurgel
Contribution: Study design, data analysis, and manuscript preparation.
Conflicts of Interest: Dr. Gurgel received a grant from CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).
Name: Paulo do Nascimento, Jr., MD, PhD
Contribution: Study design, data analysis, and manuscript preparation.
Conflicts of Interest: Dr. do Nascimento has no conflicts to declare.

REFERENCES

1. Boyd O. Optimisation of oxygenation and tissue perfusion in surgical patients. Intensive Crit Care Nurs 2003;19:171–81
2. Shoemaker WC, Appel PL, Kram HB. Measurement of tissue perfusion by oxygen transport patterns in experimental shock and in high-risk surgical patients. Intensive Care Med 1990;16:S135–44
3. Boyd O, Jackson N. How is risk defined in high-risk surgical patient management? Crit Care 2005;9:390–6
4. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988;94:1176–86
5. Donati A, Loggi S, Preiser JC, Orsetti G, Munch C, Gabbanelli V, Pelaia P, Pietropaoli P. Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. Chest 2007;132:1817–24
6. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13
7. Chalmers TC, Smith H Jr, Blackburn B, Silverman B, Schroeder B, Reitman D, Ambroz A. A method for assessing the quality of a randomized control trial. Control Clin Trials 1981;2:31–49
8. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer TT, Varonen H, Vist GE, Williams JW Jr, Zaza S. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490
9. Heyland DK, Cook DJ, King D, Kernerman P, Brun-Buisson C. Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. Crit Care Med 1996;24:517–24
10. Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care Med 2002;30:1686–92
11. Poeze M, Greve JW, Ramsay G. Meta-analysis of hemodynamic optimization: relationship to methodological quality. Crit Care 2005;9:R771–9
12. Bundgaard-Nielsen M, Holte K, Secher NH, Kehlet H. Monitoring of peri-operative fluid administration by individualized goal-directed therapy. Acta Anaesthesiol Scand 2007;51:331–40
13. Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. Anaesthesia 2008;63:44–51
14. Giglio MT, Marucci M, Testini M, Brienza N. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. Br J Anaesth 2009;103:637–46
15. Pearse RM, Harrison DA, James P, Watson D, Hinds C, Rhodes A, Grounds RM, Bennett ED. Identification and characterisation of the high-risk surgical population in the United Kingdom. Crit Care 2006;10:R81
16. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ, Laporta DP, Viner S, Passerini L, Devitt H, Kirby A, Jacka M. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003;348:5–14
17. Lobo SM, Salgado PF, Castillo VG, Borim AA, Polachini CA, Palchetti JC, Brienzi SL, de Oliveira GG. Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. Crit Care Med 2000;28:3396–404
18. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJ Jr, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA 1996;276:889–97
19. Rady MY. Bench-to-bedside review: resuscitation in the emergency department. Crit Care 2005;9:170–6
20. Bloos F, Reinhart K. Venous oximetry. Intensive Care Med 2005;31:911–3
21. Springer RR, Stevens PM. The influence of PEEP on survival of patients in respiratory failure: a retrospective analysis. Am J Med 1979;66:196–200
22. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77
23. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 2000;90:1052–9
24. Bender JS, Smith-Meek MA, Jones CE. Routine pulmonary artery catheterization does not reduce morbidity and mortality of elective vascular surgery: results of a prospective, randomized trial. Ann Surg 1997;226:229–36
25. Berlauk JF, Abrams JH, Gilmour IJ, O'Connor SR, Knighton DR, Cerra FB. Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery: a prospective, randomized clinical trial. Ann Surg 1991;214:289–97
26. Bishop MH, Shoemaker WC, Appel PL, Meade P, Ordog GJ, Wasserberger J, Wo CJ, Rimle DA, Kram HB, Umali R, Kennedy F, Shuleshko J, Stephen CM, Shori SK, Thadepalli HD. Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. J Trauma 1995;38:780–7

27. Boldt J, Papsdorf M, Piper S, Padberg W, Hempelmann G. Influence of dopexamine hydrochloride on haemodynamics and regulators of circulation in patients undergoing major abdominal surgery. Acta Anaesthesiol Scand 1998;42:941–7
28. Bonazzi M, Gentile F, Biasi GM, Migliavacca S, Esposti D, Cipolla M, Marsicano M, Prampolini F, Ornaghi M, Sternjakob S, Tshomba Y. Impact of perioperative haemodynamic monitoring on cardiac morbidity after major vascular surgery in low risk patients: a randomised pilot trial. Eur J Vasc Endovasc Surg 2002;23:445–51
29. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993;270:2699–707
30. Chytra I, Pradl R, Bosman R, Pelnar P, Kasal E, Zidkova A. Esophageal Doppler-guided fluid management decreases blood lactate levels in multiple-trauma patients: a randomized controlled trial. Crit Care 2007;11:R24
31. Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C. Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. Anaesthesia 2002;57:845–9
32. Fleming A, Bishop M, Shoemaker W, Appel P, Sufficool W, Kuvhenguwha A, Kennedy F, Wo CJ. Prospective trial of supranormal values as goals of resuscitation in severe trauma. Arch Surg 1992;127:1175–9
33. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PS. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002;97:820–6
34. Kapoor PM, Kakani M, Chowdhury U, Choudhury M, Lakshmy R, Kiran U. Early goal-directed therapy in moderate to high-risk cardiac surgery patients. Ann Card Anaesth 2008;11:27–34
35. Lobo SM, Lobo FR, Polachini CA, Patini DS, Yamamoto AE, de Oliveira NE, Serrano P, Sanches HS, Spegiorin MA, Queiroz MM, Christiano AC Jr, Savieiro EF, Alvarez PA, Teixeira SP, Cunrath GS. Prospective, randomized trial comparing fluids and dobutamine optimization of oxygen delivery in high-risk surgical patients [ISRCTN42445141]. Crit Care 2006;10:R72
36. Lopes MR, Oliveira MA, Pereira VO, Lemos IP, Auler JO Jr, Michard F. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. Crit Care 2007;11:R100
37. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg 1995;130:423–9
38. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. Br J Surg 2006;93:1069–76
39. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay: a randomised, controlled trial [ISRCTN38797445]. Crit Care 2005; 9:R687–93
40. Schultz RJ, Whitfield GF, LaMura JJ, Raciti A, Krishnamurthy S. The role of physiologic monitoring in patients with fractures of the hip. J Trauma 1985;25:309–16
41. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. BMJ 1997;315:909–12
42. Stone MD, Wilson RJ, Cross J, Williams BT. Effect of adding dopexamine to intraoperative volume expansion in patients undergoing major elective abdominal surgery. Br J Anaesth 2003;91:619–24
43. Takala J, Meier-Hellmann A, Eddleston J, Hulstaert P, Sramek V. Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. European Multicenter Study Group on Dopexamine in Major Abdominal Surgery. Crit Care Med 2000;28:3417–23
44. Ueno S, Tanabe G, Yamada H, Kusano C, Yoshidome S, Nuruki K, Yamamoto S, Aikou T. Response of patients with cirrhosis who have undergone partial hepatectomy to treatment aimed at achieving supranormal oxygen delivery and consumption. Surgery 1998;123:278–86
45. Valentine RJ, Duke ML, Inman MH, Grayburn PA, Hagino RT, Kakish HB, Clagett GP. Effectiveness of pulmonary artery catheters in aortic surgery: a randomized trial. J Vasc Surg 1998;27:203–11
46. Velmahos GC, Demetriades D, Shoemaker WC, Chan LS, Tatevossian R, Wo CC, Vassiliu P, Cornwell EE III, Murray JA, Roth B, Belzberg H, Asensio JA, Berne TV. Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial. Ann Surg 2000;232: 409–18
47. Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P. Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. Br J Anaesth 2002;88:65–71
48. Wakeling HG, McFall MR, Jenkins CS, Woods WG, Miles WF, Barclay GR, Fleming SC. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. Br J Anaesth 2005;95:634–42
49. Wilson J, Woods I, Fawcett J, Whall R, Dibb W, Morris C, McManus E. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. BMJ 1999;318:1099–103
50. Ziegler DW, Wright JG, Choban PS, Flancbaum L. A prospective randomized trial of preoperative "optimization" of cardiac function in patients undergoing elective peripheral vascular surgery. Surgery 1997;122:584–92

CRITICAL CARE

LETTER

The burden of high-risk surgery and the potential benefit of goal-directed strategies

Frederic Michard*

See related research by Cannesson *et al.*, http://ccforum.com/content/15/4/R197

The survey by Cannesson and colleagues [1] in the previous issue of *Critical Care* shows that only around 16% of anesthetists (5.4% of 210 US respondents and 30.4% of 158 European respondents) use a specific treatment protocol (that is, follow a goal-directed strategy) for the peri-operative hemodynamic management of patients undergoing high-risk surgery. In 2008, Weiser and colleagues [2] estimated the global volume of surgery to be 234.2 million procedures a year. According to Pearse and colleagues [3], high-risk surgical procedures represent around 12.5% of this total. A meta-analysis of the 29 randomized controlled trials investigating the value of peri-operative goal-directed strategies reported an average mortality rate of 9.4% in control groups and a significantly reduced mortality rate of 5.9% when a goal-directed strategy was adopted [4]. When putting all the pieces of this puzzle together, one can estimate that around 860,000 lives could potentially be saved every year (the equivalent of one life every 37 seconds) if such strategies became the standard of care around the world (Table 1).

In addition, millions of post-operative complications could be avoided. Indeed, the meta-analysis by Hamilton and colleagues [4] suggests that the post-operative complication rate could be reduced from 29.8% to 18.0% with goal-directed strategies. Given the potential volume of complications after high-risk surgery (Table 1), the direct costs of treating these complications as well as the indirect costs related to prolonged hospital length of stay are difficult to quantify precisely but without question are astronomically high. It may be time for heath-care systems and governments to consider peri-operative goal-directed strategies as part of quality improvement programs and as national priorities.

Competing interests
The author is a vice president of global medical strategy at Edwards Lifesciences (Irvine, CA, USA). The statements in this letter do not support the use of a specific treatment protocol or of a specific medical device for peri-operative goal-directed strategies.

Published: 20 October 2011

References

1. Cannesson M, Pestel G, Ricks C, Hoeft A, Perel A: **Hemodynamic monitoring and management in patients undergoing high-risk surgery: a survey among North American and European anesthesiologists.** *Crit Care* 2011, **15:**R197.
2. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA: **An estimation of the global volume of surgery: a modeling strategy based on available data.** *Lancet* 2008, **372:**139-144.
3. Pearse RM, Harrison DA, James P, Watson D, Hinds C, Rhodes A, Grounds RM, Bennett ED: **Identification and characterization of the high-risk surgical population in the United Kingdom.** *Crit Care* 2006, **10:**R81.
4. Hamilton MA, Cecconi M, Rhodes A: **A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients.** *Anesth Analg* 2011, **112:**1392-1402.

doi:10.1186/cc10473
Cite this article as: Michard F: **The burden of high-risk surgery and the potential benefit of goal-directed strategies.** *Critical Care* 2011, **15:**447.

*Correspondence: michard.frederic@free.fr
Critical Care, Edwards Lifesciences, Edwards Way, Irvine, CA 92614, USA

Table 1. Estimates of the potential worldwide benefit of peri-operative goal-directed strategies

	Yearly estimation	Reference
All surgical procedures	234,200,000	Weiser *et al*. [2]
High-risk surgical procedures (12.5%)	29,275,000	Pearse *et al*. [3]
High-risk procedures without GDS (84%)	24,591,000	Cannesson *et al*. [1]
Deaths without GDS (9.4%)	2,311,554	Hamilton *et al*. [4]
Deaths if GDS were to be adopted (5.9%)	1,450,869	Hamilton *et al*. [4]
Lives potentially saved if GDS were to be adopted	860,685	-
Complications without GDS (29.8%)	7,328,118	Hamilton *et al*. [4]
Complications if GDS were to be adopted (18.0%)	4,426,380	Hamilton *et al*. [4]
Complications potentially avoided if GDS were to be adopted	2,901,738	-

GDS, goal-directed strategies.