The parasympathetic system: a renewed role in goal-directed therapy

Lancet Respir Med 2014

Published Online
December 16, 2014
http://dx.doi.org/10.1016/S2213-2600(14)70298-X

See Online/Articles
http://dx.doi.org/10.1016/S2213-2600(14)70205-X

In *The Lancet Respiratory Medicine*, Gareth Ackland and colleagues[1] report the results of a multicentre randomised controlled trial on postoperative goal-directed therapy in high-risk surgical patients. The intervention group received fluid optimisation and inotropic support to reach or surpass preoperative oxygen delivery. The control group was treated according to standard care, including colloid fluid resuscitation based on hourly diuresis, mean arterial pressure, and central venous saturation. The primary endpoint was postoperative morbidity and a secondary endpoint was the effect of goal-directed therapy on parasympathetic function. The results were as expected. It should be noted that the specified standard care previously would have qualified as goal-directed therapy, therefore it is not that surprising that no difference was observed in morbidity between intervention groups. Interestingly, however, morbidity was lower across the groups in patients achieving their preoperative oxygen delivery level. A challenging finding was the substantial diminution of the high frequency component in heart rate variability in the intervention group as a signal of suppressed parasympathetic nervous activity. The authors offer this finding as an explanation why goal-directed therapy did not show an effect.

Recent trials also show no advantage of goal-directed therapy (eg, ARISE,[2] PROCESS,[3] and OPTIMISE[4]). However, one meta-analysis[5] concluded that goal-directed therapy was effective "irrespective of the choice of the monitored physiological parameter or haemodynamic monitor in use" and it was unclear if "the use of a haemodynamic monitor alone or the combination of an algorithm and a haemodynamic monitor confers the benefit".

These findings have led to some experts suggesting that goal-directed therapy is dead, which it is not. Instead, we are seeing the culmination of experience and knowledge about perioperative care gleaned from three decades of goal-directed therapy. However, goal-directed therapy examined in a randomised controlled trial and the concept of fluid optimisation face serious challenges.

In the complex perioperative setting, a randomised controlled trial might not be the optimal research method because its main objective is to compare the effect size of two or more treatments for a specific condition. The perioperative situation hardly qualifies as a specific condition and goal-directed therapy hardly as a treatment.[6] It has become difficult to create control groups sufficiently 'maltreated' to prove superiority of goal-directed therapy, and several suffer from negligence of the pathophysiology,[7,8] lack of equipoise, and misalignment of treatment.[9,10]

Also, the concept of fluid optimisation has to be understood in its complexity. Vascular compliance and tone are not accounted for. Repetitive fluid boli might separately increase cardiac output by less than 10% but sequentially might add up to much more than 10%. The absence of a response greater than 10% could either reflect an ineffectual excitation of the cardiovascular system or the system being on the level part of the Frank-Starling curve—without the clinician being aware that the patient is moving up the hormetic relation between fluid overload and complications. Furthermore, the optimisation procedure relies on the dissociation of cardiac output and oxygen consumption. Thus, it is pointless looking for volume responsiveness in awake volunteers and pointless looking for it in postoperative patients with cardiovascular reflexes resurging post-anaesthesia.[11]

LTH NHS Trust/Science Photo Library

This certainly runs contrary to the prevailing canon in perioperative monitoring and guidance based on volume responsiveness (pulse pressure and stroke volume variation, or fluid optimisation), although it is commonly recognised that the physiological basis is uncertain.

Ackland and colleagues[1] suggest application of goal-directed therapy towards preoperative oxygen delivery by fluid optimisation before addition of an inotrope. This is an interesting approach to individualisation but needs to be developed into perioperative continuously goal-directed oxygen delivery as a reflection of the patient's oxygen consumption, which is known to vary widely from the preoperative to the postoperative state.[12] Anchoring oxygen delivery to its preoperative value risks the creation of too low and too high oxygen tensions—also known to enter a hormetic relation with complications.[13]

We will have to refine and reinvent goal-directed therapy and base the concept on physiological terms. A coherent and exhaustive cardiovascular model based on oxygen consumption, mean arterial pressure, cardiac output, and central venous pressure is available enabling the clinician to manipulate vascular tone, compliance, and heart efficiency by means of fluid, vasoactive, or cardioactive drugs.

The present study offers the corollary of preserving the parasympathetic component for the cellular protection as yet another aim in goal-directed therapy, which has not been explored so far.[14] Possible candidates are epidural analgesia, β-blockade, central α-stimulation, or low respiratory rate.

For goal-directed therapy to experience a renaissance, this parasympathetic protection would be an obvious target to include while simultaneously adapting a more comprehensive understanding of the physiology of goal-directed therapy.

Soren Sondergaard
Department of Anaesthesia and Intensive Care, Sahlgrenska University Hospital, 41345 Gothenburg, Sweden
sondergaard.soren@gmail.com

I declare no competing interests.

1 Ackland GL, Iqbal S, Gallego Paredes L, et al, for the POM-O (PostOperative Morbidity-Oxygen delivery) study group. Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: a multicentre, randomised, double-blinded, controlled, mechanistic trial. *Lancet Respir Med* 2014; published online Dec 12. http://dx.doi.org/10.1016/S2213-2600(14)70205-X.
2 ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; **371:** 1496–506.
3 Pro CI, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; **370:** 1683–93.
4 Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA* 2014; **311:** 2181–90.
5 Arulkumaran N, Corredor C, Hamilton MA, et al. Cardiac complications associated with goal-directed therapy in high-risk surgical patients: a meta-analysis. *Br J Anaesthesia* 2014; **112:** 648–59.
6 Barahona C. Randomised control trials for the impact evaluation of development initiatives: a statistician's point of view. 2010. http://www.cgiar-ilac.org/files/publications/working_papers/ILAC_WorkingPaper_No13_Randomised%20Control%20Trials.pdf.
7 Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; **370:** 1412–21.
8 Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; **367:** 124–34.
9 Deans KJ, Minneci PC, Suffredini AF, et al. Randomization in clinical trials of titrated therapies: unintended consequences of using fixed treatment protocols. *Crit Care Med* 2007; **35:** 1509–16.
10 Hebert PC. Transfusion requirements in critical care (TRICC): a multicentre, randomized, controlled clinical study. Transfusion Requirements in Critical Care Investigators and the Canadian Critical Care Trials Group. *Br J Anaesthesia* 1998; **81** (suppl 1)**:** 25–33.
11 Bundgaard-Nielsen M, Jorgensen CC, Kehlet H, Secher NH. Normovolemia defined according to cardiac stroke volume in healthy supine humans. *Clin Physiol Funct Imag* 2010; **30:** 318–22.
12 Reinhart K, Eyrich K. Clinical aspects of O_2 transport and tissue oxygenation. Berlin: Springer-Verlag, 1989.
13 de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008; **12:** R156.
14 Olshansky B, Sabbah HN, Hauptman PJ, Colucci WS. Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy. *Circulation* 2008; **118:** 863–71.

Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: a multicentre, randomised, double-blind, controlled, mechanistic trial

*Gareth L Ackland, Sadaf Iqbal, Laura Gallego Paredes, Andrew Toner, Craig Lyness, Nicholas Jenkins, Phoebe Bodger, Shamir Karmali, John Whittle, Anna Reyes, Mervyn Singer, Mark Hamilton, Maurizio Cecconi, Rupert M Pearse, Susan V Mallett, Rumana Z Omar, for the POM-O (PostOperative Morbidity-Oxygen delivery) study group**

Summary

Background Morbidity after major surgery is associated with low oxygen delivery. Haemodynamic therapy aimed at increasing oxygen delivery in an effort to reduce oxygen debt, tissue injury, and morbidity, is controversial. The most appropriate target for this strategy is unclear and might have several off-target effects, including loss of neural (parasympathetic)-mediated cellular protection. We hypothesised that individualised oxygen delivery targeted haemodynamic therapy (goal-directed therapy) in high-risk surgical patients would reduce postoperative morbidity, while secondarily addressing whether goal-directed therapy affected parasympathetic function.

Methods In this multicentre, randomised, double-blind, controlled trial, adult patients undergoing major elective surgery were allocated by computer-generated randomisation to a postoperative protocol (fluid, with and without dobutamine) targeted to achieve their individual preoperative oxygen delivery value (goal-directed therapy) or standardised care (control). Patients and staff were masked to the intervention. The primary outcome was absolute risk reduction (ARR) in morbidity (defined by Clavien–Dindo grade II or more) on postoperative day 2. We also assessed a secondary outcome focused on parasympathetic function, using time-domain heart rate variability measures. Analyses were done on an intention-to-treat basis. The trial was registered with Controlled Clinical Trials (number ISRCTN76894700).

Findings We enrolled 204 patients between May 20, 2010, and Feb 12, 2014. Intention-to-treat analysis of the 187 (92%) patients who completed the trial intervention period showed that early morbidity was similar between goal-directed therapy (44 [46%] of 95 patients) and control groups (49 [53%] of 92 patients) (ARR –7%, 95% CI –22 to 7; p=0·30). Prespecified secondary analysis showed that 123 (66%) of 187 patients achieved preoperative oxygen delivery (irrespective of intervention). These patients sustained less morbidity (ARR 19%, 95% CI 3–34; p=0·016), including less infectious complications. Goal-directed therapy reduced parasympathetic activity postoperatively (relative risk 1·33, 95% CI 1·01–1·74).

Interpretation Achievement of preoperative oxygen delivery values in the postoperative phase was associated with less morbidity, but this was not affected by the use of an oxygen delivery targeted strategy. Reduced parasympathetic activity after goal-directed therapy was associated with the failure of this intervention to reduce postoperative morbidity.

Funding Academy of Medical Sciences and Health Foundation Clinician Scientist Award.

Lancet Respir Med 2014

Published Online December 16, 2014 http://dx.doi.org/10.1016/S2213-2600(14)70205-X

See Online/Comment http://dx.doi.org/10.1016/S2213-2600(14)70298-X

*Members listed in the appendix

Clinical Physiology (G L Ackland PhD, M Singer FRCP) **and Statistical Science** (Prof R Z Omar PhD), **University College London, UK** (S Iqbal BSc, L Gallego Paredes BSc, N Jenkins FRCA, S Karmali MRCP, J Whittle FRCA)**; St George's Hospital, London, UK** (A Toner FRCA, A Reyes BSc, M Hamilton FRCA, M Cecconi FRCA)**; Royal Free Hospital, London, UK** (C Lyness FRCA, S V Mallett FRCA)**; Royal London Hospital, London, UK** (P Bodger BSc)**; and Queen Mary University of London, London, UK** (Prof R M Pearse FRCA)

Correspondence to: Dr Gareth L Ackland, Clinical Physiology, Division of Medicine, University College London, London WC1E 6BT, UK **g.ackland@ucl.ac.uk**

See Online for appendix

Introduction

234 million patients undergo non-cardiac surgery worldwide each year,[1] with substantial morbidity or mortality in a sizeable minority.[1,2] Patients who develop complications after major surgery, but survive to leave hospital, subsequently experience reductions in functional independence leading to premature death.[3–5]

Although morbidity after major surgery is associated with lower oxygen delivery, the mechanisms underlying this association are poorly understood.[6] Patients frequently achieve or exceed oxygen delivery targets without specialised interventions, showing how as yet unidentified mechanisms might contribute to reducing the burden of surgical critical illness. A recent systematic review concluded that increased oxygen delivery might result in improved patient outcomes,[7] but a highly individualised patient approach is likely to be optimum.[8] This situation reflects uncertainty over the key components of haemodynamic therapy in surgical critical care.

Autonomic dysregulation is an early and common feature of major surgery, trauma, and sepsis.[9,10] Preservation of parasympathetic function confers cellular and anti-inflammatory protection across diverse organs.[11] Experimental data have identified that vagal nerve activity is crucial for cardioprotection during ischaemia,[12] an increasingly recognised source of perioperative morbidity.[13] Furthermore, the parasympathetic neurotransmitter acetylcholine dampens inflammation by nicotinic receptors in tissue-resident macrophages, thereby attenuating multi-organ dysfunction.[14] Fluid and inotropic therapy to increase oxygen delivery might contribute to perioperative autonomic dysregulation, as shown by marked reductions

in parasympathetic activity after administration of dobutamine during stress echocardiography.[15,16] Thus, acquired loss of parasympathetic autonomic function as an unintentional result of haemodynamic therapy could remove a crucial biological protective mechanism in the critically ill surgical population.

Therefore, we did a multicentre, randomised controlled trial to investigate the hypothesis that targeting of postoperative oxygen delivery in high-risk surgical patients to their individual preoperative oxygen delivery value (goal-directed therapy) would reduce morbidity. In parallel, we also investigated the secondary mechanistic hypothesis that the risk of reduced parasympathetic neural activity would increase with goal-directed therapy associated with postoperative morbidity.

Methods

Study design and participants

POM-O (Postoperative Morbidity Oxygen delivery) was a multicentre, double-blind, randomised controlled trial done in four university hospitals in the UK (appendix). Although originally planned as a single centre study, due to the transfer (and reorganisation) of surgical services at University College London Hospital, London, shortly after the trial commenced, additional sites were needed. Adult patients undergoing major elective surgery expected to last for at least 120 min were eligible for recruitment provided they satisfied the following high-risk criteria: American Society of Anesthesiologists classification of 3 or more; surgical procedures with an estimated or documented risk of postoperative morbidity (as defined by the Postoperative Morbidity Survey) exceeding 50%; modified Revised Cardiac Risk Score of 3 or more, as defined by age 70 years or more, a history of cardiovascular disease (myocardial infarction, coronary artery disease, cerebrovascular accident, electrocardiographic evidence for established cardiac pathology), cardiac failure, poor exercise capacity (anaerobic threshold <11 mL/kg per min assessed by cardiopulmonary exercise testing or Duke Activity Status Index), renal impairment (serum creatinine ≥130 μmol/L), or diabetes. Exclusion criteria included refusal of consent, pregnancy, lithium therapy or allergy, recent myocardial ischaemia (within the previous 30 days), acute arrhythmia, acute bleeding, and patients receiving palliative treatment only. The decision to exclude patients who developed these exclusion criteria intraoperatively was made jointly by the local principal investigator and the chief investigator. The trial was approved by the South London Research Ethics Committee Office (09/H0805/58). Written informed consent was obtained from all patients before surgery. Site visits were made by GLA, SI, LGP, and AT for training and source data verification.

For the **trial protocol** see www.ucl.ac.uk/anaesthesia/trials

Randomisation and masking

The randomisation list was generated by Stata, stratified by hospital, and then concealed by envelope. Participants were centrally allocated to treatment groups. All principal investigators were masked to study group allocation. To further minimise the possibility of bias, the medical research and nursing staff delivering the haemodynamic protocol did not reveal the study group allocation to critical care staff, attending surgical, or physician teams. Every patient enrolled had a central venous catheter, or large-bore (14–16 G) intravenous cannula, inserted after induction of anaesthesia. A syringe with saline or dobutamine was connected via extension tubing to each patient's central venous catheter (or, exceptionally, large-bore intravenous cannula), with the identity of the syringe contents covered. Patients were followed up by an investigator unaware of the patients' achievement or not of the oxygen delivery goal. Morbidity outcomes were verified according to predefined criteria using the Postoperative Morbidity Survey (POMS)[17] and severity was graded objectively using the Clavien–Dindo scale[18] by an investigator masked to the intervention. Grading of severity was verified at the end of the trial by an independent assessor masked to the intervention. All participants were admitted as elective postoperative cases to a critical care facility.

Procedures

Three-lead electrocardiographic recordings were made preoperatively using Lifecard CF digital Holter monitors (Spacelabs Healthcare, Hertford, UK). Holter data cleaning and analysis were done masked to all perioperative data. Valid segments of recordings were identified from patients in a quiet environment before the operation. Patients with atrial fibrillation, frequent ectopy, or other dysrhythmias were excluded. Data quality criteria were in accordance with Task Force guidelines.[19] We assessed time-domain measures from 5 min recordings in non-ventilated patients, which are preferred to frequency domain methods when only short-term recordings are possible and reproducible over time in a non-laboratory setting.[20] Two measures of parasympathetic activity were assessed: the square root of the mean of the sum of the squares of the successive differences between adjacent beat-to-beat intervals (root mean square of the successive differences, RMSSD); and the proportion of number of pairs of successive beat-to-beat intervals that differ by more than 50 ms, divided by total number of beat-to-beat intervals (pNN50).

We compared these parameters at baseline (preoperatively) and at the end of the intervention period. We defined abnormal parasympathetic activity as RMSSD less than 19 ms, which has been defined by a recent systematic review of normal values for short-term, time-domain heart rate variability parameters.[21]

Local investigators were trained at the lead site in the delivery of the haemodynamic therapy algorithm (appendix). Before any anaesthetic intervention, an arterial line was inserted into a radial artery under local anaesthetic in a dedicated clinical environment. We used

a calibrated, accurate cardiac output monitoring technology (LiDCOPlus; LiDCO, London, UK),[22] which enables data collection throughout the perioperative period, a key requirement because we predicted that most patients would be awake and extubated for the intervention period. Preoperative oxygen delivery was calculated after the LiDCO lithium-based calibration by determining preoperative cardiac output. At least three calibration curves were constructed routinely to ensure accuracy of haemodynamic data (appendix). Once these calibration data were obtained, anaesthetic preparation (insertion of thoracic epidural catheter, endotracheal intubation) commenced and surgery followed, during which time haemodynamic data were captured throughout, but were not revealed to any operating room staff including attending anaesthesiologists. Alternative haemodynamic monitors were permitted during surgery.

As an indicator of the severity of acute physiological derangement after surgery (before the intervention) we calculated the Acute Physiology and Chronic Health Evaluation II (APACHE II) score for each patient.

The intervention period commenced once the patient reached the critical care environment after surgery and continued for 6 h (appendix). Both randomisation groups (ie, goal-directed therapy and control patients) were managed by research staff during the postoperative study period. Before the intervention, we recalibrated the LiDCO lithium-based sensor to determine cardiac output. Research staff were entirely responsible for haemodynamic management within this period, and intensive care unit staff played no part in this aspect of care. All patients received standard measures to maintain oxygenation (SpO_2 ≥94%), haemoglobin (>80 g/L), core temperature (≥36°C), and heart rate (<100 beats per min). Supplemental oxygen, packed red cells, and forced warm-air heating were administered when any of these thresholds were breached. Compound sodium lactate was administered at 1 mL/kg per h as maintenance fluid, with additional fluid administered only by the study research staff guided by pulse rate, arterial pressure, urine output, and central venous saturation. Mean arterial pressure was maintained between 60 mm Hg and 90 mm Hg using an α_1-adrenoceptor agonist as needed. Postoperative analgesia was provided by thoracic epidural infusion (bupivacaine and fentanyl), intravenous infusion, or patient-controlled analgesia (morphine or fentanyl).

The goal-directed therapy group patients received intravenous fluid and inotropic therapy guided by the haemodynamic therapy algorithm (appendix) targeting the preoperative oxygen delivery value for each individual patient. The first hour of the intervention period was dedicated to achieving maximum stroke volume with the use of gelatin colloid only. If the preoperative oxygen delivery target was not met after the first hour of stroke volume optimisation, patients in the goal-directed therapy group also received an intravenous infusion of dobutamine (1–20 mg/kg per min) through a central venous catheter. Administration and dose of dobutamine were strictly controlled by ensuring that heart rate remained at less than 100 beats per min, or not more than 25% from baseline heart rate at the start of the intervention period. If heart rate exceeded one or more of these thresholds, the dobutamine infusion was discontinued. At the end of the 6 h intervention period, dobutamine if needed was titrated to stop over the course of the next hour. Cardiac output monitoring was not done in the usual care (control) group unless specifically requested by clinical staff because of patient deterioration. Haemodynamic parameters were recorded in the control group, but calculation of oxygen delivery values was delayed until the end of the intervention. All other management decisions were taken by senior clinicians who retained the discretion to alter any aspect of patient care, having informed the site principal or chief investigator if this affected haemodynamic management during the study intervention period.

Postoperative management was done according to local clinical guidelines, which for most upper and lower gastrointestinal surgery adhered to enhanced recovery protocols. Surgical antibiotic use at the time of the

	Control (n=102)	Control completed (n=92)	Goal-directed therapy (n=102)	Goal-directed therapy completed (n=95)
Age (years)	68 (9)	68 (9)	68 (9)	68 (9)
Sex				
Male	65 (64%)	56 (61%)	64 (63%)	60 (63%)
Female	37 (36%)	36 (39%)	38 (37%)	35 (37%)
Body-mass index (kg/m²)	27·7 (5·2)	27·7 (5·0)	27·5 (5·4)	27·5 (5·5)
Haemoglobin (g/L)	130 (16)	130 (16)	124 (16)	124 (16)
Albumin (g/L)	42 (5)	43 (5)	42 (5)	42 (5)
Anaerobic threshold (mL/kg per min)	10·8 (2·8)[22]	10·8 (2·8)[22]	10·3 (2·1)[27]	10·3 (2·1)[26]
Malignancy	70 (69%)	64 (70%)	71 (70%)	67 (71%)
Creatinine >130 µmol/L	6 (6%)	6 (7%)	6 (6%)	4 (4%)
Diabetes	22 (22%)	20 (22%)	23 (23%)	21 (22%)
Cerebrovascular disease	7 (7%)	7 (8%)	8 (8%)	8 (8%)
Cardiovascular disease	66 (65%)	62 (67%)	83 (81%)	78 (82%)
Surgical procedure				
Upper gastrointestinal	22 (22%)	21 (23%)	23 (23%)	23 (24%)
Liver resection or hepatobiliary	46 (45%)	39 (42%)	40 (39%)	37 (39%)
Lower gastrointestinal	18 (18%)	16 (17%)	25 (25%)	22 (23%)
Vascular	16 (16%)	16 (17%)	14 (14%)	13 (14%)
Hospital*				
University College London Hospital	36	33	43	40
Royal Free Hospital	41	36	38	36
Royal London Hospital	8	7	7	6
St George's Hospital	16	16	14	13

Data are mean (SD), n (%), or n. For anaerobic threshold, numbers in superscript denote number of patients who underwent preoperative cardiopulmonary exercise test. Randomisation minimisation grouping for surgeries was: upper gastrointestinal surgery; liver resection and hepatobiliary surgery; colorectal and vascular surgery. *One patient was randomised at King's College Hospital but withdrawn, due to unanticipated lack of critical care facility and staff.

Table 1: **Baseline patient characteristics**

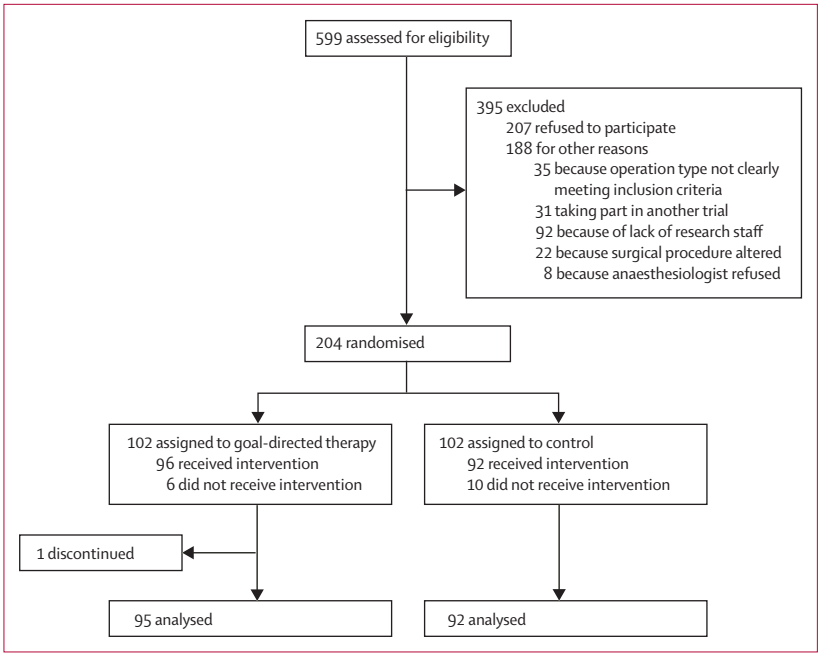

Figure 1: **Trial profile**

	Control (n=92)	Goal-directed therapy (n=95)
Duration (min)	271 (111)	259 (103)
General anaesthetic only	43 (47%)	37 (39%)
General anaesthesia plus epidural	49 (53%)	58 (61%)
Crystalloid (mL/kg per h)	9·3 (7·0–12·1)	10·1 (6·6–13·8)
Colloid (mL/kg per h)	2·1 (0–4·1)	1·4 (0–3·6)
Blood products	16 (17%)	25 (26%)
Vasopressor infusion	21 (23%)	18 (19%)
Haemoglobin (end of surgery; g/L)	108 (71)	107 (52)
Base deficit at end of surgery	−2·6 (1·9)	−2·6 (2·2)
Lactate (end of surgery; mmol/L)	2·0 (1·2)	2·2 (1·7)

Data are mean (SD), median (IQR), or n (%). Excludes patients randomised but who met exclusion criteria by the end of their operation.

Table 2: **Intraoperative clinical management**

operation at all centres was undertaken according to local microbiology policies, on a prophylactic basis (ie, preoperatively and two subsequent doses). Thus, antibiotic use beyond 24 h postoperatively was a deviation from normal postoperative care.

We defined achievement of preoperative oxygen delivery target by analysing mean oxygen delivery throughout the postoperative intervention period, and relating this value to the number of predefined hourly timepoints during the intervention where postoperative oxygen delivery met, or exceeded, preoperative values.

Data entry was done through a secure university site. Automated validation checks included plausibility ranges and cross-checks between data fields. Further manual data checks were done both centrally and through source data verification.

Outcomes

The primary endpoint was the difference in risk (absolute risk reduction, ARR) of acquiring postoperative morbidity, as defined by the Clavien–Dindo scale that deviated from normal postoperative recovery at 48 h after the end of surgery. Morbidity was first objectively identified with the POMS, which assesses morbidity over the preceding 24 h period. Because the POMS does not show severity of morbidity, significant deviations from normal postoperative recovery were graded using the Clavien–Dindo scale.[18] Clavien–Dindo scale of grade II or more defines deviation from normal postoperative recovery. A further independent assessment of Clavien–Dindo grades was done after the trial was completed (ie, all patients had been discharged from hospital), again masked to preoperative and intervention data. Secondary outcomes were time to become morbidity free, and length of hospital stay (adjusting for hospital deaths). Morbidity data were also collected prospectively on designated days beyond postoperative day 2 (appendix), again by assessors masked to the intervention.

Statistical analysis

After moderate surgery, at least 60% of patients on postoperative day 2 sustain one or more POMS-defined morbidity.[17,23] Assuming a significance level of 5% and a power of 80%, 70 patients per group would be needed to detect a clinically important 25% absolute reduction in morbidity. However, since about 15% of the patients were estimated to achieve the oxygen delivery target spontaneously, the sample size was increased by 15% to account for potential failure to adhere to the protocol. The withdrawal and dropout rates were estimated to be about 5%, and therefore the sample size was increased by a further 5%. The final sample size needed was 102 patients per treatment group. The sample size calculation was done using Stata version 10.

Analyses were done according to an a-priori statistical analysis plan including all patients on an intention-to-treat basis, irrespective of protocol compliance. A binomial regression adjusting for hospital (stratification centre) was used for the analysis of the primary outcome. Binomial regression was also used for all secondary binary outcomes. Differences in length of stay and time to become free of morbidity were tested, excluding patients who died during their hospital stay. γ regression analysis was used to assess the difference in mean length of stay. Results of primary and secondary outcomes are reported as ARR with 95% CI, and additionally reported as relative risk (RR) with 95% CI. The prespecified secondary analysis focused on the achievement of preoperative oxygen delivery target (regardless of randomisation group). Normally distributed continuous

variables are presented as mean (SD); all other continuous data are presented as median (IQR). Categorical variables are presented as n (%). Analyses were done using Stata SE version 10.1 or NCSS 8. Significance was p<0·05 (two-tailed). The trial is registered with Controlled Trials, number ISRCTN76894700 (http://www.isrctn.com/ISRCTN76894700).

Role of the funding source

The funding bodies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. All authors had full access to all the data in the study. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled 204 patients between May 20, 2010, and Feb 12, 2014 (appendix). Baseline characteristics were similar between the groups (table 1), with 95 patients allocated to goal-directed therapy and 92 patients allocated to the control group (figure 1). Patients who were enrolled but subsequently excluded from the intervention met exclusion criteria that developed during the operative period (appendix).

Intraoperative duration and management were similar across groups (table 2). In both control and goal-directed therapy groups, similar volumes of fluid were administered during surgery. On admission to the intensive care unit, APACHE II scores were similar between groups (table 3). POMS-defined morbidity on postoperative day 2 occurred in 176 (94%) of 187 patients who completed the postoperative study period (table 4). Clavien–Dindo morbidity grade II or more was recorded on postoperative day 2 in 44 (46%) of 95 patients in the goal-directed therapy group and 49 (53%) of 92 control patients (ARR –7%, 95% CI –22 to 7, p=0·30; RR 0·84, 0·63–1·11, p=0·22). Clavien–Dindo morbidity grade II or more on postoperative day 2 was associated with prolonged hospital stay (appendix). The time to become morbidity free as defined by POMS was similar between goal-directed therapy and control groups (unadjusted HR 1·09, 95% CI 0·82–1·45; figure 2), as was the duration of hospital stay (figure 3, appendix). Mortality was 5%, with no difference in deaths between goal-directed therapy or control groups (ARR 2%, 95% CI –4 to 9).

Although 49 (53%) of 92 patients achieved their preoperative oxygen delivery target in the control group, more patients in the goal-directed therapy group (74 [78%] of 95) met this goal postoperatively (RR 1·46, 95% CI 1·17–1·82). This was achieved, in part, by the goal-directed therapy group receiving more gelatin colloid (+1·2 mL/kg per h, 95% CI 0·72–1·66) than control patients (table 3). After stroke volume optimisation by the end of the first hour of the intervention period, 38 (40%) of 95 patients in the goal-directed therapy group needed dobutamine in an attempt to achieve the preoperative oxygen-delivery target (number needed to treat 3, 95% CI 2–3). A detailed haemodynamic profile

	Control (n=92)	Goal-directed therapy (n=95)
APACHE II score on intensive care unit admission	16 (5)	15 (6)
Crystalloid (mL/kg per h)	1·0 (1·0–1·1)	1·0 (1·0–1·2)
Colloid (mL/kg per h)	1·4 (0–2·8)	2·9 (1·7–3·6)
Blood transfusion	11 (12%)	22 (23%)
Dobutamine infusion	0	38 (40%)

Data presented as mean (SD), median (IQR), or n (%). Excludes patients randomised preoperatively but who met exclusion criteria by the end of their operation. APACHE II=Acute Physiology and Chronic Health Evaluation II.

Table 3: **APACHE II scores and haemodynamic therapy during the postoperative intervention period**

	Control (n=92)	Goal-directed therapy (n=95)	ARR (95% CI)	p value
Clavien–Dindo grade II or more	49 (53%)	44 (46%)	–7 (–22 to 7)	0·30
POMS-defined morbidity	85 (92%)	91 (96%)	–3 (–10 to 3)	0·32
Pulmonary	69 (75%)	79 (83%)	–10 (–22 to 1)	
Infection	34 (37%)	34 (36%)	1 (–13 to 15)	
Renal	76 (83%)	81 (85%)	–3 (–13 to 8)	
Gastrointestinal	55 (60%)	63 (66%)	–7 (–20 to 7)	
Cardiovascular	24 (26%)	27 (28%)	–2 (–15 to 10)	
Neurological	17 (18%)	9 (9%)	9 (–1 to 19)	
Wound	3 (3%)	3 (3%)	0 (–5 to 5)	
Haematological	8 (9%)	11 (12%)	–3 (–12 to 6)	
Pain	67 (73%)	79 (83%)	–10 (–22 to 1)	
Mobility	80 (87%)	85 (89%)	–3 (–12 to 7)	

Data are n (%) unless otherwise stated. Excludes patients randomised preoperatively but who met exclusion criteria by the end of their operation. p values are for prespecified primary outcomes. ARR=absolute risk reduction. POMS=Postoperative Morbidity Survey.

Table 4: **Morbidity on postoperative day 2**

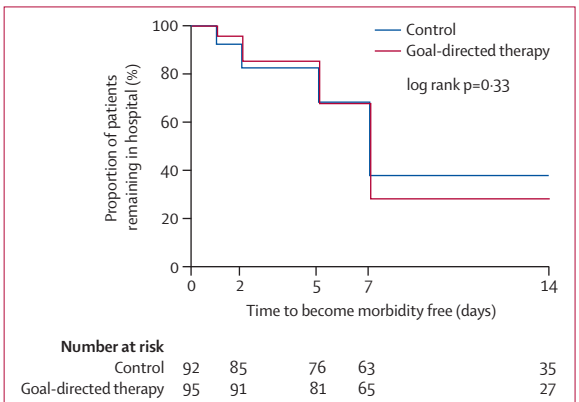

Figure 2: **Kaplan-Meier survival curve by treatment allocation for time to become morbidity free after start of surgery**

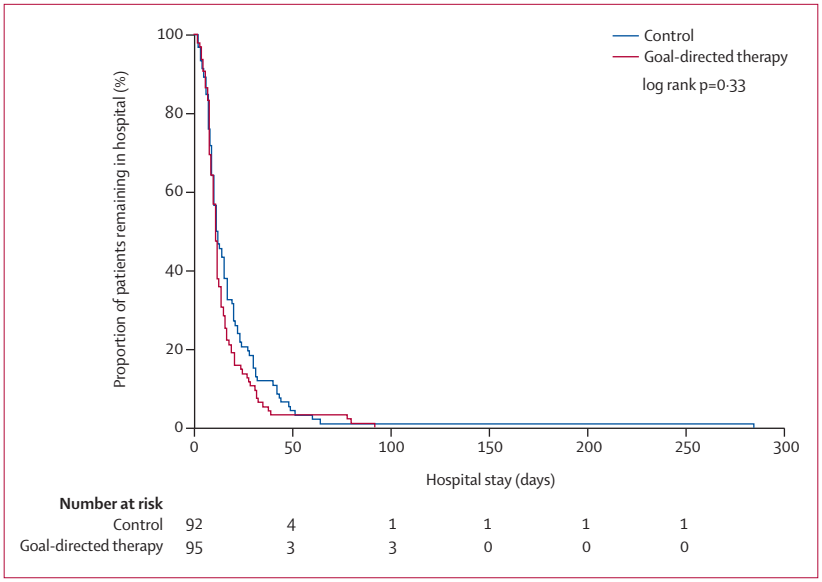

Figure 3: **Kaplan-Meier survival curves by treatment allocation for hospital stay after start of surgery**

	Non-achiever (n=64)	Achiever* (n=123)
Base deficit (end of surgery)	−2·4 (1·9)	−2·7 (2·0)
Lactate at end of surgery (mmol/L)	2·1 (1·2)	2·0 (1·3)
Colloid during intervention (mL/kg per h)	2·1 (0·8–3·2)	2·2 (0·7–3·3)
Dobutamine	15 (23%)	23 (19%)

Data are mean (SD), median (IQR), or n (%). Excludes patients randomised but who met exclusion criteria by the end of their operation. *Achiever defined by at least 2 h of meeting preoperative oxygen delivery target, after fluid resuscitation in first hour of intervention period (see appendix).

Table 5: **Perioperative characteristics of patients who achieved, or failed to achieve, preoperative oxygen delivery target value**

for both control and goal-directed therapy groups is provided in the appendix. There were no serious adverse cardiac events during or after the administration of dobutamine. However, the dobutamine infusion was discontinued in four (11%) of 38 patients who breached the stopping criteria defined by changes in heart rate. There was no deviation from the allocated intervention for patients in either group once the intervention had commenced. One patient returned to the operating room because of bleeding identified within the first hour of the intervention period. No patients needed unmasking of study allocation to attending nurses or physicians on the intensive care unit.

We found that achieving 100% or more mean oxygen delivery of individualised preoperative values throughout the postoperative intervention period was associated with the target being achieved at two or more timepoints (appendix). Sustained achievement of the individual patients' preoperative target was associated with higher oxygen delivery throughout the intervention period. This prespecified secondary analysis showed that achievement of oxygen delivery target (table 5), adjusted for the randomisation group, was associated with a reduction in the number of patients with Clavien–Dindo graded morbidity of II or more on postoperative day 2 (ARR 19%, 95% CI 3–34, p=0·016; appendix). As defined by the POMS, achievement of oxygen delivery target (adjusted for the randomisation group) was associated with fewer patients sustaining infection (ARR 19%, 95% CI 4–34) and wound (ARR 7%, 95% CI 0·2–14) morbidity 48 h postoperatively (appendix). Sensitivity analyses did not show any substantial effect of operation type on ARR in Clavien–Dindo morbidity grade II or more on postoperative day 2 (appendix).

Consistent with our hypothesis that impaired parasympathetic function would be associated with goal-directed therapy, we found that using time-domain measures of parasympathetic activity (n=120 patients), pNN50 and RMSSD were only reduced in patients randomised to the oxygen delivery target (figure 4). These changes occurred despite similar heart rates between the control and goal-directed therapy groups both preoperatively and during the intervention period (figure 4, appendix). Patients randomly assigned to goal-directed therapy were more likely to have abnormal levels (RMSSD <19 ms) of parasympathetic activity (RR 1·33, 95% CI 1·01–1·74). Thoracic epidural analgesia blunts cardiac sympathetic neural drive activity and promotes relative vagal dominance.[24] Exploratory subgroup analysis showed that goal-directed therapy appeared to reduce RMSSD, but no association with thoracic analgesia was observed (figure 4).

Discussion

This multicentre trial is the second largest trial of its type with a specific haemodynamic target in non-cardiac surgery after the OPTIMISE randomised controlled trial.[7] The principal finding of this trial is that achievement of preoperative oxygen delivery soon after major surgery is associated with a reduction in early postoperative morbidity, yet this occurred irrespective of additional postoperative haemodynamic manipulation over and above standard of care. We focused the primary outcome on early postoperative morbidity because the most direct plausible link between pathophysiological mechanisms and deviations from normal postoperative recovery is likely to be most apparent at this timepoint. By contrast with OPTIMISE,[7] our trial was primarily designed to address key mechanistic questions prompted by previous smaller trials of this type of complex intervention.

Minimisation of harmful practices in modern critical care has improved outcomes, rather than any novel therapeutic interventions.[25] In this respect, therapies that result in the unintentional, off-target consequence of reduced parasympathetic activity might be indirectly injurious. The novel mechanistic interrogation from this study suggests that parasympathetic autonomic dysfunction might make a clinically significant

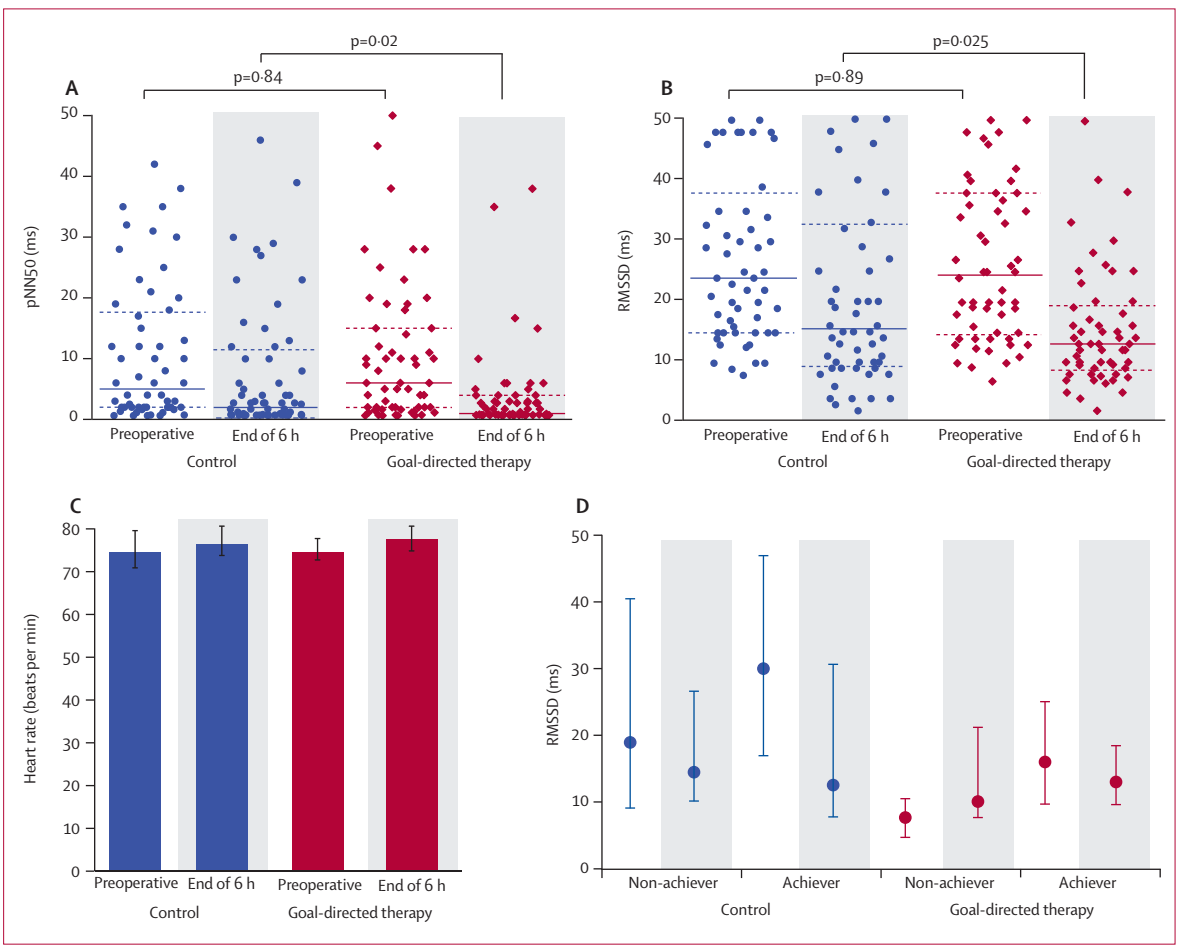

Figure 4: **Perioperative changes in parasympathetic autonomic activity**
(A) Effect of goal-directed therapy on pNN50 (median, 25–75th centiles). Shaded bars show end of intervention period. (B) Effect of goal-directed therapy on RMSSD (median, IQR). Shaded bars show end of intervention period. (C) Parallel values for heart rate (mean, 95% CI). Shaded bars show end of intervention period. (D) Effect of epidural analgesia and successful attainment of preoperative oxygen delivery on RMSSD (median, IQR). Shaded bars show use of thoracic epidural. pNN50=the proportion of number of pairs of successive beat-to-beat intervals that differ by more than 50 ms, divided by total number of beat-to-beat intervals. RMSSD=root mean square of the successive differences.

pathophysiological contribution to postoperative morbidity. Parasympathetic activity at the end of the intervention was reduced in patients randomly assigned to the oxygen delivery target, consistent with the hypothesis that the use of inotropic therapy causes the relatively greater loss of parasympathetic activity. The failure of oxygen target achievement in this group of patients to translate into reduced infectious morbidity might be explained, in part, by reduced parasympathetic activity.

These data confirm the findings of a recent Cochrane systematic review,[8] which concluded that harm was unlikely to be conferred by this type of intervention but that only a subsection of patients might benefit. Preceding trials have not systematically used individualised oxygen delivery targets, but rather aimed at population-based values associated with improved clinical outcomes in observational studies (panel). The extra colloid fluid needed to optimise stroke volume in goal-directed therapy was of a similar magnitude to that reported in preceding studies.[7] A trend to receive increased packed red cells associated with goal-directed therapy was observed in this study. Our data suggest that achievement of preoperative oxygen delivery is sufficient to confer a reduction in morbidity, and therefore minimise the potential off-target effects of inotropic therapy, excess fluid, and iatrogenic blood transfusions. Therefore, our data provide the first prospective dataset supporting the findings of two large retrospective propensity-matched studies that suggested the perioperative use of inotropes (including dobutamine) is associated with worse outcomes after cardiac surgery—independent of oxygen delivery.[26,27]

The strengths of this study include the trial design, which minimised bias by ensuring that both control and intervention haemodynamic management was delivered by research staff with attending intensive care unit staff masked to this complex intervention. Undoubtedly, the trial design by default led to increased attention to

Panel: Research in context

Systematic review

When we designed our study, we searched for articles published between Jan 1, 1980, and April 10, 2009. We searched PubMed and Embase using the terms "oxygen delivery", "preoperative", "goal-directed therapy", and "surgery". The retrieved articles were scrutinised for clinical trials where individualised preoperative oxygen delivery was targeted as a postoperative goal. The retrieved list of articles included a wide range of studies, none of which used individualised oxygen delivery targets to guide postoperative haemodynamic therapy. Secondarily, we assessed whether goal-directed therapy studies in surgical patients assessed autonomic activity, dysfunction of which might occur as a result of this strategy.

Interpretation

Our trial findings confirm that an individualised approach to haemodynamic therapy in higher risk surgery patients is warranted. These data also suggest that there are potentially deleterious, off-target effects of implementing goal-directed therapy (stroke volume optimisation and inotropic support), as evidenced by the development of parasympathetic autonomic dysfunction.

haemodynamic management even in the control group. Nevertheless, operation types included have often been under-represented in preceding trials, perhaps in part because of a widespread—although poorly evidence-based—view that intraoperative minimisation of fluid therapy in liver resection[28] and oesophagectomy[29] surgery is beneficial. Furthermore, the APACHE II scores recorded on admission to the critical care unit postoperatively are indicative of this trial focusing on high-risk patients or procedures. In addition to the difficulties of maintaining masking of fluid administration during complex operations, we elected to undertake this study as an immediate postoperative intervention when preservation of masking is achievable and physiological stability established. The challenges of embarking on such a trial were borne out by about a 7% dropout rate, primarily due to adverse intraoperative events or substantial changes in planned surgery because of disseminated malignancy (slightly more than we had estimated in the trial design). Importantly, outcomes data were collected and verified by masked assessors. The intervention design took into account the increasingly recognised risk of myocardial injury because of undue tachycardia, with tightly controlled criteria to avoid potential harmful effects of fluid and inotropic therapy.

The study had several limitations. Although the control group is likely to have benefited from dedicated research staff delivering haemodynamic management, this does not reflect standard practice. The postoperative APACHE II scores show that this was a particularly high-risk population, and for lower-risk patients there might be a different risk–benefit profile. In many hospitals, similar patients would be discharged postoperatively to a general ward. We also acknowledge that beyond clinical trials, the real-world manipulation of Starling cardiac physiology and Guyton's model of venous return function generates substantial pragmatic challenges. Our predicted event rate for early morbidity deviating from the normal trajectory for postoperative recovery was accurate, but the crossover of postoperative oxygen delivery achievers in the control group was substantially higher than we had anticipated (and exceeded several previous trials). This factor alone substantially reduces the power of the trial, but does not alter several key observations. Although several patients' Holter data could not be used (mainly because of dysrhythmias, logistic reasons, and poor data quality), this is a common and widely acknowledged challenge of doing such studies in real-world clinical environments. Even in highly controlled situations with minimum interference (eg, critical care neuromyopathy), more than 25% of data cannot be used.[30] We acknowledge that this clinical setting does not lend itself to standardisation of controlled recording conditions, but serial measurement of these autonomic parameters indicates substantial changes perioperatively. Heart rate variability analysis provides little information about the localisation of where such neural dysfunction might occur. The reduction in parasympathetic heart rate variability could occur because of changes at the level of the cardiac pacemaker cells rather than dysfunction of the parasympathetic division of the autonomic nervous system. Although gelatin colloid was specified in the trial protocol, the avoidance of starch as a standard of care appears warranted in this patient group with a high risk of developing postoperative sepsis.[31]

Several trials in high-risk surgical patients have suggested that adequate postoperative oxygen delivery is associated with improved outcomes. By contrast, the recent PROCESS[32] and ARISE[33] trials reported that early goal-directed therapy in early sepsis or systemic inflammation failed to show any benefit over and above routine care. Consistent with these data, we have shown that achievement of preoperative oxygen delivery values was associated with reduced postoperative morbidity, irrespective of postoperative intervention. Our data are the first to prospectively show that haemodynamic management strategies might result in off-target effects that potentially disrupt homoeostatic mechanisms conferring cellular protection. Further work is needed to establish whether autonomic dysfunction exerts a direct, or indirect, effect on the development of postoperative morbidity. These data suggest that an enhanced mechanistic understanding of the consequences of haemodynamic management might reveal novel strategies to improve surgical critical care outcomes.

Contributors

GLA developed the study concept. GLA and MS developed the study design. GLA, SVM, MH, MC, and RMP were responsible for trial administration and data collection at each site. GLA obtained trial

funding and did some of the statistical analyses. RZO contributed to the design and did some of the statistical analyses. SI, LGP, AT, CL, JW, AR, and PB were responsible for postoperative haemodynamic care or postoperative data collection. SK checked postoperative morbidity data. NJ cleaned and analysed Holter data. GLA drafted the manuscript for critical appraisal by all authors. GLA is the guarantor.

Declaration of interests

GLA, JW, and AT through UCL Business have a patent filed related to assessment of autonomic function (patent application 1414161.8). RP has received equipment loans from LiDCO, a research grant from Circassia Holdings, and has done consultancy work for Edwards Lifesciences, Covidien, and Masimo. Cardiac output monitoring equipment and consumables were provided without charge by LiDCO. MS reports consultancy fees and research funds from Deltex Medical. MC has received honoraria or travel expenses or both from Edwards Lifesciences, LiDCO, Cheetah Medical, Bmeye, Masimo, and Deltex Medical. The other authors declare no competing interests.

Acknowledgments

The trial was funded through an Academy of Medical Sciences and Health Foundation Clinician Scientist Award held by GLA. Part of this work was done at University College London Hospital and University College London which received a proportion of funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centre's funding scheme.

References

1 Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; **372:** 139–44.

2 Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; **380:** 1059–65.

3 Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 2005; **242:** 326–41.

4 Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med* 2009; **360:** 1418–28.

5 Head J, Ferrie JE, Alexanderson K, et al. Diagnosis-specific sickness absence as a predictor of mortality: the Whitehall II prospective cohort study. *BMJ* 2008; **337:** a1469.

6 Ackland GL, Edwards M. Defining higher-risk surgery. *Curr Opin Crit Care* 2010; **16:** 339–46.

7 Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA* 2014; **311:** 2181–90.

8 Grocott MP, Dushianthan A, Hamilton MA, et al. Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery. *Cochrane Database Syst Rev* 2012; **11:** CD004082.

9 Amar D, Fleisher M, Pantuck CB, et al. Persistent alterations of the autonomic nervous system after noncardiac surgery. *Anesthesiology* 1998; **89:** 30–42.

10 Annane D, Trabold F, Sharshar T, et al. Inappropriate sympathetic activation at onset of septic shock: a spectral analysis approach. *Am J Respir Crit Care Med* 1999; **160**: 458–65.

11 Andersson U, Tracey KJ. Neural reflexes in inflammation and immunity. *J Exp Med* 2012; **209:** 1057–68.

12 Mastitskaya S, Marina N, Gourine A, et al. Cardioprotection evoked by remote ischaemic preconditioning is critically dependent on the activity of vagal pre-ganglionic neurones. *Cardiovasc Res* 2012; **95:** 487–94.

13 Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; **120:** 564–78.

14 Andersson U, Tracey KJ. Reflex principles of immunological homeostasis. *Annu Rev Immunol* 2012; **30:** 313–35.

15 Hogue CW Jr, Davila-Roman VG, Stein PK, et al. Alterations in heart rate variability in patients undergoing dobutamine stress echocardiography, including patients with neurocardiogenic hypotension. *Am Heart J* 1995; **130:** 1203–09.

16 van de Borne P, Heron S, Nguyen H, et al. Arterial baroreflex control of the sinus node during dobutamine exercise stress testing. *Hypertension* 1999; **33:** 987–91.

17 Bennett-Guerrero E, Welsby I, Dunn TJ, et al. The use of a postoperative morbidity survey to evaluate patients with prolonged hospitalization after routine, moderate-risk, elective surgery. *Anesth Analg* 1999; **89:** 514–19.

18 Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250:** 187–96.

19 Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; **93:** 1043–65.

20 Sinnreich R, Kark JD, Friedlander Y, et al. Five minute recordings of heart rate variability for population studies: repeatability and age–sex characteristics. *Heart* 1998; **80:** 156–62.

21 Nunan D, Sandercock GR, Brodie DA. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *Pacing Clin Electrophysiol* 2010; **33:** 1407–17.

22 Cecconi M, Dawson D, Grounds RM, Rhodes A. Lithium dilution cardiac output measurement in the critically ill patient: determination of precision of the technique. *Intensive Care Med* 2009; **35:** 498–504.

23 Ackland GL, Moran N, Cone S, et al. Chronic kidney disease and postoperative morbidity after elective orthopedic surgery. *Anesth Analg* 2010; **112:** 1375–81.

24 Licker M, Spiliopoulos A, Tschopp JM. Influence of thoracic epidural analgesia on cardiovascular autonomic control after thoracic surgery. *Br J Anaesth* 2003; **91:** 525–31.

25 Singer M, Glynne P. Treating critical illness: the importance of first doing no harm. *PLoS Med* 2005; **2:** e167.

26 Fellahi JL, Parienti JJ, Hanouz JL, et al. Perioperative use of dobutamine in cardiac surgery and adverse cardiac outcome: propensity-adjusted analyses. *Anesthesiology* 2008; **108:** 979–87.

27 Shahin J, DeVarennes B, Tse CW, et al. The relationship between inotrope exposure, six-hour postoperative physiological variables, hospital mortality and renal dysfunction in patients undergoing cardiac surgery. *Crit Care* 2011; **15:** R162.

28 Mise Y, Sakamoto Y, Ishizawa T, et al. A worldwide survey of the current daily practice in liver surgery. *Liver Cancer* 2013; **2:** 55–66.

29 Wei S, Tian J, Song X, et al. Association of perioperative fluid balance and adverse surgical outcomes in esophageal cancer and esophagogastric junction cancer. *Ann Thorac Surg* 2008; **86:** 266–72.

30 Wieske L, Chan Pin Yin DR, Verhamme C, et al. Autonomic dysfunction in ICU-acquired weakness: a prospective observational pilot study. *Intensive Care Med* 2013; **39:** 1610–17.

31 Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med* 2013; **369:** 2462–63.

32 Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; **370:** 1683–93.

33 Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; **371:** 1496–506.