ORIGINAL CLINICAL RESEARCH REPORT

Central Venous-to-Arterial CO_2 Difference–Assisted Goal-Directed Hemodynamic Management During Major Surgery—A Randomized Controlled Trial

Lohith Kumar H N, MD,*† Swagata Tripathy, MD, DNB, IDCC, EDIC,‡§ and Prasanta Kumar Das, MD, DM*

BACKGROUND: Different goals have guided goal-directed therapy (GDT). Protocols aiming for central venous-to-arterial carbon dioxide gap (DCO_2) <6 mm Hg have improved organ function in septic shock. Evidence for use of DCO_2 in the perioperative period is scarce. We aimed to determine if a GDT protocol using central venous saturation of oxygen ($SCvo_2$) and DCO_2 reduced organ dysfunction and intensive care unit (ICU) stay in American Society of Anesthesiologist (ASA) I and II patients undergoing major surgeries compared to pragmatic goal-directed care.

METHODS: One hundred patients were randomized. Arterial and venous blood-gas values were recorded every 2 hours perioperatively for all patients. Intervention group (GrI) with access to both values was managed per protocol based on DCO_2 and $SCvo_2$. Dobutamine infusion 3 to 5 µg/kg/min started if DCO_2 >6 mm Hg after correcting all macrocirculatory end points. Control group (GrC) had access only to arterial-gas values and managed per "conventional" goals without DCO_2 or $SCvo_2$. Patients were followed for 48 hours after surgery. Organ dysfunction, sequential organ failure assessment (SOFA) scores—primary outcome, length of stay in ICU, and duration of postoperative mechanical ventilation and hospital stay were recorded. The patient, surgeons, ICU team, and analyzer were blinded to group allocation.

RESULTS: The groups (44 each) did not significantly differ with respect to baseline characteristics. Perioperative fluids, blood products, and vasopressors used did not significantly differ. The GrI had less organ dysfunction although not significant (79% vs 66%; $P = .2$). Length of ICU stay in the GrI was significantly less (1.52; standard deviation [SD], 0.82 vs 2.18; SD, 1.08 days; $P = .002$). Mechanical ventilation duration (0.9 days in intervention versus 0.6 days in control; $P = .06$) and length of hospital stay did not significantly differ between the groups. Perioperative DCO_2 (5.8 vs 8.4 mm Hg; $P < .001$) and $SCvo_2$ (73.5 vs 68.4 mm Hg; $P < .001$) were significantly better in the GrI.

CONCLUSIONS: GDT guided by DCO_2 did not improve organ function in our cohort. It resulted in greater use of dobutamine, improved tissue oxygen parameters, and decreased length of ICU stay. More evidence is needed for the routine use of DCO_2 in sicker patients. In the absence of cardiac output monitors, it may be a readily available, less-expensive, and underutilized parameter for major surgical procedures. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Does a central venous-to-arterial CO2 difference (DCO_2)–based goal-directed protocol improve perioperative outcomes in patients undergoing major surgeries compared to pragmatic goal-directed therapy?
- **Findings:** Patients in the intervention group received more inotrope, had significantly better tissue oxygenation (central venous saturation of oxygen [$SCvo_2$] and DCO_2) for the duration of implementation of the protocol, and had a shorter intensive care unit (ICU) stay, but there was no significant difference in organ dysfunction between the groups.
- **Meaning:** DCO_2-based protocol can guide perioperative fluid management and improve outcomes; it may be explored further as an economic, physiologic substitute for CO monitoring devices.

GLOSSARY

ABG = arterial blood gas; **ARDSnet** = Acute Respiratory Distress Syndrome Clinical Network; **ARDSnet** = Acute Respiratory Distress Syndrome Clinical Network; **ASA** = American Society of Anesthesiologist; **CG** = control group; **CI** = cardiac index; **CO** = cardiac output; **CONSORT** = Consolidated Standards of Reporting Trials; **CvBG** = baseline arterial blood gas and central venous; **CVP** = central venous pressure; **DCO_2** = central venous to arterial CO_2 difference; **DO_2** = delivery of oxygen; **FIO_2** = fraction of oxygen in inspired air; **GCS** = Glasgow Coma Scale; **GD** = goal-directed; **GDT** = goal-directed therapy; **GrC** = control group; **GrI** = intervention group; **Hb** = hemoglobin; **HCO_3** = bicarbonate; **IABP** = invasive arterial blood pressure; **ICU** = intensive care unit; **IG** = interventional group; **MAP** = mean arterial pressure; **OPTIMISE** = Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcomes; **OR** = odds ratio; **$Paco_2$** = arterial partial pressure of

carbon dioxide; **Pa_{O_2}** = arterial Po_2; **PCv_{O_2}** = central venous Po_2; **PEEP** = positive end-expiratory pressure; **PF** = Pao2/Fio2; **P_{O_2}** = partial pressure of oxygen; **POD** = postoperative day; **PP** = pulse pressure; **PPV** = pulse pressure variation; **PRBC** = packed red blood cells; **RASS** = Richmond Agitation Sedation Score; **RCT** = randomized controlled trial; **Sa_{O_2}** = arterial saturation of oxygen; **SCv_{O_2}** = central venous saturation of oxygen; **SD** = standard deviation; **SICU** = surgical intensive care unit; **SOFA** = Sequential Organ Failure Assessment; **VO_2** = oxygen consumption

The optimal protocol for perioperative fluid management is debated: goal-directed fluid therapy (GDT), restrictive fluid management, and perioperative "zero balance" advocated by different groups.[1–3] In a recent meta-analysis of perioperative fluid administration-outcomes over 20 years,[4] complete hemodynamics bundle protocols (protocolized fluids, inotrope, and vasopressor) had better outcomes than fluid-only management.[5]

The ultimate aim of resuscitation is to match metabolic oxygen consumption (VO_2) to the oxygen delivery (DO_2).[6] In critically ill patients, GDT directed by macrocirculatory goals of arterial pressure (MAP), central venous pressure (CVP), or cardiac index (CI) have failed to improve outcomes.[7] Macrocirculatory end points predict peripheral demand-supply poorly and miss hypoperfusion-related organ dysfunction.[8] In this context, central venous oxygen saturation (SCv_{O_2}) has been used to indicate tissue oxygenation and trigger transfusion of fluids, blood products, and inotropes in septic shock and high-risk surgery patients.[9] However, severe fluctuations in values, unclear thresholds, and limited interpretation in high SCv_{O_2} situations have restricted its utility as a marker of adequate tissue microcirculation.[10]

The venous-to-arterial carbon dioxide difference ($P[v\text{-}a]CO_2$, or central venous to arterial CO2 difference [DCO_2]) has shown promising results as a surrogate for tissue perfusion.[8,11] It is considered more reliable than SCv_{O_2} and lactate[12] in detecting underresuscitation after optimizing parameters like SCv_{O_2} and CI. Raised DCO_2 can guide the individualized use of inotropes.[13,14] The complementary use of DCO_2 helps adjust the right DO_2 to both VO_2 and CO2 production since the impaired oxygenation threshold value for SCv_{O_2} is unclear.[6] Used along with SCv_{O_2} in GDT protocols, it has improved outcomes and predicted morbidity in patients in intensive care units (ICUs).[15] DCO_2 has been used in conjunction with SCv_{O_2} perioperatively to identify persistent low flow after preload optimization in observational studies.[16,17] There are no randomized controlled trials (RCTs) comparing a DCO_2-based GDT protocol over non-DCO_2–based care.

We hypothesized that a GDT protocol incorporating SCv_{O_2} and DCO_2 would improve patient outcomes than management based on pragmatic goals (routine care) in patients undergoing major surgeries. Therefore, we aimed to compare the incidence of postoperative organ dysfunction (primary outcome), duration of mechanical ventilation, length of ICU, and hospital stay (secondary outcomes) between a group managed with DCO_2-guided GDT protocol and 1 guided by pragmatic goals.

METHODS

Trial Design

This was a single-center, double-blinded, parallel-group, randomized clinical trial conducted in an 800-bedded university teaching institute from July 2018 to May 2020. The institutional ethical committee of All India Institute of Medical Sciences, Bhubaneswar, approved the study. It was conducted in accordance with the Declaration of Helsinki, externally audited, and supported by the All India Institute of Medical Sciences Research Unit as a part of the postgraduate thesis assessment. The university's institutional review board (Institutional Review Board Institutional Ethical Committee AIIMS BBSR/PG Thesis/2018-19/07) approved this study, and written informed consent was obtained from all subjects participating in the trial. The trial was registered prospectively at Central Trials Registry of India—CTRI/2018/07/014987 on 20/07/2018 by Principal Investigator S. Tripathy. The Consolidated Standards

From the *Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, Bhubaneswar, India; †Department of Neuroanaesthesia, National Institute of Mental Health and Neurosciences, Bengaluru, India; ‡Department of Neuroanesthesia & Critical Care, Liverpool, United Kingdom; and §Department of Anesthesia & Intensive Care, Central ICU, All India Institute of Medical Sciences, Bhubaneswar, India

Accepted for publication October 27, 2021.

Funding: The study, being a postgraduate MD thesis research, was funded by the institute.

The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

We have presented a subset of our findings at the Yuva Indian Society of Anaesthesia National Online Conference, for which the first prize was awarded on September 6, 2020.

Reprints will not be available from the authors.

The trial was registered prospectively at Central Trials Registry of India—CTRI/2018/07/014987 on July 20, 2018, by Principal Investigator S. Tripathy; http://ctri.nic.in/Clinicaltrials/login.php?id=

Address correspondence to Swagata Tripathy, MD, DNB, IDCC, EDIC, Room no. 406, Academic Block, Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, Bhubaneswar 750019, India. Address e-mail to tripathyswagata@gmail.com.

DOI: 10.1213/ANE.0000000000005833

of Reporting Trials (CONSORT) statement and the extension on pragmatic trials adhered to.[18]

Participants and Inclusion Criteria

American Society of Anesthesiologist (ASA) I and II patients undergoing elective major surgeries and planned for arterial and central venous catheters were included. All surgeries expected to last >4 hours, opening great cavities of the body, holding a possibility of extensive fluid shift or blood loss, and posing a threat to life were considered major surgeries.[19] Patients who refused to consent, with a history of organ failure, preoperative sepsis, or undergoing emergency surgery were excluded.

Study Protocol

Experienced anesthetists supervised major surgeries and used a balanced anesthesia technique. General Electric Avance CS2 or Drager Primus anesthesia machines were used with routine intraoperative invasive monitoring. Premedication consisted of midazolam (0.01 mg kg^{-1}), and standard general anesthesia was induced with fentanyl 1 to 2 µg kg^{-1}, propofol 1.5 to 2 mg kg^{-1}, and atracurium 0.5 mg kg^{-1} or vecuronium 0.08 mg kg^{-1}. After intubation, patients were ventilated to maintain normocapnia (end-expiratory partial pressure of carbon dioxide level 32–38 mm Hg) using a constant fresh gas flow of 1 to 2 L min^{-1}. Maintenance of anesthesia was with 1.2% to 1.5% end-tidal isoflurane:fentanyl, and relaxant was given as needed. Standard monitoring included electrocardiogram, invasive arterial blood pressure via right or left radial artery, pulse oximetry, temperature, and inspiratory and expiratory gas concentrations.

In both the groups, central lines were inserted after induction of anesthesia under a real-time ultrasound-guided technique, confirming the position of the tip.[20] Patients were ventilated with a 6 to 8 mL per kg tidal volume, increased to 10 mL/kg when assessing pulse pressure variation (PPV).[21]

Arterial blood gases (ABGs) and lab investigations were available within a 5- and 15-minute turnaround time, respectively. Baseline ABG and central venous (CvBG) samples were obtained before incision in both groups, ensuring that, then and after that, all paired samples were taken simultaneously. The samples were taken every 2 hours, until the end of surgery. Both the groups could start an infusion of noradrenaline if MAP was <65 mm Hg (or 10% below preanesthesia levels in hypertensive patients) despite correction of other parameters.

Control Group. Patients were managed toward normotension, normovolemia, normocarbia, and normothermia. Targets were an MAP >65 mm Hg (in normotensives and adjusted to 10% of premorbid status for hypertensives), urine output >0.5 mL/kg/min, lactate <2 mmol/dL, and hemoglobin (Hb) >8 gm%. Anesthetists had access to hemodynamic parameters (central venous and arterial blood pressures), hourly urine output, second hourly arterial (but not central venous) blood gas, lactates, intraoperative ultrasonogram, and clinical judgment to guide fluid therapy. While an automated PPV module was not available on all anesthesia monitors, the control-group anesthetists could use a manual measurement (admittedly less accurate, by slowing the invasive arterial blood pressure [IABP] sweep speed, applying cursors, freezing the screen, and using the formula PPV = [(pulse pressure {PP} max − PP min) / PP mean] × 100) or by simply eyeballing the waveform.[22] The anesthetist was provided the ABG results but kept blind to the CvBG results. A fixed number of senior staff members in the anesthesia team (4) handled all cases among themselves. The hemodynamic protocol was broadly similar for all control patients but not guided by DCO_2 or $SCvo_2$.

Intervention Group. The hemodynamic management was protocolized in the intervention group (GrI) (Figure 1). A "Mindray Beneview T8" monitor was used to monitor PPV values. Both the arterial and venous sample analysis reports were available to the anesthetist. An $SCvo_2$ >75% with DCO_2 >6 mm Hg was managed with a crystalloid bolus of 250 mL (if PPV >12) or dobutamine at 3 µg/kg/min (if PPV <12). If $SCvo_2$ was <75% and arterial saturation of oxygen (Sao_2) <95%, fractional inspired oxygen (FIo_2), and positive end-expiratory pressure (PEEP) were adjusted following ARDSnet (Acute Respiratory Distress Syndrome Clinical Network) low-PEEP high-FIo_2 protocol. If $SCvo_2$ was <75% and Sao_2 >95% with optimum Hb, DCO_2 was enquired. If DCO_2 was >6 mm Hg, a crystalloid bolus of 250 mL (if PPV >12) or dobutamine infusion started at 3 µg/kg/min (if PPV <12) and titrated to response of the DCO_2 values, maximum up to 5 mcg/kg/min. There was no further intervention if DCO_2 was ≤6 mm Hg. Lactate values were not considered for intervention.

Postoperative

All patients, extubated or not, were shifted to the surgical intensive care unit (SICU) postoperatively. The respective hemodynamic management protocols were followed for either group until 12 hours after surgery.

Patients of both groups received the sedation (if intubated) and analgesics as per ICU protocol—aiming for a visual analog pain score of <4 and a Richmond Agitation Sedation Score (RASS) score of −1 to +1. After 12 hours of surgery, all documentary evidence that would indicate the patients' group was removed from the files. The ICU team (without anyone from the research team) decided on the weaning and extubation for intubated patients.

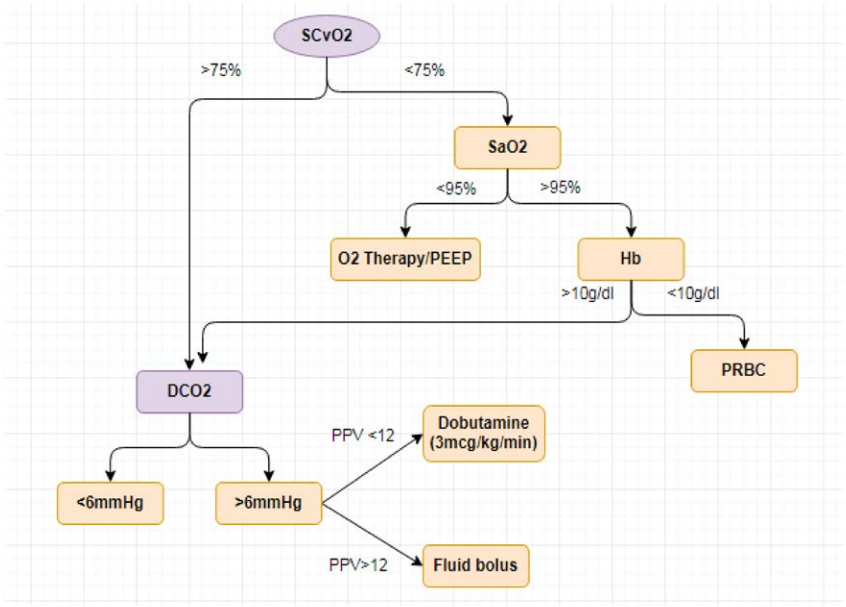

Figure 1. Protocol diagram. DCO_2 indicates central venous to arterial CO_2 difference; Hb, hemoglobin; PEEP, positive end-expiratory pressure; PPV, pulse pressure variation; PRBC, packed red blood cells; SaO_2, arterial saturation of oxygen; $SCvo_2$, central venous oxygen saturation.

Fluid bolus given was 4ml/kg or 250 ml, whichever is lower.

Before recording PPV, tidal volume was set to 10ml/kg

Discharge from the ICU was by a surgeon-ICU team combined decision, based on objective criteria, similar for all patients (patient is conscious and extubated, maintaining arterial partial pressure of oxygen (Po2) [Pao_2] >80 mm Hg on FIo_2 <35%; hemodynamically stable without inotropes; serum lactate <3 mmol/L; urine output >1.0 mL/kg/h; organ function (SOFA) the same as or better than preoperative values; they have a pain management plan in place).

Data Collected

Patient demographics, type of surgery, comorbidities, and organ function status by SOFA scores[23] were collected. Intraoperative hemodynamic and respiratory parameters (heart rate, mean arterial pressures [MAPs], PPV, minute ventilation, fluid-blood product balance, dobutamine, and noradrenaline infusion rates) were recorded at the time of blood sampling. $SCvo_2$, central venous Po2 ($PCvo_2$), DCO_2, arterial partial pressure of carbon dioxide ($Paco_2$), Sao_2, Po_2, Hb, bicarbonate (HCO_3), chloride, and lactate were documented from each blood gas report fourth hourly for 12 hours after shifting to ICU. In the ICU, Pao_2, FIo_2, platelet count, bilirubin levels, MAP, Glasgow Coma Scale (GCS), and creatinine levels were noted to calculate the Sequential Organ Failure Assessment (SOFA) scores up to day 2 after surgery. All data were collected for both groups.

Outcomes

Postoperative organ dysfunction data were collected as a dichotomous variable using the SOFA score based on the following 6 variables: Pao_2/FIo_2 (PF) for the respiratory function, bilirubin for the hepatic function, hypotension for the cardiovascular function, creatinine or urine output for the renal function, and the Glasgow Coma Scale for the central nervous system status. A rise from preoperative SOFA score (usually 0, in ASA I/II patients) by one or more points was interpreted as organ dysfunction. The dysfunction incidence was compared between the 2 groups on postoperative days (PODs) 0, 1, and 2.

Lengths of mechanical ventilation, ICU stay, and hospital stay were recorded in days.

Randomization and Blinding

Patients were randomized into interventional and control groups through computer-generated random numbers. Independent personnel, not a part of the study team, prepared the allocation sequence. Sealed opaque envelopes concealed allocation. Eligible patients were explained the trial and signed the consent form the evening before the surgery. The next day, they were randomized in the operation theater and randomly allocated to intervention or control groups by assigning them a sequentially numbered envelope. An operation theater personnel not involved in the study opened the sealed envelope. A laminated printout of the protocol was hung on the anesthesia machine if randomized to the GrI.

In the postoperative period, the ICU team was blind to group allocation made inside the operation theater. One member of the research team followed

the CvBG reports of all patients for the first 12 hours after surgery and gave protocol-based instructions as appropriate. The end points—hemodynamics, blood gas reports and lab parameters for SOFA scores, and length of ventilation were objective parameters, with blood samples being dispatched and data entered by a team separate from the research team, blind to the protocol. Teams deciding ICU discharge were separate from the research team: all indications of the research were removed from the patient file after 12 hours and before discharge (discharge being a minimum of 12 hours postsurgery). The patient, team deciding discharge, persons dispatching investigations, data collector, and analyzer were blinded.

Sample Size and Statistical Analysis

The number of patients required in each group was determined before the study by a power calculation based on the results of a similar previous study[24] by using a 2-sample proportion test to compare the rate of organ dysfunction between the groups. To detect a 30% difference in the primary end point of organ dysfunction, with an assumed α error of 0.05 (2-sided) and type II error of 0.2, 38 patients per group were required. The assumed effect size was 0.4 (relative risk for developing organ failure in the GrI) based on the previous observational study. To compensate for possible dropouts, we decided to include 45 patients per group.

Variables such as gender and ASA physical status were tabulated and presented with standardized differences between the groups. Continuous variables such as age, Hb, $SCvo_2$, DCO_2, lactate, fluid input, urine output, ICU, and hospital stay were expressed as central tendency (mean) dispersion (standard deviation [SD]) and analyzed using the unpaired Student *t* test. Incidence of events was tabulated as frequencies and compared between the groups using the χ^2 test or Fisher exact test. All variables were checked for normal distribution using the Shapiro-Wilk test. All statistical analysis was performed using SPSS (Version 25, IBM Corp).

RESULTS

Of 135 patients assessed for eligibility, 35 were excluded: 20 for not meeting the inclusion criteria, 9 for lack of consent, and 6 for unanticipated surgery postponement. One hundred patients were randomized: 6 from each group were excluded for missed postoperative blood samples, calibration issues with the ABG machine, and inoperability leading to abandoned surgery (Figure 2).

Baseline Characteristics

The groups were well balanced in terms of age, gender, ASA status, surgical subspecialties, and duration of surgery (Table 1).

Intraoperative Parameters. The intraoperative DCO_2 level in the GrI (mean, 5.64; SD, 1.83 mm Hg) was significantly less than the control group (mean, 8.29; SD, 2.93 mm Hg), t (86) = 5.1; P = <.001. The intraoperative hemodynamics, Hb, $SCvo_2$, lactate, fluid input, and urine output did not significantly differ between the interventional and control groups (Table 2). A significantly greater number of patients in the GrI were administered dobutamine (12 vs 0; P < .001), dose ranging from 3 to 5 µg/kg/min (Figure 3).

Postoperative Parameters. The postoperative DCO_2 level in the GrI was significantly less (mean, 5.8; SD, 1.4 mm Hg) versus (8.4; SD, 2.3 mm Hg), t(86) = 6.4; P = <.001. The postoperative $SCvo_2$ level in interventional group (M = 73.56; S = 5.16) compared with control group (M = 68.38; S = 6.45) was significantly greater, t(86) = −4.1; P = <0.001 (Figure 3). The hemoglobin, lactate, fluid input, and urine output did not significantly differ between the groups (Table 2).

Outcome Parameters. The incidence of organ dysfunction was not significantly different between the groups, although the incidence was greater in the control group (79% vs 66%; odds ratio, 0.5; P = .2). The organ-system wise changes in SOFA scores were not significantly different between the groups in the postoperative follow-up (Supplemental Digital Content 1, Table 1, http://links.lww.com/AA/D758). Among the different organ systems assessed by the SOFA scores, a post hoc analysis showed significantly better pulmonary status (PF ratio) on PODs 1 and 2 in the GrI: POD 1, 436 (38.2) vs 418 (33.4) mm Hg; P = .02; CI, −33 to −3; and POD 2, 428 (30.3) vs 416 (17.0) mm Hg; P = .03; CI, −22 to −1.

The length of ICU stay in the interventional group (mean, 1.52; SD, 0.82 days) was significantly less than the control group (mean, 2.18; SD, = 1.08 days) (t = 3.21; P = .002). The mechanical ventilation duration was less in the GrI than the control group (0.6 vs 0.9 days; P = .06). The length of hospital stay did not significantly differ between the groups (Table 3).

DISCUSSION

In this double-blind RCT, we hypothesized that DCO_2 would be useful for individualizing microvascular targeted GDT in major surgeries[16] and conducted a randomized trial to test the theory. We found that using a protocol targeting both macro (MAP and PPV) and microcirculatory goals ($SCvo_2$ and DO_2) did not significantly reduce the incidence of organ dysfunction in our patients. The length of ICU stay was significantly decreased in the GrI. There was no difference in the length of mechanical ventilation or hospital stay.

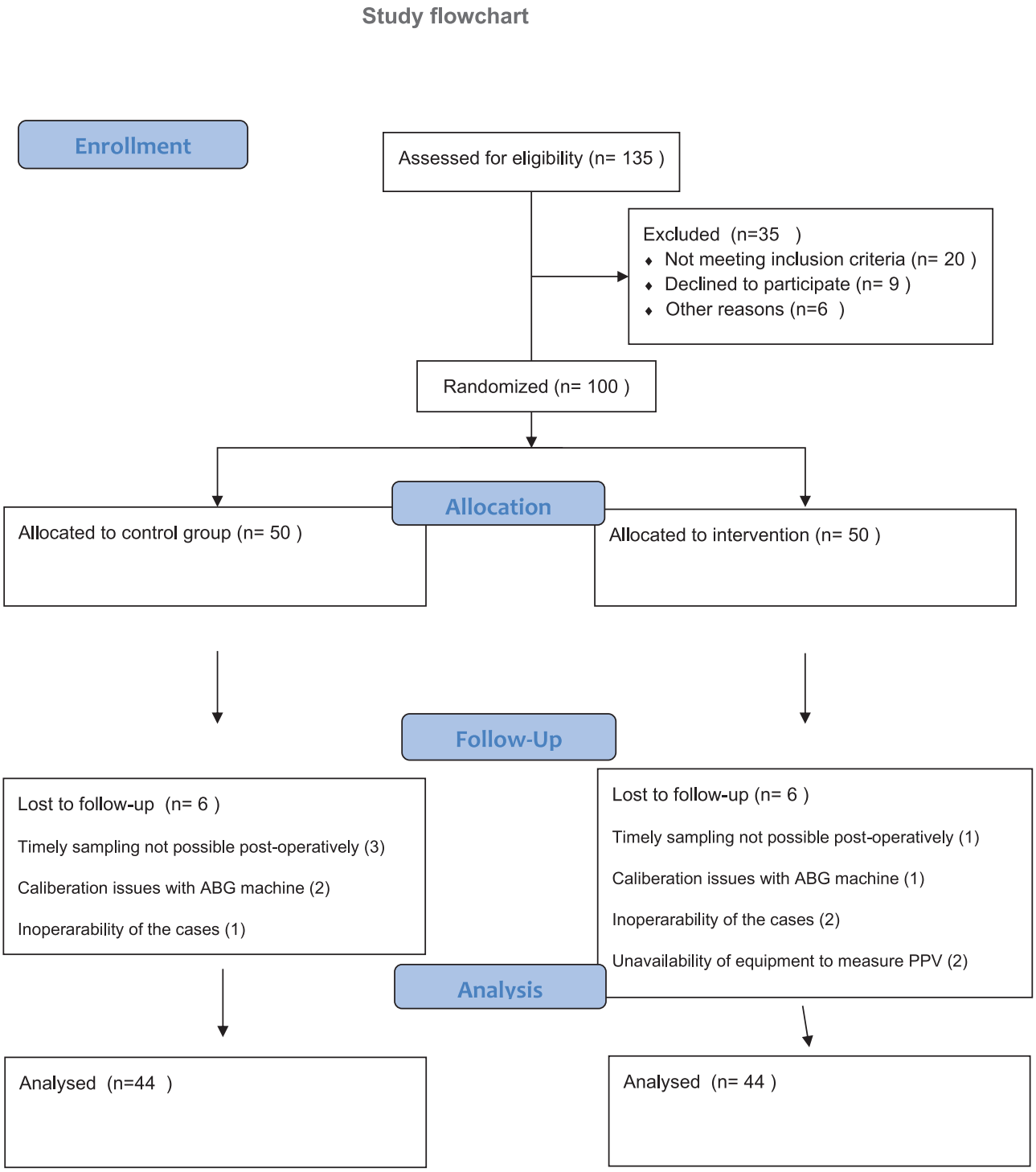

Figure 2. Study flowchart as per CONSORT guidelines. ABG indicates arterial blood gas; CONSORT, Consolidated Standards of Reporting Trials; PPV, pulse pressure variation.

Outcome Parameters

The absence of difference in organ dysfunction between groups is perhaps due to the low-risk status of our cohort. GDT demonstrates greatest benefit in patients with the highest risk.[25] Previous studies using goal-directed (GD) hemodynamic intervention in low-to-moderate risk patients undergoing major surgeries have failed to differentiate between the groups.[26] Ito et al,[27] in patients with risk profiles similar to ours, demonstrated improved global oxygen delivery and tissue oxygenation in the GrI: barring a decrease in acute kidney injury, complication rates between groups.

A decrease in ICU stay, without (a significant) difference in organ dysfunction, was likewise observed by Pearse et al[7] in a patient cohort with predominantly

Table 1. Demographic Information and Baseline Characteristics

Variable	Control group CG (n = 44)	Interventional group IG (n = 44)	Standardized difference (95% CI)
Age (y),[b] mean ± SD	50.61 ± 12.38	47.34 ± 13.61	−0.25 (−0.75 to 0.7)
Gender, n[a]			
Male/female	21/23	21/23	0
ASA, n[a]			
I/II	22/22	27/17	0.22 (−0.11 to 0. 39)
Surgical specialties, [a] n (%)			
Neurosugery	7 (15%)	10 (22%)	0.18 (−0.2 to 0.3)
Oncosurgery	29 (66%)	27 (61%)	−0.14 (−0.48 to 0.26)
Thoracic surgery	2 (5%)	4 (9%)	0.15 (−0.13 to 0.31)
Urology	6 (14%)	3 (7%)	−0.22 (−0.54 to 0.26)
Duration of surgery (h),[b] mean ± SD	5.3 ± 0.7	5.2 ± 0.8	−0.13 (−0.48 to 0.24)

Standardized difference was defined as difference in means or proportions divided by pooled SD.
Abbreviations: ASA, American Society of Anesthesiologist; CG, control group; CI, confidence interval; IG, interventional group; SD, standard deviation.
Differences (IG − CG) were expressed as difference in proportions,
[a]or means.
[b]

Table 2. Comparison of Parameters Between Groups

Variable	Control group (n = 44)	Interventional group (n = 44)	*P* value
Intraoperative, mean ± SD			
Hb (g/dL)	13.1 ± 5.9	12.1 ± 1.6	.29
$SCvo_2$ (%)	80.23 ± 6.37	80.71 ± 4.87	.69
DCO_2 (mm Hg)	8.29 ± 2.93	5.64 ± 1.83	<.001
Lactate (mmol/L)	2.02 ± 1.3	1.69 ± 0.8	.15
Fluid input (L)	2015 ± 634	1938 ± 511	.53
Urine output (L)	408 ± 232	396 ± 234	.8
Postoperative, mean ± SD			
Hb (g/dL)	12 ± 1.45	12.4 ± 1.9	.29
$SCvo_2$ (%)	68.38 ± 6.45	73.56 ± 5.16	<.001
DCO_2 (mm Hg)	8.45 ± 2.3	5.8 ± 1.45	<.001
Lactate (mmol/L)	7.3 ± 5.8	5.9 ± 3.2	.18

Values averaged over the intra- and postoperative periods.
Abbreviations: DCO_2, difference in central venous to arterial carbon dioxide saturation; Hb, hemoglobin; $SCvo_2$, central venous oxygen saturation; SD, standard deviation.

ASA I and II patients. As the team deciding discharge was blinded and used objective discharge criteria, we hypothesize that a slight worsening in organ status, not amounting to "dysfunction" might have resulted in more extended observation predischarge resulting in the significantly different lengths of ICU stay. For example, a patient with a rise in serum creatinine from 0.6 to 1.2 meq/dL (not renal dysfunction by definition), coupled with borderline urine output, may be kept on the unit longer for observation and optimal management.

Some of the largest studies evaluating the effect of GDT involving hemodynamic intervention have also been unable to show improvement in complications, length of hospital stay, mechanical ventilation, and mortality. The Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcomes (OPTIMISE) study 734 randomized high-risk patients to study the effect of cardiac output–guided administration of intravenous fluid and inotropic drugs as part of an algorithm. It failed to detect a benefit.[7] Inclusion of these data by the authors in an updated meta-analysis, however, indicated a reduction in complication rates with the intervention.

Evidence for the superiority of microcirculation-targeted GDT in critically ill patients was growing when the protocol for this study was prepared.[28] The biochemical basis for predicting tissue hypoperfusion has since been explored further.[8,15,29] Mixed-venous CO_2 levels correlate well with $SCvo_2$,[30] and a DCO_2 <6 mm Hg indicates adequate venous flow (ie, cardiac output) when used along with $SCvo_2$ to guide GDT.[8,14,15,29,31–33]

Baseline Parameters

The 2 groups in our study were similar in all respects except the goal of achieving "normal" DCO_2 by using dobutamine infusion.

Perioperative hemodynamics, transfusion (fluid and blood products), and urine output did not significantly differ between the groups suggesting equipoise in the decision to transfuse. This is not uncommon in recent studies where "conventional" practices are evidence-based. Several "negative" studies of GD fluid treatment involving experienced physicians delivering "conventional care" have demonstrated similar equipoise.[34] DCO_2 was normal and significantly less in the GrI throughout, indicating successful implementation

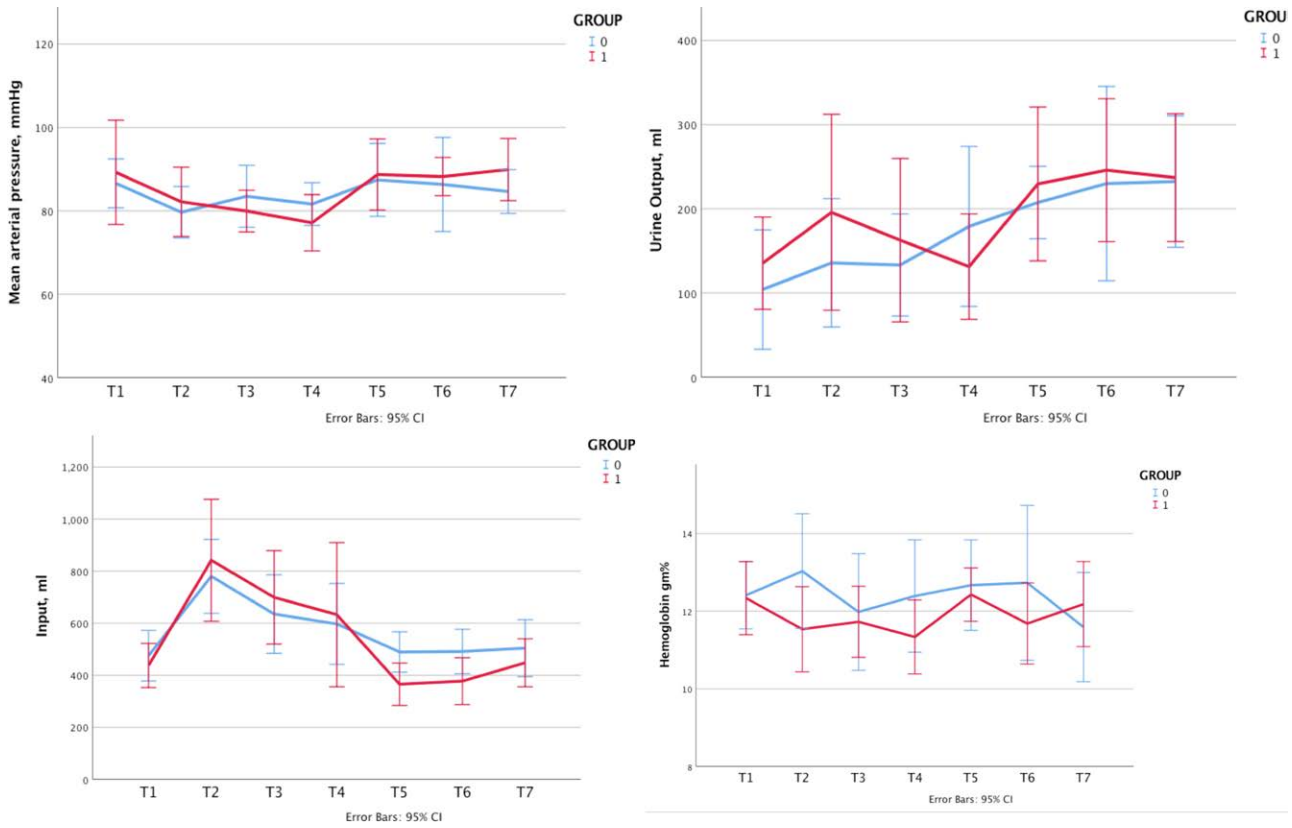

Figure 3. Change in different perioperative variables over time. CI indicates confidence interval.

Table 3. Comparison of Outcome Measures Between Groups

Variable	Control group (n = 44)	Interventional group (n = 44)	*P* value
Postoperative organ dysfunction, No. of patients (incidence)			
POD 0	35 (79%)	30 (66%)	.22
POD 1	23 (52%)	21 (47%)	.67
POD 2	20 (45%)	19 (43%)	.83
Length of ICU stay (d), mean ± SD	2.18 ± 1.08	1.52 ± 0.82	*.002*
Length of hospital stay (d), mean ± SD	10.09 ± 4.32	9.18 ± 4	.3

Abbreviations: ICU, intensive care unit; POD, postoperative day; SD, standard deviation.

of the protocol. Previous studies in the ICU have titrated dobutamine (0–5 µg/kg/min) to DCO_2 levels; at these low doses, dobutamine's main impact is improved organ perfusion and CO_2 clearance.[35] At higher doses, its thermogenic effect predominates, increasing VO_2 and CO2 production.[10] Our patients being less severely ill, required doses <4 µg/kg/min.

No patient in the control group received dobutamine, compared to 27% (intraoperative) and 32% patients (postoperative) in the GrI. There was no difference in rates of noradrenaline infusion between the groups. This observation is similar to the multicentric study by Salzwedel et al,[36] where compared to 42% of intraoperative dobutamine receivers in the GrI, none (0%) got an inotrope in the conventional group. As the cardiac output (CO) monitoring terminated at the end of the surgery, no patient in either group received dobutamine postoperatively. It would seem, therefore, that in the absence of objective end points (cardiac output in Salzwedel et al[36]'s study or DCO_2 in ours), anesthesiologists hesitate to transfuse dobutamine (or another inotrope), thereby emphasizing the need to have a readily available, sensitive marker of tissue perfusion throughout the perioperative period. As the trend toward avoiding ICU admission for elective surgery in perioperative medicine grows, we feel a DCO_2-guided regimen that is readily available may be well utilized outside the ICU.[37]

Postoperative Parameters

Reduced $SCvo_2$ in the postoperative period has been associated with greater complications.[38] Postoperative $SCvo_2$ in the GrI dropped less than that in the control group (8% vs 15%). Although lactate is a marker of microcirculation and has been used with $SCvo_2$ to predict outcome in surgery, DCO_2 reflects tissue hypoxia and microcirculatory status earlier than a rise in lactates.[8]

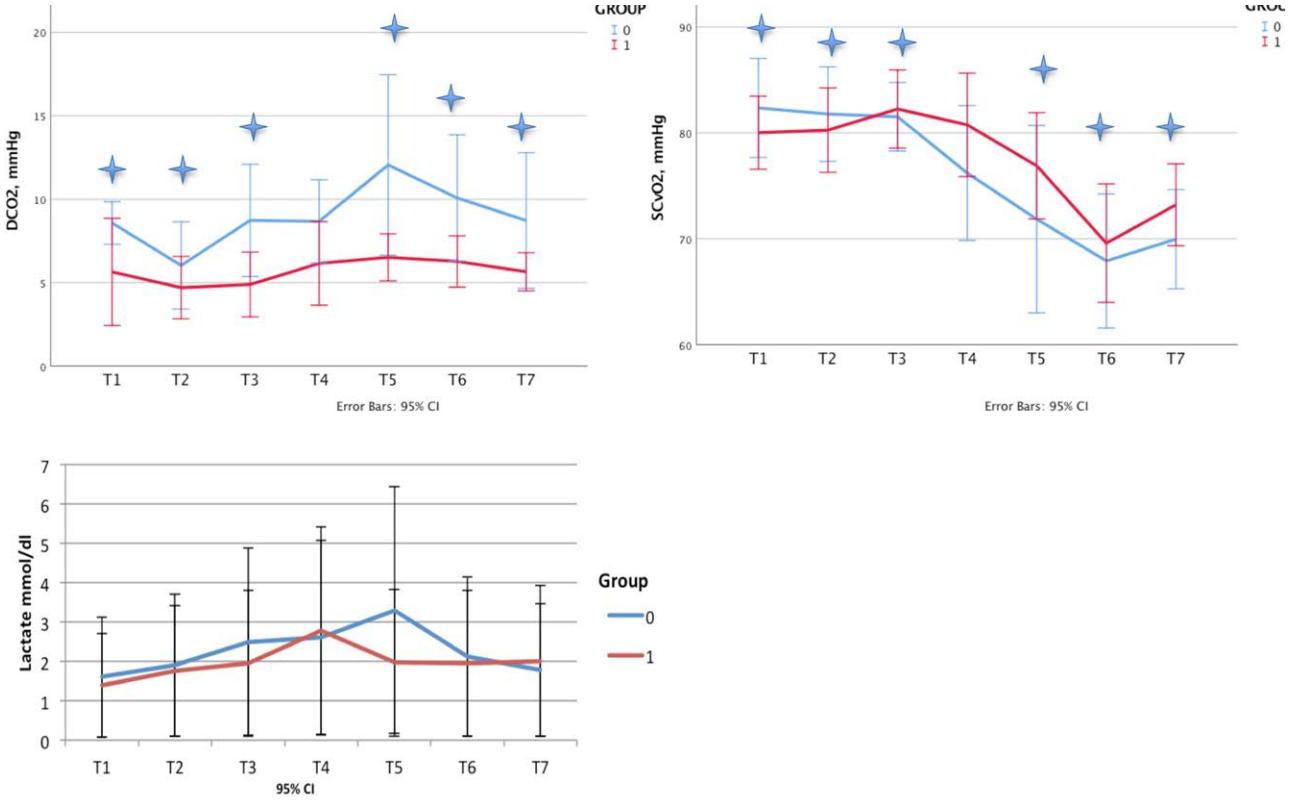

Figure 3. Continued.

Future Research Opportunities

Further proof of decrease in ICU length of stay may justify using DCO_2-specific GDT modalities more frequently in ASA I and II patients undergoing major surgeries.

Trials with high-risk patients may demonstrate further benefits. Significantly, inotropes such as dobutamine were rarely administered in the perioperative period without objective end points. DCO_2-guided GDT seems a cost-effective alternative to high-end CO monitoring devices limited in availability at many centers. Future noninferiority trials comparing CO monitor–guided GDT with DCO_2-based protocols are needed to validate this observation.

The study's strengths lie in its prepublished protocol (as part of the postgraduate thesis program) and robust methodology. Furthermore, with objective end points and "goals" readily available to the anesthetist and intensivist in the perioperative period, the protocol can be replicated in other, more extensive studies. We have included patients undergoing major surgery from a broader spectrum to improve the generalizability of our results. Although neurosurgical patients have more minor fluid shifts, brain swelling is a major concern. Trails have shown a benefit of goal-directed fluid therapy on postoperative outcomes in neurosurgical patients.[39] The definition and assessment of organ dysfunction have varied between studies, leading us to adopt the SOFA score, a more pragmatic and widely accepted definition.

There are limitations of this study. Our sample size was based on a study with sicker patients[24] and used different definitions for organ dysfunction. Due to time and resource limitations, the cohort was limited to ASA I and ASA II patients undergoing elective surgeries: ASA III patients and emergency surgeries might have benefited more from the intervention. Anesthetists in the pragmatic goal group did not have consistent access to an automated module for PPV. Manual PPV calculation may have been underused, making it more a comparison of GDT with PPV, $SCvo_2$, and DCO_2 versus a "choice of using" PPV: not uncommon for anesthetists in many centers worldwide. Observational bias cannot be ruled out completely. However, efforts were made to minimize it by keeping objective end points dispatched, collected, and recorded by personnel not related to the study.

CONCLUSIONS

Perioperative DCO_2-guided GDT using macro and microcirculatory end points significantly decreased ICU length of stay without a significant decrease in organ dysfunction in ASA I and II patients undergoing major surgeries. $SCvo_2$ and DCO_2 values used to guide management are readily available and result in greater use of low-dose inotropes than that in the

pragmatic goal managed group. More studies in high-risk patients will guide the widespread use of $SCvo_2$- and DCO_2-based clinical practice protocols.

ACKNOWLEDGMENTS

The authors thank the faculty and staff of the Department of Anesthesia and Critical Care and Surgical intensive care unit doctors and staff for support during the study.

DISCLOSURES

Name: Lohith Kumar H N, MD.
Contribution: This author helped in patient recruitment, data collection, study conduct, data evaluation, writing the manuscript, and editing and approval of the manuscript.
Name: Swagata Tripathy, MD, DNB, IDCC, EDIC.
Contribution: This author helped in study design, protocol design, being advisor for study protocol and management of the study, study conduct, study monitoring, data analysis, data evaluation, writing the manuscript, and editing and approval of the manuscript.
Name: Prashanta Kumar Das, MD, DM.
Contribution: This author helped in study design, protocol design, patient recruitment, study monitoring, data analysis, data evaluation, and editing and approval of the manuscript.
This manuscript was handled by: Stefan G. De Hert, MD.

REFERENCES

1. Myles PS, Bellomo R, Corcoran T, et al; Australian and New Zealand College of Anaesthetists Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Restrictive versus liberal fluid therapy for major abdominal surgery. *N Engl J Med.* 2018;378:2263–2274.
2. Wrzosek A, Jakowicka-Wordliczek J, Zajaczkowska R, et al. Perioperative restrictive versus goal-directed fluid therapy for adults undergoing major noncardiac surgery. *Cochrane Database Syst Rev*. 2017;2017:CD012767.
3. Gustafsson UO, Scott MJ, Schwenk W, et al; Enhanced Recovery After Surgery (ERAS) Society, for Perioperative Care; European Society for Clinical Nutrition and Metabolism (ESPEN); International Association for Surgical Metabolism and Nutrition (IASMEN). Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS(®)) Society recommendations. *World J Surg*. 2013;37:259–284.
4. Messina A, Robba C, Calabrò L, et al. Association between perioperative fluid administration and post-operative outcomes: a 20-year systematic review and a meta-analysis of randomized goal-directed trials in major visceral/noncardiac surgery. *Crit Care*. 2021;25:1–14.
5. Herzog N, Dablin JB, Giacardi C, Danguy des Déserts M. Goal-directed therapy in the perioperative management: is a complete hemodynamics bundle of care better? *Crit Care*. 2021;25:105.
6. Vallet B, Futier E, Robin E. Tissue oxygenation parameters to guide fluid therapy. *Transfus Altern Transfus Med*. 2010;11:113–117.
7. Pearse RM, Harrison DA, MacDonald N, et al; OPTIMISE Study Group. 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;311:2181–2190.
8. Janotka M, Ostadal P. Biochemical markers for clinical monitoring of tissue perfusion. *Mol Cell Biochem*. 2021;476:1313–1326.
9. Vallet B, Robin E, Lebuffe G. Venous oxygen saturation as a physiologic transfusion trigger. *Crit Care*. 2010;14:213.
10. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Multicenter study of central venous oxygen saturation (ScvO(2)) as a predictor of mortality in patients with sepsis. *Ann Emerg Med*. 2010;55:40–46. e1.
11. Mallat J, Pepy F, Lemyze M, et al. Central venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: a prospective observational study. *Eur J Anaesthesiol*. 2014;31:371–380.
12. Felice VB, Araujo DT, Meregalli AF, Friedman G. Value of central venous to arterial CO2 difference after early goal-directed therapy in septic shock patients. *Indian J Crit Care Med*. 2019;23:449–453.
13. Ñáñez-Varona DP, Tróchez-Zuleta AL, Vargas-Garzón WA. Restoring microcirculation in anesthesia: impact, usefulness and controversies. *Colomb J Anesthesiol*. 2016;44:140–145.
14. Yuan S, He H, Long Y. Interpretation of venous-to-arterial carbon dioxide difference in the resuscitation of septic shock patients. *J Thorac Dis*. 2019;11(suppl 11):S1538–S1543.
15. Al Duhailib Z, Hegazy AF, Lalli R, et al. The use of central venous to arterial carbon dioxide tension gap for outcome prediction in critically ill patients: a systematic review and meta-analysis. *Crit Care Med*. 2020;48:1855–1861.
16. Futier E, Robin E, Jabaudon M, et al. Central venous O_2 saturation and venous-to-arterial CO_2 difference as complementary tools for goal-directed therapy during high-risk surgery. *Crit Care*. 2010;14:R193.
17. Robin E, Futier E, Pires O, et al. Central venous-to-arterial carbon dioxide difference as a prognostic tool in high-risk surgical patients. *Crit Care*. 2015;19:227.
18. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869.
19. Susan RW. Anesthesiology - choosing wisely Canada; CLINICAL PRACTICE GUIDELINE WRHA Professional Advisory Council. 2016. Accessed May 11, 2021. https://choosingwiselycanada.org/anesthesiology/.
20. Lamperti M, Pittiruti M. Central venous catheter tip position: another point of view. *Eur J Anaesthesiol*. 2015;32:3–4.
21. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent J-L. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med*. 2005;31:517–523.
22. Susan RW. ACEP // American College of Emergency Physicians. Critical care medicine. 2016. Accessed May 11, 2021. https://www.acep.org/how-we-serve/sections/critical-care-medicine/news/april-2016/tips-and-tricks-pulse-pressure-variation/.
23. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707–710.
24. Mayer J, Boldt J, Mengistu AM, Röhm KD, Suttner S. Goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized, controlled trial. *Crit Care*. 2010;14:R18.

25. Cecconi M, Corredor C, Arulkumaran N, et al. Clinical review: goal-directed therapy-what is the evidence in surgical patients? The effect on different risk groups. *Crit Care*. 2013;17:209.
26. Stens J, Hering JP, van der Hoeven CWP, et al. The added value of cardiac index and pulse pressure variation monitoring to mean arterial pressure-guided volume therapy in moderate-risk abdominal surgery (COGUIDE): a pragmatic multicentre randomised controlled trial. *Anaesthesia*. 2017;72:1078–1087.
27. Ito K, Ito M, Ando A, et al. Simplified intraoperative goal-directed therapy using the FloTrac/Vigileo system: an analysis of its usefulness and safety. *Open J Anesthesiol*. 2017;7:1–14.
28. Charlton M, Sims M, Coats T, Thompson JP. The microcirculation and its measurement in sepsis. *J Intensive Care Soc*. 2017;18:221–227.
29. Bitar ZI, Maadarani OS, El-Shably AM, Elshabasy RD, Zaalouk TM. The forgotten hemodynamic (PCO2 gap) in severe sepsis. *Crit Care Res Pract*. 2020;2020:9281623.
30. Cuschieri J, Rivers EP, Donnino MW, et al. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. *Intensive Care Med*. 2005;31:818–822.
31. Joffre J, Legrand M. Microcirculation-targeted resuscitation in septic shock: can complex problems have simple answers? *Ann Intensive Care*. 2021;11:1.
32. Gelman S. Is goal-directed haemodynamic therapy dead? *Eur J Anaesthesiol*. 2020;37:159–161.
33. Waldauf P, Jiroutkova K, Duska F. Using pCO2 gap in the differential diagnosis of hyperlactatemia outside the context of sepsis: a physiological review and case series. *Crit Care Res Pract*. 2019;2019:5364503.
34. Mallat J, Benzidi Y, Salleron J, et al. Time course of central venous-to-arterial carbon dioxide tension difference in septic shock patients receiving incremental doses of dobutamine. *Intensive Care Med*. 2014;40:404–411.
35. Mallat J, Lemyze M, Tronchon L, Vallet B, Thevenin D. Use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock. *World J Crit Care Med*. 2016;5:47–56.
36. Salzwedel C, Puig J, Carstens A, et al. Perioperative goal-directed hemodynamic therapy based on radial arterial pulse pressure variation and continuous cardiac index trending reduces postoperative complications after major abdominal surgery: a multi-center, prospective, randomized study. *Crit Care*. 2013;17:R191.
37. Taccone P, Langer T, Grasselli G. Do we really need postoperative ICU management after elective surgery? No, not any more! *Intensive Care Med*. 2017;43:1037–1038.
38. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Changes in central venous saturation after major surgery, and association with outcome. *Crit Care*. 2005;9:R694–R699.
39. Bloria SD, Panda NB, Jangra K, et al. Goal-directed fluid therapy versus conventional fluid therapy during craniotomy and clipping of cerebral aneurysm. *J Neurosurg Anesthesiol*. Published online April 8, 2021. doi: 10.1097/ana.0000000000000769.