Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Thursday September 18, 2014
1800 HOURS

LOCATION:
Milestones
27 Princess Street

PRESENTING ARTICLES:
Dr. Glenio Mizubuti & Dr. Julie Zalan

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SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
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Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants, who will be expected to contribute pending suspension of bar privileges.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?
    b) Is it detailed enough to be reproducible?
    c) Is the methodology validated?
    d) Are the drugs/equipment used detailed?
    e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?
3. Was the food and wine up to the high standards expected by self-respecting anesthesiologists?

British Journal of Anaesthesia **107** (2): 209–17 (2011)
Advance Access publication 3 June 2011 · doi:10.1093/bja/aer150

BJA

NEUROSCIENCES AND NEUROANAESTHESIA

Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients

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Editor's key points

- Effects of different vasopressor agents on cerebral oxygenation have been unclear.
- Ephedrine and phenylephrine, used for intraoperative hypotension, were investigated in a cross-over design study.
- Phenylephrine, but not ephedrine, decreased cardiac output (CO) and brain oxygenation.
- This study highlights the importance of CO in preserving brain oxygenation during management of intraoperative hypotension.

Background. How phenylephrine and ephedrine treatments affect global and regional haemodynamics is of major clinical relevance. Cerebral tissue oxygen saturation (Sct_{O_2})-guided management may improve postoperative outcome. The physiological variables responsible for Sct_{O_2} changes induced by phenylephrine and ephedrine bolus treatment in anaesthetized patients need to be defined.

Methods. A randomized two-treatment cross-over trial was conducted: one bolus dose of phenylephrine (100–200 μg) and one bolus dose of ephedrine (5–20 mg) were given to 29 ASA I–III patients anaesthetized with propofol and remifentanil. Sct_{O_2}, mean arterial pressure (MAP), cardiac output (CO), and other physiological variables were recorded before and after treatments. The associations of changes were analysed using linear-mixed models.

Results. The CO decreased significantly after phenylephrine treatment [$\triangle CO = -2.1$ (1.4) litre min^{-1}, $P<0.001$], but was preserved after ephedrine treatment [$\triangle CO = 0.5$ (1.4) litre min^{-1}, $P>0.05$]. The Sct_{O_2} was significantly decreased after phenylephrine treatment [$\triangle Sct_{O_2} = -3.2$ (3.0)%, $P<0.01$] but preserved after ephedrine treatment [$\triangle Sct_{O_2} = 0.04$ (1.9)%, $P>0.05$]. CO was identified to have the most significant association with Sct_{O_2} ($P<0.001$). After taking CO into consideration, the other physiological variables, including MAP, were not significantly associated with Sct_{O_2} ($P>0.05$).

Conclusions. Associated with changes in CO, Sct_{O_2} decreased after phenylephrine treatment, but remained unchanged after ephedrine treatment. The significant correlation between CO and Sct_{O_2} implies a cause–effect relationship between global and regional haemodynamics.

Keywords: cardiac output; cerebral tissue oxygen saturation; ephedrine; mean arterial pressure; phenylephrine

Accepted for publication: 26 April 2011

Phenylephrine and ephedrine are routinely used in the perioperative setting to treat anaesthesia-related hypotension in order to maintain mean arterial pressure (MAP) and cerebral perfusion pressure.[1] However, phenylephrine and ephedrine have very different pharmacological effects: phenylephrine is a pure α_1-agonist, whereas ephedrine is a mixed-acting agent with positive inotropic and chronotropic effects.[2] Indeed, the distinctive effects of phenylephrine and ephedrine on global haemodynamics (such as cardiac output, CO)[3] and regional haemodynamics (such as cerebral tissue oxygen saturation, Sct_{O_2})[4] have been demonstrated.

Recently published studies show that near-infrared spectroscopy (NIRS)-guided brain protection protocols in cardiac surgery might lead to reduced neurocognitive complications and improved postoperative outcomes.[5] Because the endpoint of haemodynamic optimization is to improve oxygen delivery, monitoring cerebral oxygenation may help to elucidate the effects of various clinical interventions on global and regional haemodynamics.[6] Moreover, several studies have demonstrated that changes in Sct_{O_2} correlate with changes in cerebral blood flow (CBF) when cerebral metabolic rate of oxygen ($CMRO_2$) and arterial blood oxygen content are kept constant.[7] Understanding how the administration of phenylephrine and ephedrine affects cerebral perfusion and oxygenation is of major clinical relevance because both agents are routinely used to treat anaesthesia-related hypotension in surgical patients.

Consequently, the aims of our study were (i) to investigate the effect of phenylephrine and ephedrine bolus administration on cerebral oxygenation in anaesthetized patients and (ii) to identify the physiological variables [MAP, CO, heart rate (HR), stroke volume (SV), end-tidal CO_2 (E'_{CO_2}), oxygen saturation via pulse oximetry (Sp_{O_2}), and bispectral index (BIS)] which are responsible for the changes in Sct_{O_2} induced by phenylephrine and ephedrine treatments.

Methods

Patients

After Institutional Research Board approval, a total of 33 patients undergoing elective surgery at University of California, Irvine Medical Center, were recruited for this study. Both verbal and written informed consents were obtained. Inclusion criteria were: age >18 yr, elective surgery, ASA physical status I–III, presenting with at least a 20% decrease in MAP or an MAP of <60 mm Hg after induction of general anaesthesia. Exclusion criteria were symptomatic cardiovascular disease, poorly controlled hypertension (systolic arterial pressure ≥160 mm Hg), cerebrovascular disease, and poorly controlled diabetes mellitus (blood glucose ≥200 mg dl^{-1}).

Study protocol

After the patient's arrival in the operating theatre, a radial intra-arterial catheter, a BIS monitor, and two frequency-domain NIRS[8] probes (left and right forehead) were placed in addition to the other routine monitors. After anaesthesia induction with fentanyl (1.5–2 μg kg^{-1}) and propofol (2–3 mg kg^{-1}), all patients were intubated and maintained with total i.v. anaesthesia (TIVA) using propofol 100–150 μg kg^{-1} min^{-1} and remifentanil 0.3–0.5 μg kg^{-1} min^{-1}. The infusion rates of TIVA were based on the patient's age, ASA physical status, and BIS monitoring. The goal was to keep BIS between 25 and 35. An oesophageal Doppler probe was placed after tracheal intubation. Anaesthesia-related hypotension (at least a 20% decrease in MAP or MAP<60 mm Hg) was treated with either phenylephrine or ephedrine. This initial agent is referred to as the first treatment. The agent used for the first treatment was randomized based on a computer-generated randomization list (http://www.random.org). The first treatment was given at least 10 min after the start of TIVA in order to achieve relatively stable blood propofol and remifentanil concentrations. If hypotension persisted for more than 10 min after the first treatment, the alternative agent (the one not chosen for the first treatment) was then administered. This second agent is referred to as the second treatment. Each patient received one dose of phenylephrine and one dose of ephedrine as either the first or the second treatment. There were no additional doses given during the study period. Owing to interindividual differences in body weight, haemodynamic responses to pressor treatment, and severity of hypotension, varying doses of phenylephrine (100–200 μg) and ephedrine (5–20 mg) were used to increase MAP by at least 20% or above 60 mm Hg. The pressor treatments and physiological measurements were performed before the start of surgery in order to avoid the influence of surgical stimuli on systemic and cerebral haemodynamics.

Measurements

The cerebral oximeter used in this study was the Oxiplex TS (ISS, Inc., Champaign, IL, USA), a non-invasive, portable, and quantitative frequency-domain NIRS device.[8] It emits and detects near-infrared light at two different wavelengths (690 and 830 nm). The emitted light is amplitude-modulated (i.e. turned on and off) at 110 MHz. The spacing between the source and detector fibres on the optical probe (1.96, 2.46, 2.92, and 3.45 cm) is sufficient for light to access the surface of the brain.[9] The measured optical properties characterize cerebral tissues, primarily the haemoglobin in the capillary bed, and are not appreciably influenced by skin or surface contributions.[10] The measured absolute concentrations of cerebral tissue oxyhaemoglobin and deoxyhaemoglobin are used to calculate Sct_{O_2}. The sampling frequency was set at 1.25 Hz. Sct_{O_2} values from the right and left frontal lobes were averaged to represent regional cerebral oxygenation.

CO was monitored using an oesophageal Doppler (CardioQ, Deltex Medical, UK). The oesophageal Doppler measures blood flow velocity in the descending aorta and estimates SV via multiplying the cross-sectional area of the aorta by the blood flow distance (velocity multiplied by flow time). The aortic diameter is obtained from a built-in nomogram. The SV and CO values used for analysis were based on every 10 successive measurements by oesophageal Doppler. MAP was monitored at the external ear canal level via an intra-arterial catheter system (Vigileo-FloTrac, Edwards Lifesciences, Irvine, CA, USA). E'_{CO_2} was determined by the gas analyzer built in the anaesthesia machine (Aisys, GE Healthcare, Madison, WI, USA). Sp_{O_2} was determined by pulse oximeter (LNOP Adt, Masimo Corp., Irvine, CA, USA). The depth of anaesthesia was monitored via the BIS monitor (Aspect Medical System, Norwood, MA, USA).

All measurements were recorded before each treatment and repeated once MAP increased to the maximum level after each treatment. Owing to the fact that the maximal change in Sct_{O_2} lagged the maximal change in MAP (an observation in both this study and a previous study),[11] Sct_{O_2} measurements were recorded when corresponding changes reached the maximum level. The mean value of three successive recordings for each parameter was used for analysis. All measurements were performed before surgical incision. All patients were kept supine and still. The infusion rates of TIVA were kept constant. Volume-controlled ventilation was used with a tidal volume of 8–10 ml kg^{-1} and a ventilatory frequency of 8–12 bpm with a target E'_{CO_2} between 4.7 and 5.3 kPa.

Statistical analysis

Data are expressed as mean (SD). According to a previously published study, we calculated that 24 patients were

required to detect a 10% decrease in Sct_{O_2} induced by phenylephrine administration with a two-tailed α risk of 5% and a β risk of 20%.[4] Because this two-treatment cross-over study involved repeated measurements, we investigated the effect of drug treatment and physiological covariates (MAP, CO, HR, SV, E'_{CO_2}, Sp_{O_2}, and BIS) on Sct_{O_2} using linear-mixed models. When testing the effect of drug treatment, we adjusted the potential effects of carry-over (the influence of the first treatment on the second treatment) by adding carry-over into our linear-mixed model. For a similar reason, when examining the effect of each physiological covariate, the effects of treatment and carry-over were also adjusted in our linear-mixed model. The differences in physiological values (Sct_{O_2}, MAP, CO, HR, SV, E'_{CO_2}, Sp_{O_2}, and BIS) between pre- and post-treatments were analysed using paired Student's *t*-test. The differences in selected physiological values (Sct_{O_2}, MAP, and CO) between the first and the second treatments were analysed using unpaired Student's *t*-test. Relationships between variables were tested using Pearson's correlation.

Results

Patient characteristics

Of the 33 patients recruited, we were able to administer both phenylephrine and ephedrine and finish all measurements before surgical incision in 29 patients [20 males, 9 females, age 59 (13) yr, height 173 (9) cm, weight 77 (13) kg]. Among the 29 patients, 10 were ASA I, 12 ASA II, and 7 ASA III. Detailed patients characteristics and planned surgeries are described in Supplementary Table S1. In 13 patients, phenylephrine was given as the first treatment and ephedrine as the second treatment. In 16 patients, ephedrine was given as the first treatment and phenylephrine as the second treatment. The interval between the first and the second treatments was 20 (14) min. In two patients, we did not administer phenylephrine or ephedrine because changes in MAP after anaesthesia induction did not meet the predefined criteria. In another two patients, Sct_{O_2} data were not analysable because of strong signal interference.

Responses to phenylephrine bolus treatment

An example of changes in MAP, CO, and Sct_{O_2} after a typical first phenylephrine treatment is illustrated in Figure 1A–C, respectively. MAP increased from the pretreatment level of ≈70 mm Hg to the highest level of ≈110 mm Hg within 1 min after phenylephrine administration. At the same time, CO decreased from the pretreatment level of ≈8 litre min^{-1} to the lowest level of ≈2 litre min^{-1}, and Sct_{O_2} decreased from the pretreatment level of ≈65% to the lowest level of ≈58%. The measurements of MAP, CO, and Sct_{O_2} before and after phenylephrine treatment for every patient are presented in Figure 2A–C, respectively.

Grouped responses after the first and the second phenylephrine treatments are summarized in Table 1. MAP was consistently increased after the first [△MAP=29.5 (9.3) mm Hg, $P<0.001$] and the second [△MAP=42.6 (15.7) mm Hg, $P<0.001$] phenylephrine treatments. CO was significantly decreased after the first (△CO=−1.7 (1.0) litre min^{-1}, $P<0.001$) and the second (△CO=−2.3 (1.7) litre min^{-1}, $P<0.001$) phenylephrine treatments. Sct_{O_2} was also significantly decreased after the first ($\triangle Sct_{O_2}$=−4.9 (2.8) %, $P<0.001$) and the second ($\triangle Sct_{O_2}$=−1.8 (2.4) %, $P<0.01$) phenylephrine treatments. However, the difference in Sct_{O_2} decreases between the first and the second phenylephrine treatments was significant ($P<0.01$; Fig. 3).

Changes in Sct_{O_2} correlated well with changes in CO after the first ($r=0.74$, $P=0.004$) and the second ($r=0.67$, $P=0.005$) phenylephrine treatments (Fig. 4B), but only weakly correlated with changes in MAP after the first ($r=0.40$, $P=0.17$) and the second ($r=0.48$, $P=0.06$) phenylephrine treatments (Fig. 4A).

Responses to ephedrine bolus treatment

An example of changes in MAP, CO, and Sct_{O_2} after one of the first ephedrine treatments is illustrated in Figure 1D–F, respectively. MAP increased from the pretreatment level of ≈50 mm Hg to the highest level of ≈80 mm Hg within 2 min after ephedrine administration. However, CO remained unchanged at ≈5 litre min^{-1} and Sct_{O_2} remained unchanged at ≈62%. The measurements of MAP, CO, and Sct_{O_2} before and after ephedrine treatment for every patient are presented in Figure 2D–F, respectively.

Grouped responses after the first and second ephedrine treatments are summarized in Table 1. MAP was consistently increased after the first [△MAP=24.1 (13.5) mm Hg, $P<0.001$] and the second [△MAP=28.3 (13.3) mm Hg, $P<0.001$] ephedrine treatments. CO was slightly, but insignificantly, increased after the first [△CO=0.5 (1.7) litre min^{-1}, $P=0.15$] and the second [△CO=0.4 (0.9) litre min^{-1}, $P=0.28$] ephedrine treatments. The changes in Sct_{O_2} were also insignificant after the first [$\triangle Sct_{O_2}$=−0.4 (2.3)%, $P=0.11$] and the second [$\triangle Sct_{O_2}$=0.5 (1.1)%, $P=0.54$] ephedrine treatments. The difference in Sct_{O_2} changes between the first and second ephedrine treatments was not significant ($P=0.19$) (Fig. 3).

Changes in Sct_{O_2} correlated with changes in CO after the first ($r=0.84$, $P<0.001$) and the second ($r=0.68$, $P=0.01$) ephedrine treatments (Fig. 4D), but very weakly correlated with changes in MAP after the first ($r=0.24$, $P=0.38$) and the second ($r=0.39$, $P=0.18$) ephedrine treatments (Fig. 4C).

Associations between Sct_{O_2} and physiological covariates (pooled data)

We first fitted a linear-mixed model to examine the effects of treatment and carryover on Sct_{O_2}. Our results showed that the treatment effect on Sct_{O_2} was significant ($P<0.001$) and that the carry-over effect on Sct_{O_2} was not significant ($P=0.11$). After adjusting the effects of treatment and carry-over on Sct_{O_2}, linear-mixed models showed that there were significant associations (in the order of significance from

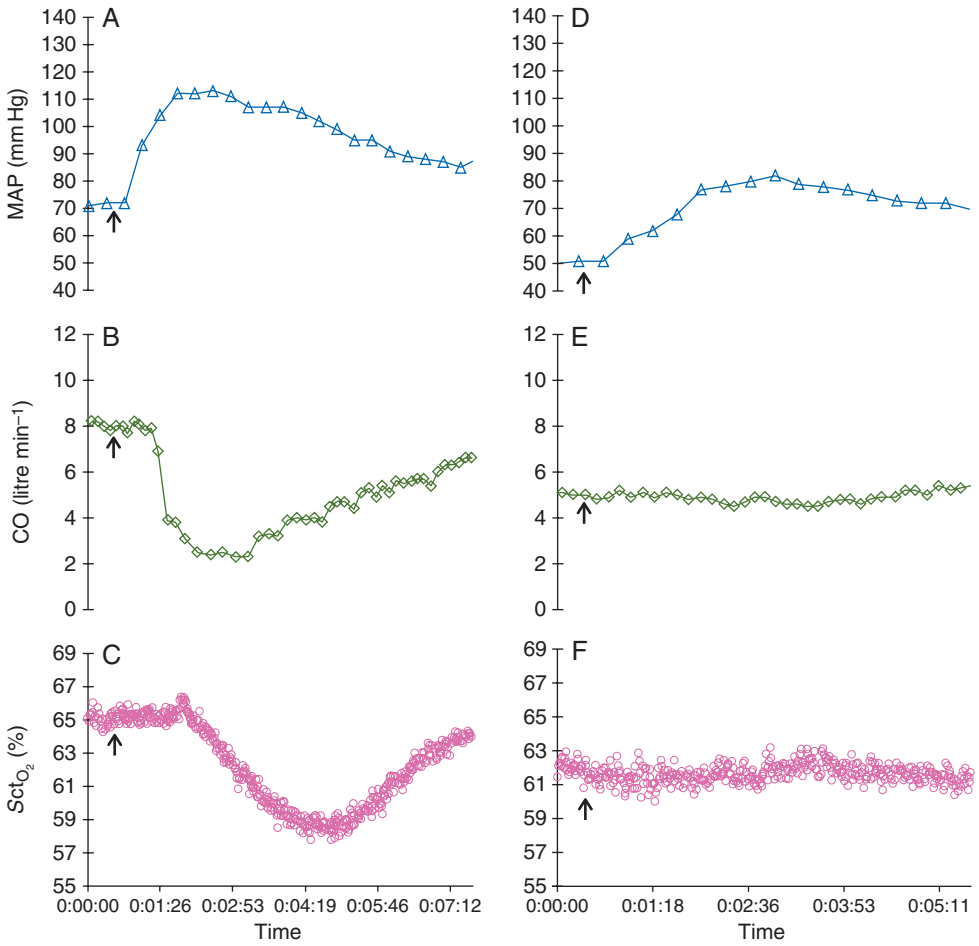

Fig 1 Continuous MAP, CO, and SctO_2 recordings from two selected patients. (A–C) Recordings during phenylephrine treatment. (D–F) Recordings during ephedrine treatment. Both agents were given during the first treatment. Vertical arrows indicate the drug administration time.

high to low, data available upon request) between SctO_2 and CO ($P<0.001$), between SctO_2 and SV ($P<0.001$), between SctO_2 and HR ($P<0.001$), between SctO_2 and MAP ($P<0.001$), and between SctO_2 and E'_{CO_2} ($P<0.01$); however, there were no significant associations between SctO_2 and SpO_2 ($P=0.60$) and between SctO_2 and BIS ($P=1.0$). After taking CO into consideration, SV ($P=0.85$), HR ($P=0.95$), MAP ($P=0.48$), and E'_{CO_2} ($P=0.64$) were no longer significantly associated with SctO_2. Further analysis showed that the associations between CO and SV ($P<0.001$), between CO and HR ($P<0.001$), between CO and MAP ($P<0.001$), and between CO and E'_{CO_2} ($P<0.001$) were all significant.

Discussion

This study demonstrates that concordant with changes in CO, cerebral oxygenation (SctO_2) significantly decreased after phenylephrine bolus treatment and remained unchanged after ephedrine bolus treatment, even though MAP was significantly increased by both agents. Among all physiological variables being considered (MAP, CO, HR, SV, E'_{CO_2}, SpO_2, and BIS), CO was identified as the variable associated most significantly with SctO_2. The other variables (MAP, HR, SV, and E'_{CO_2}) which associated significantly with SctO_2 became insignificant after taking CO into consideration.

Cerebral oxygenation is determined by oxygen delivery to the brain and oxygen consumption by the brain ($CMRO_2$). Oxygen delivery to the brain depends on cerebral perfusion (CBF) and arterial blood oxygen content. Studies have shown that changes in SctO_2 correlate with changes in CBF if $CMRO_2$ and arterial blood oxygen content are kept constant.[7] In the present study, we considered $CMRO_2$ to be constant because our patients were under general Anaesthesia and the infusion rates of propofol and remifentanil were kept constant. Moreover, in order to achieve stable blood propofol and remifentanil concentrations, we waited for at least 10 min between starting TIVA and giving the first pressor treatment. We also considered arterial blood oxygen content to be constant because there was no surgical haemorrhage and no sign of desaturation. Therefore, we submit that the observed changes of SctO_2 in this study were mainly caused by changes in CBF.

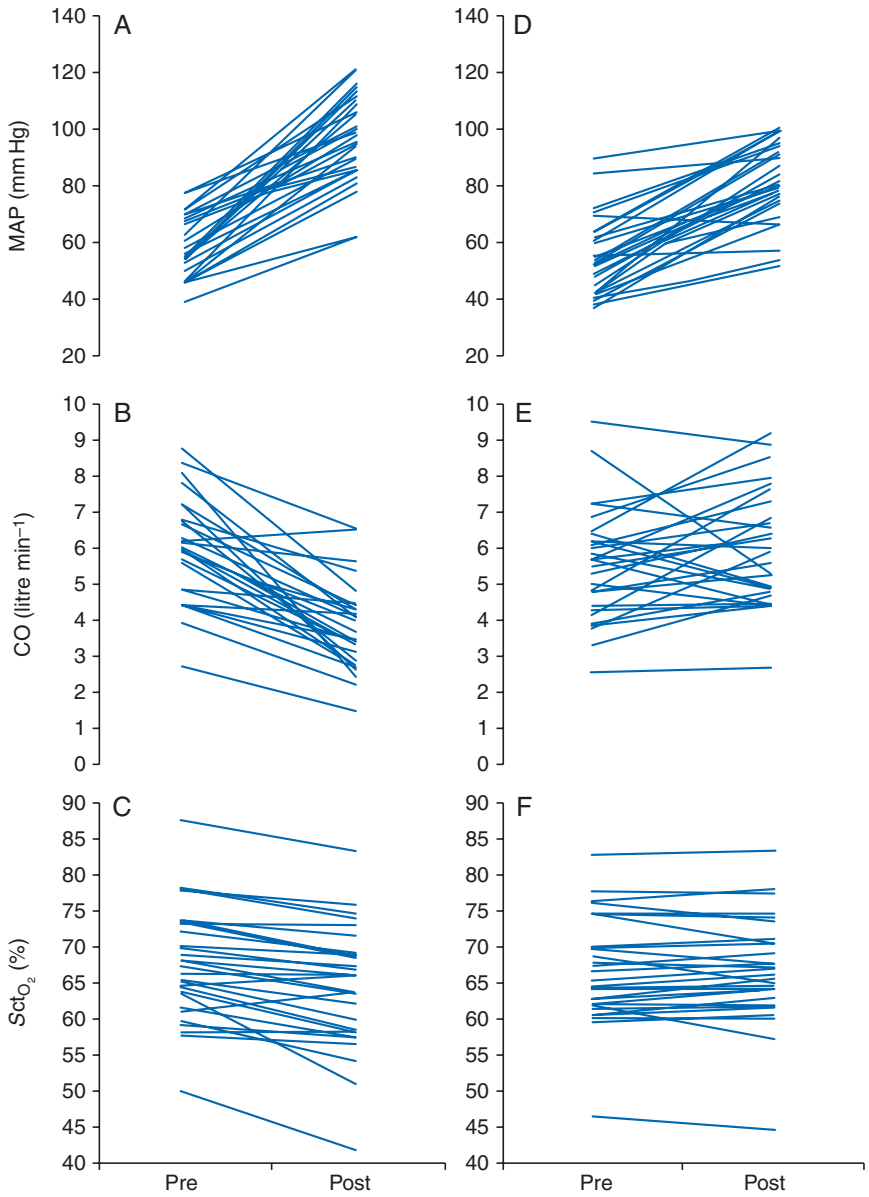

Fig 2 Measurements of MAP, CO, and Sct_{O_2} for every patient. (A–C) Measurements before (pre) and after (post) phenylephrine treatments. (D–F) Measurements before (pre) and after (post) ephedrine treatments.

The importance of arterial pressure management in patients undergoing anaesthesia has been substantiated by the significant relationship between intraoperative hypotension and postoperative neurocognitive impairment.[12] Despite the fact that arterial pressure monitoring is a standard practice, consensus in terms of when and how to treat intraoperative hypotension is still lacking. Among all options, phenylephrine and ephedrine belong to the set of typical sympathomimetic agents routinely chosen to increase arterial pressure.[2] However, little is known about the impacts of these agents on cerebral oxygenation and the relationship between global and regional haemodynamics. If treating hypotension is an attempt to avoid organ ischaemia and hypoxia, we are actually achieving the opposite result (decreased cerebral oxygenation) by administering phenylephrine, as demonstrated in this study using a quantitative NIRS device and in previous studies using a trend NIRS device.[4 11 13] Another study also demonstrated the negative impact of norepinephrine infusion on cerebral oxygenation.[14] Thus, the routine and indiscriminate use of vasopressors might be less beneficial than previously thought. Nonetheless, prospective and randomized studies are needed to address whether the negative impact of vasopressor treatment on Sct_{O_2} relates to adverse patient

Table 1 Summarized physiological measurements before (pre) and after (post) treatments (Tx). Data are presented as means (SD). Δ=post–pre; Sct_{O_2}, cerebral tissue oxygen saturation; MAP, mean arterial pressure; CO, cardiac output; HR, heart rate (beats min^{-1}); SV, stroke volume; E'_{CO_2}, end-tidal CO_2; Sp_{O_2}, oxygen saturation per pulse oximetry; BIS, bispectral index. *$P<0.001$, †$P<0.01$, and ‡$P<0.05$ (post *vs* pre, paired Student's *t*-test)

	Phenylephrine first Tx ($n=13$)			Phenylephrine second Tx ($n=16$)			Ephedrine first Tx ($n=16$)			Ephedrine second Tx ($n=13$)		
	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ
Sct_{O_2} (%)	68.8 (8.8)	63.9 (10.4)	−4.9 (2.8)*	66.4 (6.7)	64.5 (6.7)	−1.8 (2.4)†	67.4 (6.3)	67.1 (6.0)	−0.4 (2.3)	65.7 (8.5)	66.2 (8.9)	0.5 (1.1)
MAP (mm Hg)	60.8 (12.1)	90.3 (14.5)	29.5 (9.3)*	58.8 (9.3)	101.3 (14.7)	42.6 (15.7)*	48.1 (8.9)	72.3 (10.7)	24.1 (13.5)*	62.4 (5.3)	90.7 (13.7)	28.3 (13.3)*
CO (litre min^{-1})	5.3 (1.1)	3.6 (0.7)	−1.7 (1.0)*	6.8 (1.7)	4.5 (2.2)	−2.3 (1.7)*	6.0 (1.8)	6.5 (1.8)	0.5 (1.7)	5.0 (0.9)	5.4 (1.0)	0.4 (0.9)
HR (beats min^{-1})	71.2 (15.2)	53.9 (8.6)	−17.3 (11.4)*	64.7 (12.1)	48.0 (6.6)	−16.7 (12.1)*	65.3 (14.1)	67.6 (12.6)	2.3 (5.8)†	59.5 (9.6)	67.0 (11.3)	7.5 (7.8)
SV (ml)	77.2 (16.7)	68.7 (14.4)	−8.5 (9.2)†	105.8 (31.0)	90.7 (39.5)	−15.2 (22.3)‡	92.2 (30.4)	97.4 (29.7)	5.3 (21.6)	85.5 (17.9)	83.1 (18.0)	−2.4 (11.9)
E'_{CO_2} (kPa)	5.1 (0.7)	4.9 (0.6)	−0.2 (0.3)‡	4.7 (0.4)	4.6 (0.5)	−0.1 (0.3)	4.7 (0.4)	4.7 (0.4)	0.04 (0.3)	4.9 (0.7)	5.0 (0.6)	0.2 (0.3)
Sp_{O_2} (%)	99.5 (0.7)	99.9 (0.3)	0.4 (0.7)	99.1 (1.4)	99.5 (1.2)	0.4 (0.7)	99.3 (1.4)	99 (2.7)	−0.3 (1.8)	99.1 (1.9)	99.4 (0.9)	0.3 (1.2)
BIS	25.5 (11.9)	27.8 (11.4)	2.3 (5.2)	34.9 (7.8)	30.5 (11.0)	−4.3 (8.4)	25.7 (12.5)	26.5 (8.5)	0.7 (6.0)	29.8 (12.9)	29.0 (11.2)	−0.9 (3.3)

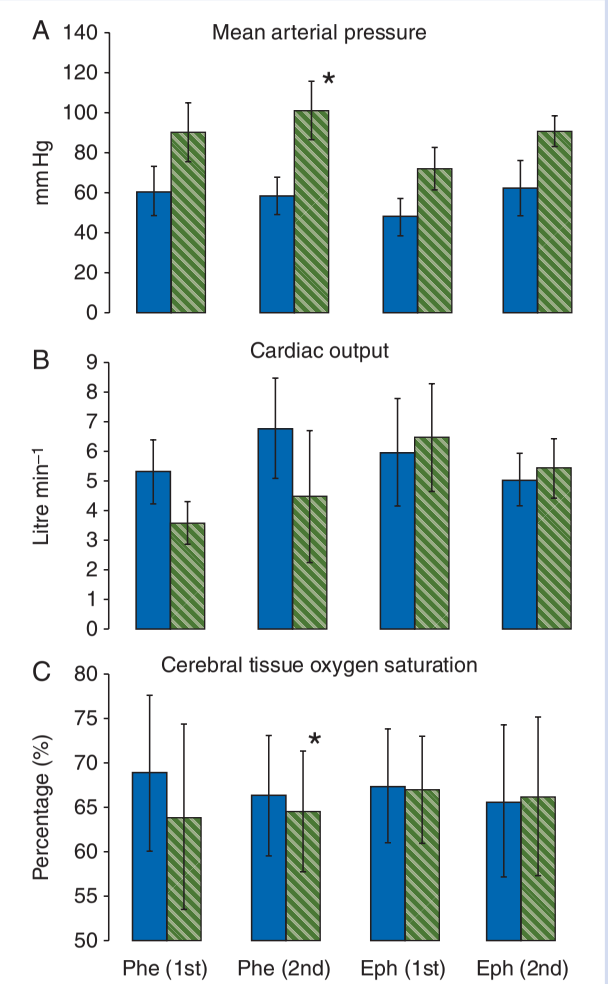

Fig 3 Grouped MAP (A), CO (B), and Sct_{O_2} (C) changes after the first and second phenylephrine (Phe) and the first and second ephedrine (Eph) treatments. The blue bars represent pretreatment values; the green striped bars represent post-treatment values. *$P<0.01$ (first treatment *vs* second treatment, unpaired Student's *t*-test).

outcomes, especially because recent studies have suggested that low Sct_{O_2} values are related to poor postoperative outcome.[5] In contrast, ephedrine's Sct_{O_2}-preserving ability is reassuring. However, studies are again needed to demonstrate whether or not the administration of ephedrine rather than phenylephrine relates to a better outcome.

The mechanism of how phenylephrine administration leads to a decreased cerebral oxygenation is intriguing. It has been found that sympathetic nerve activity (SNA) originating from the superior cervical ganglion increases promptly after pharmacologically (including phenylephrine) induced rapid increase in arterial pressure.[15] Considering that the cerebral vasculature is largely innervated by the superior cervical ganglion,[16] we speculate that phenylephrine bolus treatment may constrict cerebral resistance vessels indirectly via reflexively increased SNA to the brain. This assertion is supported by the findings that cerebral

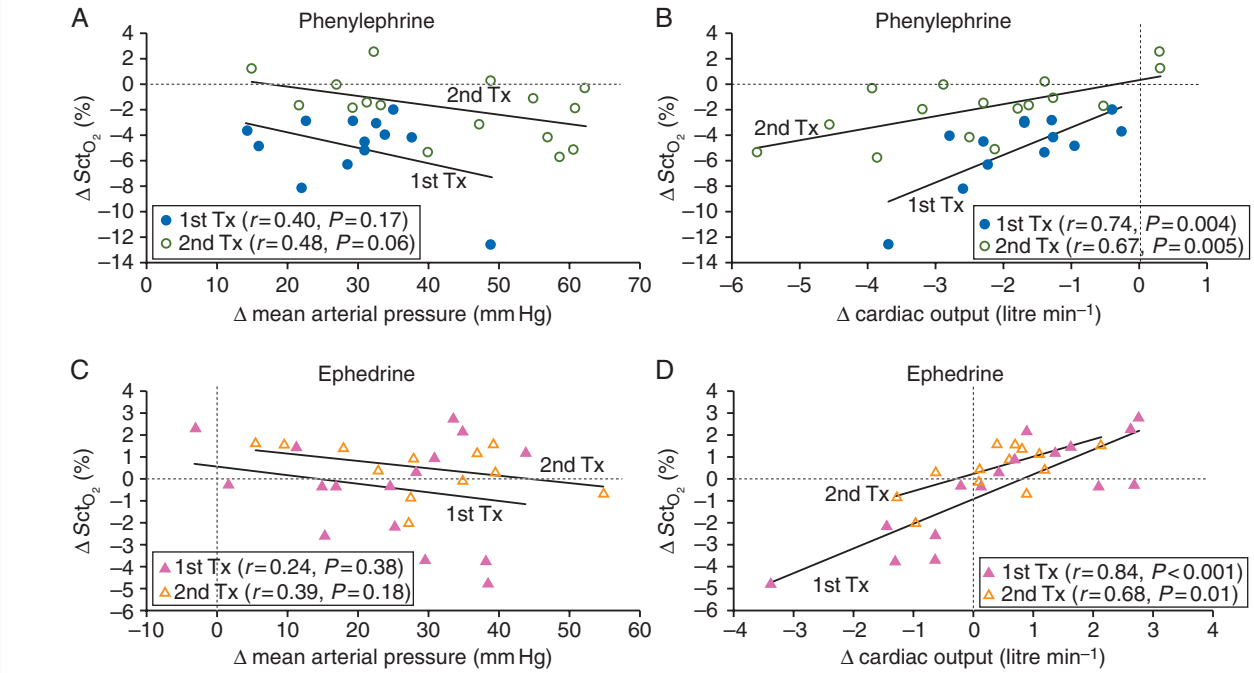

Fig 4 Pearson's correlations between Sct_{O_2} and global haemodynamics (MAP and CO) during the first and second phenylephrine (A and B) and the first and second ephedrine treatments (Tx) (C and D). Δ=post–pre.

arteries are abundantly innervated by sympathetic nerve fibres[17] and that both α- and β-adrenoceptors are demonstrated in the vascular walls in the brain.[18] It is also supported by the finding that stellate ganglion block leads to a decreased cerebral vascular tone.[19] Nonetheless, the discussion over whether or not SNA affects cerebral perfusion and oxygenation has lasted for more than 100 yr, witnessed by the recently well-organized point[20]–counterpoint[21] debate. It should be noted that direct action of either phenylephrine or ephedrine on cerebral resistance vessels is practically nil since we know that vasoactive amines do not cross the blood–brain barrier.[22]

To the best of our knowledge, this study is the first one to demonstrate a significant relationship between global haemodynamics (CO) and regional haemodynamics (Sct_{O_2}) in situations where CO changes are induced by sympathomimetic agents in anaesthetized patients. The distinctive effects of phenylephrine and ephedrine on Sct_{O_2} are thus explained by their distinctive impacts on CO. Our data concur with previous reports that a reduced CO correlates with decreased cerebral haemodynamics, despite maintained MAP in situations where CO changes are induced by preload swing in healthy non-anaesthetized volunteers.[23 24] The mechanism behind the modulation of cerebral haemodynamics by CO is believed to be sympathetically mediated vasoconstriction consequent to a reduced CO.[20] This assertion is supported by the finding that dynamic inputs from CO and SV are important in the regulation of baroreflex control of muscle SNA in healthy, normotensive humans.[25] Alternatively, the influence of CO on cerebral haemodynamics may depend on circulating blood volume distribution rather than autonomic control.[20] Consequently, our study emphasizes the relationship between global and regional haemodynamics and supports the importance of studies focusing on this relationship as well as studies evaluating the impact of regional haemodynamics on patients' outcome.[26 27] Our finding also supports the emerging practice of goal-directed haemodynamic optimization because optimized global haemodynamics is related to a minimized risk of regional ischaemia and hypoxia.[28]

Interestingly, our data showed that the difference in Sct_{O_2} changes was significant between the first and second phenylephrine treatments ($P<0.01$) and not significant between the first and second ephedrine treatments ($P=0.19$) based on unpaired Student's *t*-test. These results suggest that the effect of phenylephrine treatment on cerebral haemodynamics is negated by the previous ephedrine treatment. In contrast, the effect of ephedrine treatment is less affected by phenylephrine. This finding may be caused by the longer clinical half-life of ephedrine than phenylephrine (clinical observation). Our analysis of the carry-over effect based on linear-mixed models showed that this is not significant ($P=0.11$) at the 0.05 level. This might be due to the fact that testing carry-over effects usually requires a larger sample size than that of our study.

The main methodological considerations are as follows. The method of phenylephrine and ephedrine administration in this study was bolus, not infusion. The effects of bolus

and infusion administrations on systemic and cerebral haemodynamics may be different. For example, the gradual increase in MAP caused by infusion might not be able to elicit the same increase in SNA in the superior cervical ganglion as that seen with bolus. A comparison study between bolus and infusion would be informative. Secondly, we used Sct_{O_2} based on NIRS measurements to assess cerebral haemodynamics. Middle cerebral artery flow velocity (MCA_V) based on transcranial Doppler (TCD) measurement, which is also non-invasive and portable, is another technology being used for the same purpose. However, MCA_V may not provide a valid CBF estimation should vessel calibre or flow profile change.[29] Indeed, in studies where both technologies were adopted, it was found that MCA_V increased, whereas Sct_{O_2} decreased after phenylephrine bolus and infusion administration in healthy non-anaesthetized volunteers.[11 13] One of the possible explanations for this discrepancy lies in the fact that TCD measures flow velocity in large cerebral arteries, whereas NIRS measures oxygen saturation mainly at the capillary bed.

In summary, associated with the changes in CO, cerebral oxygenation decreases after phenylephrine but remains unchanged after ephedrine bolus treatment in anaesthetized patients, even though both agents consistently increase MAP. The significant correlation between CO and Sct_{O_2} implies a cause–effect relationship between global haemodynamics (CO) and regional haemodynamics (Sct_{O_2}).

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Acknowledgements

We acknowledge the generous loan of the Oxiplex TX oximeter from ISS, Inc. Special thanks go to Debra E. Morrison, MD, for her insightful discussions.

Conflict of interest

The authors (A.E.C., B.J.T., and W.W.M.) consult for ISS, Inc.

Funding

This study is supported by the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) through the following programmes: the Institute for Clinical and Translational Science (ICTS) grant UL1 RR031985 (B.J.T.); the Laser Microbeam and Medical Program [LAMMP, an NIH BRTP resource (P41-RR01192)] (B.J.T.); and the Laboratory for Fluorescence Dynamics (LFD) grant P41 RR03155 (W.W.M.). It is also supported by the Department of Anesthesiology and Perioperative Care, University of California, Irvine, CA, USA.

References

1 Sookplung P, Siriussawakul A, Malakouti A, *et al.* Vasopressor use and effect on blood pressure after severe adult traumatic brain injury. *Neurocrit Care* Online First™ 2010, September 28

2 Moss J, Glick D. The autonomic nervous system. In: Miller RD, ed. *Miller's Anesthesia*, 6th Edn. Philadelphia: Elsevier Churchill Livingstone, 2005; 617–77

3 Dyer RA, Reed AR, van Dyk D, *et al.* Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. *Anesthesiology* 2009; **111**: 753–65

4 Nissen P, Brassard P, Jørgensen TB, *et al.* Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. *Neurocrit Care* 2010; **12**: 17–23

5 Vohra HA, Modi A, Ohri SK. Does use of intra-operative cerebral regional oxygen saturation monitoring during cardiac surgery lead to improved clinical outcomes? *Interact Cardiovasc Thorac Surg* 2009; **9**: 318–22

6 Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br J Anaesth* 2009; **103**: i3–13

7 Wong FY, Nakamura M, Alexiou T, *et al.* Tissue oxygenation index measured using spatially resolved spectroscopy correlates with changes in cerebral blood flow in newborn lambs. *Intensive Care Med* 2009; **35**: 1464–70

8 Fantini S, Franceschini-Fantini MA, Maier JS, *et al.* Frequency-domain multichannel optical detector for non-invasive tissue spectroscopy and oximetry. *Opt Eng* 1995; **34**: 32–42

9 Choi J, Wolf M, Toronov V, *et al.* Noninvasive determination of the optical properties of adult brain: near-infrared spectroscopy approach. *J Biomed Opt* 2004; **9**: 221–9

10 Liu H, Chance B, Hielscher AH, *et al.* Influence of blood vessels on the measurement of hemoglobin oxygenation as determined by time-resolved reflectance spectroscopy. *Med Phys* 1995; **22**: 1209–17

11 Brassard P, Seifert T, Wissenberg M, *et al.* Phenylephrine decreases frontal lobe oxygenation at rest but not during moderately intense exercise. *J Appl Physiol* 2010; **108**: 1472–8

12 Yocum GT, Gaudet JG, Teverbaugh LA, *et al.* Neurocognitive performance in hypertensive patients after spine surgery. *Anesthesiology* 2009; **110**: 254–61

13 Lucas SJ, Tzeng YC, Galvin SD, *et al.* Influence of changes in blood pressure on cerebral perfusion and oxygenation. *Hypertension* 2010; **55**: 698–705

14 Brassard P, Seifert T, Secher NH. Is cerebral oxygenation negatively affected by infusion of norepinephrine in healthy subjects? *Br J Anaesth* 2009; **102**: 800–5

15 Cassaglia PA, Griffiths RI, Walker AM. Sympathetic nerve activity in the superior cervical ganglia increases in response to imposed increases in arterial pressure. *Am J Physiol Regul Integr Comp Physiol* 2008; **294**: R1255–61

16 Arbab MA, Wiklund L, Svendgaard NA. Origin and distribution of cerebral vascular innervation from superior cervical, trigeminal and spinal ganglia investigated with retrograde and anterograde WGA-HRP tracing in the rat. *Neuroscience* 1986; **19**: 695–708

17 Hamel E. Perivascular nerves and the regulation of cerebrovascular tone. *J Appl Physiol* 2006; **100**: 1059–64

18 Edvinsson L, Owman C. Pharmacological characterization of adrenergic alpha and beta receptors mediating the vasomotor responses of cerebral arteries in vitro. *Circ Res* 1974; **35**: 835–49

19 Gupta MM, Bithal PK, Dash HH, *et al.* Effects of stellate ganglion block on cerebral haemodynamics as assessed by transcranial Doppler ultrasonography. *Br J Anaesth* 2005; **95**: 669–73

20 van Lieshout JJ, Secher NH. Point:counterpoint: sympathetic activity does/does not influence cerebral blood flow. Point: sympathetic activity does influence cerebral blood flow. *J Appl Physiol* 2008; **105**: 1364–6

21 Strandgaard S, Sigurdsson ST. Point:counterpoint: Sympathetic activity does/does not influence cerebral blood flow. Counterpoint: Sympathetic nerve activity does not influence cerebral blood flow. *J Appl Physiol* 2008; **105**: 1366–7

22 Olesen J. The effect of intracarotid epinephrine, norepinephrine, and angiotensin on the regional cerebral blood flow in man. *Neurology* 1972; **22**: 978–87

23 van Lieshout JJ, Pott F, Madsen PL, *et al.* Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. *Stroke* 2001; **32**: 1546–51

24 Ogoh S, Brothers RM, Barnes Q, *et al.* The effect of changes in cardiac output on middle cerebral artery mean blood velocity at rest and during exercise. *J Physiol* 2005; **569**: 697–704

25 Charkoudian N, Joyner MJ, Johnson CP, *et al.* Balance between cardiac output and sympathetic nerve activity in resting humans: role in arterial pressure regulation. *J Physiol* 2005; **568**: 315–21

26 Jhanji S, Lee C, Watson D, *et al.* Microvascular flow and tissue oxygenation after major abdominal surgery: association with postoperative complications. *Intensive Care Med* 2009; **35**: 671–7

27 Jhanji S, Vivian-Smith A, Lucena-Amaro S, *et al.* Haemodynamic optimisation improves tissue microvascular flow and oxygenation after major surgery: a randomised controlled trial. *Crit Care* 2010; **14**: R151

28 Giglio MT, Marucci M, Testini M, *et al.* Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. *Br J Anaesth* 2009; **103**: 637–46

29 Taylor GA, Short BL, Walker LK, *et al.* Intracranial blood flow: quantification with duplex Doppler and color Doppler flow US. *Radiology* 1990; **176**: 231–6

Improving Perioperative Outcomes: Fluid Optimization with the Esophageal Doppler Monitor, a Metaanalysis and Review

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Optimizing intravascular volume status in patients undergoing major surgery is essential to reduce the risk of complications and poor outcomes.[1] Evidence suggests that using conventional physiologic signs such as heart rate and blood pressure may not be able to detect subclinical hypovolemia, contributing to an increase in morbidity and complications including postoperative gastrointestinal dysfunction.[2,3] Recent evidence showed that some forms of invasive intravascular hemodynamic monitoring, such as central venous oxygen saturation, may be very useful in improving outcomes in patients undergoing major operations[4] or those with severe sepsis.[5] But central venous and pulmonary artery catheterization are invasive,[6] and not all studies have consistently shown that they are beneficial.[7]

An esophageal Doppler monitor (ODM) is a cardiac output monitoring device that measures the descending aortic blood flow using transesophageal Doppler ultrasound.[8] Cardiac output and stroke volume are estimated using the descending thoracic aortic blood flow velocity integral and a nomogram using age, height, and weight. ODM is used as a continuous cardiac output or stroke volume monitor and as such, intravascular volume status or preload of the left ventricle can be optimized by titrating IV fluid boluses (usually 250 mL of colloid fluid) to a flow chart based in large part on the Frank-Starling principle. Because the ODM is much smaller than an ordinary transesophageal echocardiographic probe, it is less invasive and has a very good safety record. Specifically, there have been no case reports of esophageal perforation and only reports of minor complications such as mucosal trauma and endobronchial placement, which is readily identified and repositioned.

We hypothesized that using intraoperative ODM to guide IV fluid therapy will optimize patient's intravascular volume status or preload and may improve perioperative outcomes. A number of studies have been published suggesting that this device may be useful to improve perioperative outcomes.[9] These studies were, however, limited by their small sample size and their assessment of only a specific subgroup of surgical patients.[10-12] As such, we meta-analyzed the existing randomized controlled studies to quantify the potential benefits of ODM and to assess whether its benefits are generalizable to different groups of surgical patients.

Disclosure Information: Nothing to disclose.

Received June 4, 2008; Revised August 1, 2008; Accepted August 4, 2008.
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METHODS

Search criteria

Because the technique and first clinical use of ODM were described in 1971,[13] we searched Medline (1970 to 2008, week 5) and EMBASE (1980 to 2008, week 19) databases and the Cochrane Controlled Trial Register for eligible randomized controlled trials. During the database searches, the following MeSH terms were used: *fluid therapy*, *fluid treatment*, *resuscitation*, *hydration*, *cardiac output* with the *esophageal Doppler*. We also assessed the bibliographies of all potentially eligible studies and relevant review articles to avoid missing any randomized controlled trials.

Inclusion criteria

In this metaanalysis, we included only randomized controlled trials that had an intervention arm in which intraoperative IV fluid therapy was guided by using ODM to optimize intravascular volume status (or stroke volume) in the perioperative setting.

Exclusion criteria

The review was restricted to randomized control trials and also excluded studies that did not use the ODM to guide IV fluid to optimize intravascular volume status or stroke volume.

Data extraction

Two assessors evaluated each included article independently and extracted data in a tabulated format. Where

ISSN 1072-7515/08/$34.00
doi:10.1016/j.jamcollsurg.2008.08.007

Abbreviations and Acronyms

LOS = length of stay
ODM = esophageal Doppler monitor
OR = odds ratio
WMD = weighted mean difference

there was a difference between assessors, a consensus was reached in a meeting.

Outcomes of interest

Length of hospital stay

The primary outcome of this metaanalysis was length of hospital stay (LOS), defined as the number of postoperative days in an acute care hospital setting. Extended stay in a rehabilitation hospital after the initial stay in an acute care hospital was excluded.

Return to oral diet

This was defined as return to full oral diet or solids.

Morbidity – total number of complications

The review of the result was difficult because of a lack of standardization in the definitions of complications and in how they were measured and reported. Some studies presented the total number of complications among all patients; others expressed the complication rate as the proportion of patients who experienced one or more complications. With these limitations in mind, we reported the incidence of these complications as defined by each of the pooled studies.

Colloid and crystalloid volumes

We reported the amount of intraoperative IV crystalloid and colloid fluid used.

Mortality

Mortality was defined as death occurring either intraoperatively or within 30 to 60 days after operation.

Risk of bias assessment

After identifying the eligible studies, the quality of each study was assessed by its risk of possible bias by two independent reviewers. Risk of bias was graded as A, B, or C, corresponding to low, moderate, or high risk of bias, respectively, depending on the study's blinding, allocation concealment, randomization, and intention-to-treat analysis.[14]

Statistical analysis

Continuous outcomes variables such as LOS, time to return to full oral diet, and volume of IV fluid used were presented as weighted mean difference (WMD) using a fixed effect model. Where only medians were available, we used them to represent the mean; standard deviation (SD) was estimated from interquartile range (IQR) if SD was not available.[14,15] Binary outcomes such as morbidity (or proportion of patients with postoperative complications) were presented as odds ratios (OR), also using a fixed effect model. All data were analyzed by Review Manager.[16] Heterogeneity was assessed by the chi-square statistic, and if heterogeneity was present, data were further examined to explore the possible reasons for it. We used funnel plot to

Table 1. Summary of Studies and Risk of Bias Classification

First author, year	Risk of bias*	Type of operation	n	Intervention†	Colloid	Outcomes
Conway, 2002[21]	B	Major bowel	57	SV > 10%, ftc < 0.35	HES	LOS, diet, critical care days
Gan, 2002[2]	A	Major gynecologic, general, urology	100	SV > 10% ftc < 0.35	200 mL 6% HES	LOS, diet, complications
Wakeling, 2005[19]	A	Colorectal	128	SV > 10%	250 mL Haemacel or Gelofusine	LOS, diet, endotoxin, complications
Noblett, 2006[3]	A	Colorectal	103	ftc < 0.35 SV > 10%	7 mL/kg intial bolus, then 3 mL/kg colloid	LOS, diet, morbidity, critical care days, cytokines
Sinclair, 1997[22]	B	PFF	40	ftc < 0.35, SV > 10%	3 mL/kg HES	LOS, hemodynamics
Venn, 2002[20]	A	PFF	90	ftc < 0.35, SV > 10%	200 mL Gelofusine	LOS, complications
Mythen, 1995[17]	C	Cardiac	60	CVP < 3, rise in SV	200 mL 6% HES	LOS, pHi, complications, ICU days
McKendry, 2004[23]	A	Postoperative cardiac	170	svi > 10% fluid loss	200 mL colloid or blood	LOS, complications
Chytra, 2007[18]	C	Trauma	162	SV > 10%, ftc < 0.35	HES, Gelofusine	LOS, ICU days, infection, lactate

CVP, central venous pressure; diet, time to establishment of oral intake; ftc, flow corrected time (sec); HES, hydroxyethyl starch; LOS, length of stay; PFF, proximal femoral fracture; pHi, gastric intestinal pH; SV, stroke volume change, eg >10%; svi, stroke volume index.

*_Cochrane Handbook of Systematic Reviews._[14]

†Main triggers for fluid administration in the protocol group.

assess potential publication bias using the LOS as an end-point.

RESULTS

Eligible studies

We identified 58 potentially eligible studies using the predefined search criteria; 9 of these were judged eligible for metaanalysis (Table 1, Fig. 1).[2,3,17-23] Two randomized controlled studies were excluded because one used the ODM as a monitor in both the protocol and control groups with dopexamine as an intervention,[24] and one used the ODM as a cardiac output monitor in laparoscopic surgery without using the data derived from the ODM to guide fluid therapy.[25] Details of the pooled studies are described in Figure 1.

All nine studies were prospective randomized controlled studies and five studies were classified as having a very low risk of bias (ie, class A). Within these five studies, only one study by Noblett and colleagues[3] achieved definite double blinding. In the other four studies, the anesthesiologist was blinded to the data derived from the ODM and the outcomes assessment but not the intervention (ie, IV fluid administered). Two studies were classified as having moderate risk of bias (class B) because sequence generation or allocation concealment or both were unclear. Two studies were classified as having high risk of bias (class C). Mythen and Webb[17] did not clearly describe adequate blinding, allocation concealment, and intention-to-treat analysis. Chytra and coworkers[18] had inadequate sequence allocation, did not attempt to conceal allocation, and did not attempt to blind either the investigators or outcomes assessors.

We contacted seven of the nine lead authors of the included studies to obtain unpublished data, which we received from two of them.[3,19] A total of 915 patients were randomized in 8 studies, and 439 of them were randomized to receive ODM-guided intraoperative IV fluid therapy. Two "control" groups were used to compare with groups receiving ODM in the study by Venn and colleagues.[20] One control group used central venous pressure (CVP) to guide IV fluid therapy and one control did not use any additional monitor. For the purposes of metaanalysis, we compared the ODM group twice with both of these "control" groups and referred to them as Venn Con and Venn CVP in the forest plot.

Metaanalysis

Primary outcomes

All nine studies reported data on LOS, with six studies reporting the median and three studies reporting the mean. Of the studies reporting LOS as medians, unpublished data with means were obtained from two of the authors. Use of ODM was associated with a significant reduction in LOS (WMD −2.34 days, 95% CI −2.91 to −1.77; $p < 0.00001$) when compared with the control group (Fig. 2). Restricting the analysis to the four studies that evaluated patients undergoing colorectal surgery did not change the results of the analysis (WMD −2.17 days, 95% CI −3.16 to −1.17), but reduced the heterogeneity of the results (Fig. 3).

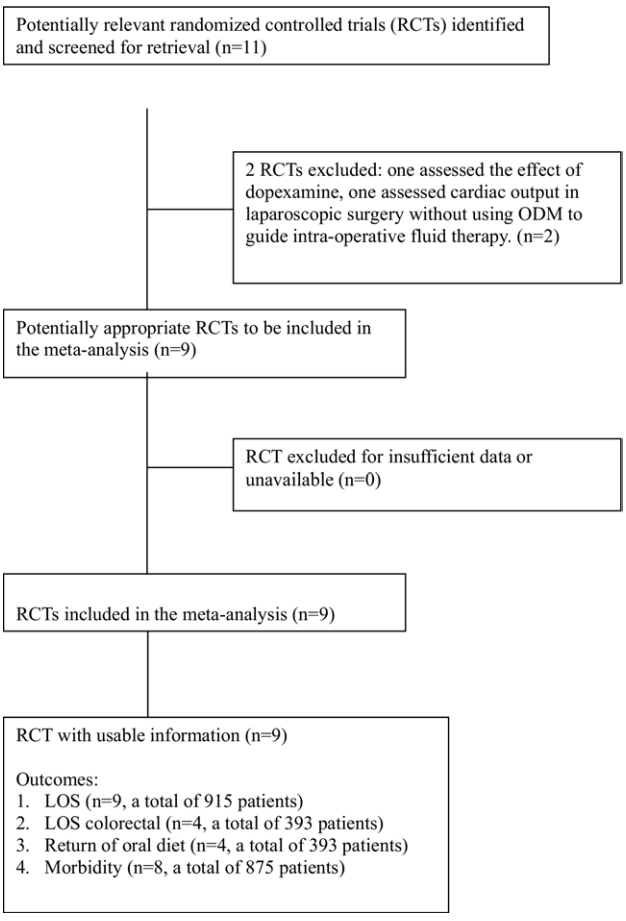

Figure 1. Flow chart showing the selection and exclusion of different trials for the metaanalysis. LOS, hospital length of stay; ODM, esophageal Doppler monitor; RCT, randomized controlled trial.

Secondary outcomes

Four studies on colorectal surgery reported data on time to return of gastrointestinal function as indicated by resuming oral or solids diet. Use of ODM was associated with a significant reduction in the time to resume oral diet (WMD −1.65 days, 95% CI −1.83 to −1.46; $p < 0.00001$; Fig. 4). Use of ODM was also associated with a reduction in risk of having postoperative morbidity or complications (OR 0.37, 95% CI 0.27 to 0.50; $p < 0.00001$; Fig. 5). The use of ODM was not associated with a significant difference in mortality.

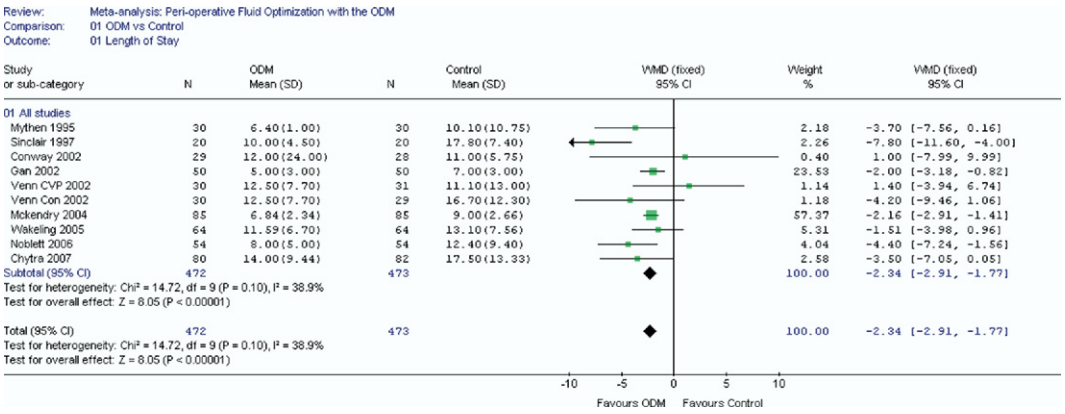

Figure 2. Forest plot showing the effect of esophageal Doppler monitoring (ODM) on length of stay from all studies. Chi^2, chi-squared; df, degrees of freedom; I^2, I-squared value; WMD, weighted mean difference; Z, Z-value.

As expected from the cardiac output or stroke volume optimization algorithm of the ODM device, intraoperative use of ODM was associated with an increase in the amount of IV colloid fluid administered (WMD 736 mL, 95% CI 680 to 792; $p < 0.00001$; Fig. 6). Most studies used 4% hydroxyethylstarch, two studies used gelatin-based fluids, one study used both, and two studies did not specify the type of colloid fluid used. The amount of IV crystalloid fluid used was not different between the ODM and control groups.

Sensitivity analysis

We used a fixed effect model to address the issue of heterogeneity. Having done so, we then incorporated heterogeneity in the model by performing a sensitivity analysis using a random effects model. This did not change the outcomes significantly; the use of ODM remained significantly associated with an improvement in LOS (WMD −2.69, 95% CI −3.71 to −1.67; $p < 0.00001$) and morbidity (OR 0.38, 95% CI 0.26 to 0.54; $p < 0.00001$). Similarly, when two studies with a high risk of bias (class C) were excluded,[17,18] improvement in LOS (WMD −2.60, 95% CI −3.79 to −1.42; $p < 0.00001$) and morbidity (OR 0.42, 95% CI 0.29 to 0.62; $p < 0.00001$) remained statistically significant.

Publication bias

The funnel plot was unusual and showed that there was a lack of small positive studies (absence of dots at the bottom left corner, Fig. 7). The most likely explanation for this asymmetry was the small number of studies instead of publication bias.[26]

DISCUSSION

Our results showed that using an esophageal Doppler monitor (ODM) to guide intraoperative IV fluid therapy will increase the administration of intraoperative IV colloid fluid and reduce length of hospital stay, time to resume full oral diet, and postoperative morbidity or complications.

Evidence suggests that using conventional physiologic signs such as heart rate and blood pressure to guide IV fluid therapy may lead to subclinical hypovolemia, contributing to an increase in morbidity and complications including postoperative gastrointestinal dysfunction.[2,3] Our results

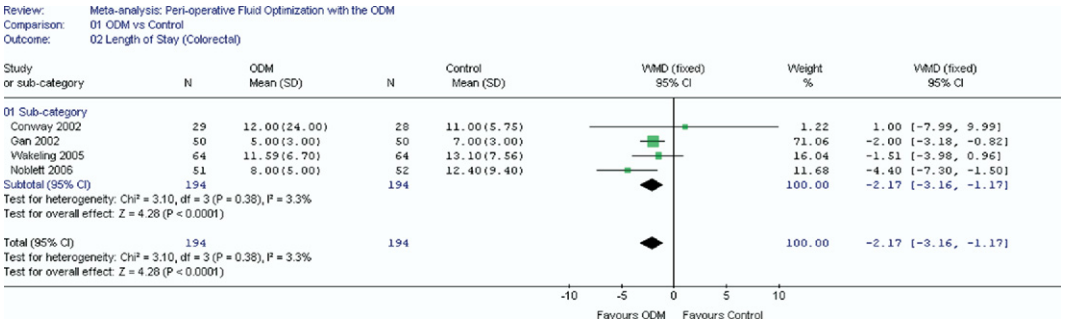

Figure 3. Forest plot showing the effect of esophageal Doppler monitoring (ODM) on length of stay restricting the analysis to four studies that evaluated patients undergoing colorectal surgery. Chi^2, chi-squared; df, degrees of freedom; I^2, I-squared value; WMD, weighted mean difference; Z, Z-value.

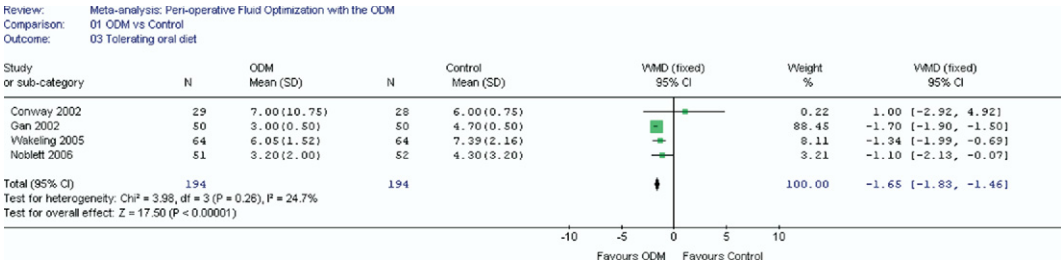

Figure 4. Forest plot showing the effect of esophageal Doppler monitoring (ODM) on time to resume full oral diet after colorectal surgery. Chi^2, chi-squared; df, degrees of freedom; I^2, I-squared value; WMD, weighted mean difference; Z, Z-value.

are consistent with results from these earlier studies and confirm that the use of additional intraoperative hemodynamic monitoring may improve hemodynamic optimization of patients undergoing major surgery, resulting in faster recovery of bowel function and a reduction in postoperative complications and length of hospital stay. It has been suggested that the splanchnic circulation is very sensitive to subclinical hypovolemia, and gastrointestinal complications are the most common complications after major surgery, affecting more than 50% of patients.[27,28] Our results support the hypothesis that subclinical hypovolemia may contribute to significant postoperative bowel dysfunction and this complication may, at least to some extent, be preventable by using ODM to optimize intraoperative fluid therapy.

There has been increasing emphasis on length of hospital stay and the impact of protocol-driven management plans or "fast tracking," to shorten length of stay.[28-31] Protocols usually specify analgesic regime, mobilization, introduction of oral diet, and avoidance of routine nasogastric drainage.[30,32] These protocols have been shown to reduce postoperative length of hospital stay to between 3 and 5 days. The importance of optimal fluid balance as a component of the anesthesia in these protocols has been highlighted.[33] Pharmacologic approaches to minimize postoperative ileus have also been considered with the use of alvimopam.[32] Whether the benefits of fluid balance management on postoperative ileus, as demonstrated in this metaanalysis, can have additional benefits in combination with alvimopam remains uncertain, but this merits further investigation.

None of the pooled studies reported on cost-effectiveness of ODM. The use of ODM is, however, potentially cost-effective because it significantly reduces the length of hospital stay and postoperative complications. In this regard, future studies on ODM should consider a vigorous cost-effective assessment. There was also no direct comparison of the ODM with other monitoring devices including central venous oxygen saturation and pulse contour cardiac output devices to guide fluid therapy.[4,5,34] The accuracy of latter technology has been studied recently[35]; and its use to guide fluid therapy did not show a difference in outcomes[34]; perhaps the use of intrathoracic blood volume as the endpoint of fluid therapy may not be as accurate as using ODM to optimize fluid therapy.

This study has significant limitations. Overall, the studies and the data reported in the pooled studies were of good quality. But two studies were assessed as having a high risk

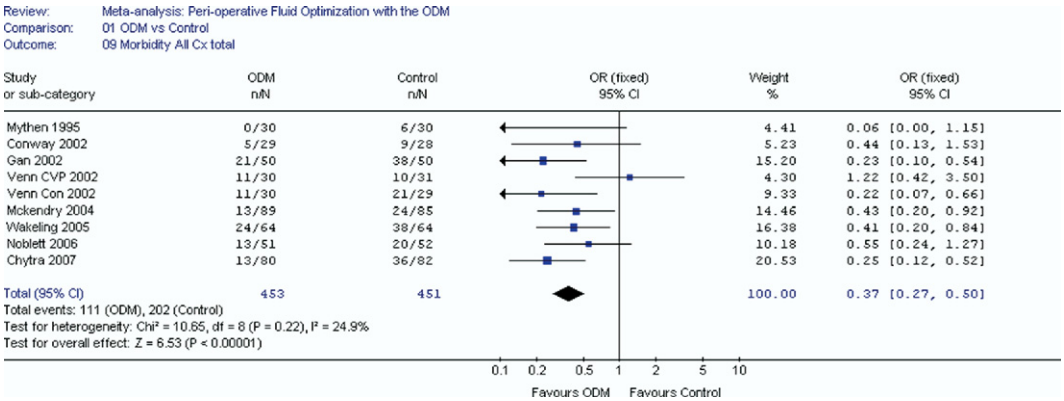

Figure 5. Forest plot showing the effect of esophageal Doppler monitoring (ODM) on postoperative morbidity and complications. Chi^2, chi-squared; df, degrees of freedom; I^2, I-squared value; WMD, weighted mean difference; Z, Z-value.

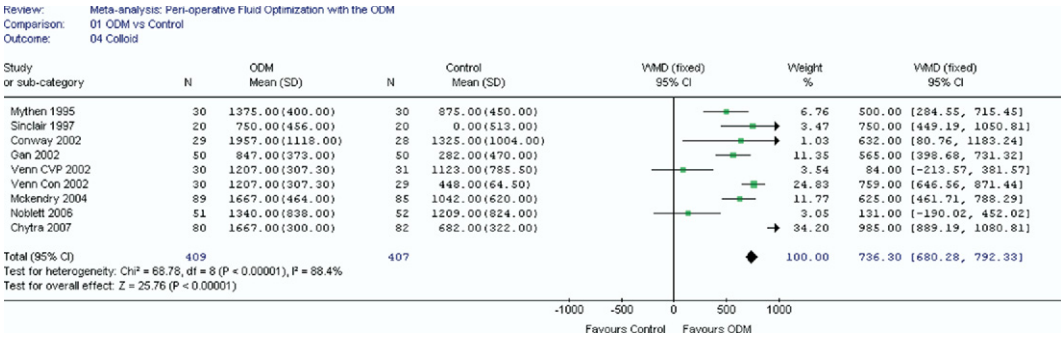

Figure 6. Forest plot showing the effect of esophageal Doppler monitoring (ODM) use on amount of IV colloid fluid administered. Chi^2, chi-squared; df, degrees of freedom; I^2, I-squared value; WMD, weighted mean difference; Z, Z-value.

of bias; excluding these two studies did not change our results. Second, the existing studies did not include a comprehensive range of surgical patients. So our results may not be generalizable to patients undergoing major plastic, vascular, and gynecologic surgery or operations under regional anesthesia. Third, we used the ODM group twice to compare with two control groups in one study.[20] If we use Bonferroni correction to adjust for multiple comparisons, the p value will be slightly larger than those reported in the forest plot. Finally, the pooled studies did not address some issues in perioperative IV fluid therapy and these may potentially confound our results. These issues include the total amount of blood loss, timing of administration of IV fluid, and whether the fluid protocol in the control group was "restrictive" or "liberal." Recent studies suggested that administration of excessive amounts of IV fluid without guidance from an ODM or alternative monitor can lead to a fluid-overloaded state with adverse perioperative outcomes.[36-38]

In summary, with the limited data available, our results suggest that using an esophageal Doppler monitor can lead to an increase in use of perioperative colloid fluid and a reduction in length of hospital stay, time to resume full oral diet or bowel function, and in complications after major surgery. Additional research on the cost-effectiveness of ODM, its utility in other groups of surgical patients, and its comparative beneficial effects against other intraoperative or postoperative monitoring devices is needed.

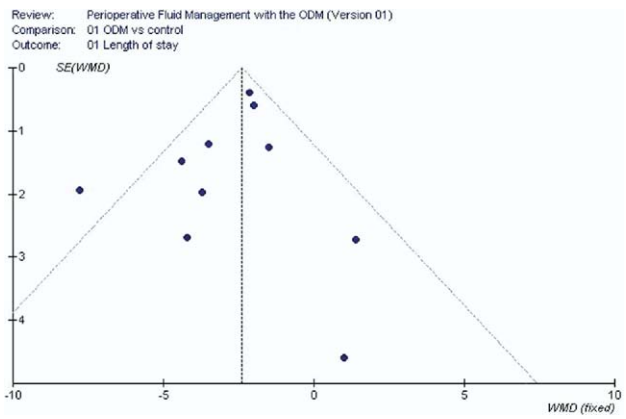

Figure 7. Funnel plot using length of stay as an end-point. ODM, esophageal Doppler monitoring; WMD, weighted mean difference.

Author Contributions

Study conception and design: Phan, Ismail, Heriot
Acquisition of data: Phan, Ismail
Analysis and interpretation of data: Phan, Ismail, Heriot, Ho
Drafting of manuscript: Phan, Ismail, Heriot, Ho
Critical revision: Phan, Ismail, Heriot, Ho

REFERENCES

1. Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. Arch Surg 1973;106:630–636.
2. Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002;97:820–826.
3. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. Br J Surg 2006;93:1069–1076.
4. Pearse R, Dawson D, Fawcett J, et al. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Crit Care 2005;9:R687–693.
5. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–1377.
6. Connors AF Jr, Castele RJ, Farhat NZ, Tomashefski JF Jr. Complications of right heart catheterization. A prospective autopsy study. Chest 1985;88:567–572.
7. Polanczyk CA, Rohde LE, Goldman L, et al. Right heart cathe-

terization and cardiac complications in patients undergoing noncardiac surgery: an observational study. JAMA 2001;286: 309–314.
8. Chamberlain BM, Spencer T, Lowe Graham D. Oesophageal Doppler guided stroke volume optimisation - a technical review. Deltex Medical Technical Review 2005;1–8.
9. Bundgaard-Nielsen M, Holte K, Secher NH, Kehlet H. Monitoring of peri-operative fluid administration by individualized goal-directed therapy. Acta Anaesthesiol Scand 2007;51:331–340.
10. Price JD, Sear JW, Venn RM. Perioperative fluid volume optimization following proximal femoral fracture. Cochrane Database Syst Rev 2004;CD003004.
11. Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. Anaesthesia 2008;63:44–51.
12. Walsh SR, Tang T, Bass S, Gaunt ME. Doppler-guided intraoperative fluid management during major abdominal surgery: systematic review and meta-analysis. Int J Clin Pract 2008;62: 466–470.
13. Side CD, Gosling RG. Non-surgical assessment of cardiac function. Nature 1971;232:335–336.
14. Higgins JPT, GSe. Cochrane handbook for systematic reviews of interventions, version 5.0.0. The Cochrane Collaboration 2008.
15. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
16. Review manager [computer program] version 4.2 for Windows. Edited, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2003.
17. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg 1995;130:423–429.
18. Chytra I, Pradl R, Bosman R, et al. Esophageal Doppler-guided fluid management decreases blood lactate levels in multiple-trauma patients: a randomized controlled trial. Crit Care 2007; 11:R24.
19. Wakeling HG, McFall MR, Jenkins CS, et al. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. Br J Anaesth 2005;95:634–642.
20. Venn R, Steele A, Richardson P, et al. Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. Br J Anaesth 2002;88:65–71.
21. Conway DH, Mayall R, Abdul-Latif MS, et al. Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. Anaesthesia 2002;57:845–849.
22. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. BMJ 1997;315:909–912.
23. McKendry M, McGloin H, Saberi D, et al. Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery. BMJ 2004;329:258.
24. Stone MD, Wilson RJ, Cross J, Williams BT. Effect of adding dopexamine to intraoperative volume expansion in patients undergoing major elective abdominal surgery. Br J Anaesth 2003; 91:619–624.
25. Alijani A, Hanna GB, Cuschieri A. Abdominal wall lift versus positive-pressure capnoperitoneum for laparoscopic cholecystectomy: randomized controlled trial. Ann Surg 2004;239:388–394.
26. Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. J Clin Epidemiol 2005;58:894–901.
27. Hamilton-Davies C, Mythen MG, Salmon JB, et al. Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. Intensive Care Med 1997;23:276–281.
28. Delaney CP, Zutshi M, Senagore AJ, et al. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum 2003;46:851–859.
29. King PM, Blazeby JM, Ewings P, et al. The influence of an enhanced recovery programme on clinical outcomes, costs and quality of life after surgery for colorectal cancer. Colorectal Dis 2006;8:506–513.
30. Kehlet H. Fast-track colorectal surgery. Lancet 2008;371:791–793.
31. Basse L, Thorbol JE, Lossl K, Kehlet H. Colonic surgery with accelerated rehabilitation or conventional care. Dis Colon Rectum 47:271–277, 2004; discussion 277–278.
32. Delaney CP, Wolff BG, Viscusi ER, et al. Alvimopan, for postoperative ileus following bowel resection: a pooled analysis of phase III studies. Ann Surg 2007;245:355–363.
33. White PF, Kehlet H, Neal JM, et al. The role of the anesthesiologist in fast-track surgery: from multimodal analgesia to perioperative medical care. Anesth Analg 2007;104:1380–1396, table of contents.
34. Szakmany T, Toth I, Kovacs Z, et al. Effects of volumetric vs. pressure-guided fluid therapy on postoperative inflammatory response: a prospective, randomized clinical trial. Intensive Care Med 2005;31:656–663.
35. Della Rocca G, Costa MG, Coccia C, et al. Cardiac output monitoring: aortic transpulmonary thermodilution and pulse contour analysis agree with standard thermodilution methods in patients undergoing lung transplantation. Can J Anaesth 2003; 50:707–711.
36. Brandstrup B, Tonnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg 2003;238:641–648.
37. Nisanevich V, Felsenstein I, Almogy G, et al. Effect of intraoperative fluid management on outcome after intraabdominal surgery. Anesthesiology 2005;103:25–32.
38. Lobo DN, Bostock KA, Neal KR, et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. Lancet 2002; 359:1812–1818.