BMJ Open

A randomised controlled trial to investigate the relationship between mild hypercapnia and cerebral oxygen saturation in patients undergoing major surgery

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029159
Article Type:	Original research
Date Submitted by the Author:	14-Jan-2019
Complete List of Authors:	Wong, Clarence; Austin Hospital, Department of Anaesthesia Churilov, Leonid; The Florey Institute of Neuroscience and Mental Health; University of Melbourne Cowie, Dean; Austin Hospital, Department of Anaesthesia Tan, Chong; Austin Hospital, Department of Anaesthesia Hu, Raymond; Austin Hospital, Department of Anaesthesia Tremewen, David; Austin Hospital, Department of Anaesthesia Pearce, Brett; Austin Hospital, Department of Anaesthesia Pillai, Param; Austin Hospital, Department of Anaesthesia Karalipillai, Dharshi; Austin Hospital, Department of Anaesthesia Bellomo, Rinaldo; Austin Hospital, Department of Intensive Care; University of Melbourne Weinberg, Laurence; Austin Hospital, Department of Anaesthesia; University of Melbourne
Keywords:	hypercapnia, oximetry, Spectroscopy, Near-Infrared, Respiration, Artificial, Delirium

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A randomised controlled trial to investigate the relationship between mild hypercapnia and cerebral oxygen saturation in patients undergoing major surgery

Authors: Clarence Wong[1,2], Leonid Churilov[2,3], Dean Cowie[1], Chong Tan[1], Raymond Hu[1], David Tremewen[1], Brett Pearce[1], Param Pillai[1], Dharshi Karalipillai[1], Rinaldo Bellomo[1,2], Laurence Weinberg[1,2]

1. Department of Anaesthesia, Austin Hospital, Heidelberg, Victoria, Australia;

2. University of Melbourne, Parkville, Victoria, Australia;

3. The Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia

Correspondence

A/Prof Laurence Weinberg

Department of Anesthesia, Austin Hospital

145 Studley Road, Heidelberg, Victoria 3084, Australia

Phone number: (61) 03 94965000

Email: laurence.weinberg@austin.org.au

Word Count

Abstract: 279

Introduction: 239

Methods: 1553

Results: 741

Discussion: 1213

Conclusion: 81

Body text: 3827

Abstract

Background: The effects of hypercapnia on regional cerebral oxygen saturation (rSO_2) during surgery are unclear. We hypothesised that, compared with targeted normocapnia (TN), targeted mild hypercapnia (TMH) during major surgery would increase rSO_2.

Methods: We performed a prospective, randomised controlled trial in adult participants undergoing major surgery at a tertiary centre in Victoria, Australia. TMH ($PaCO_2$ 45-55 mmHg) or TN ($PaCO_2$ 35-40 mmHg) was delivered via controlled ventilation throughout surgery. The primary endpoint was the absolute difference between two groups in percentage change in rSO_2 from baseline to completion of surgery. Secondary endpoints included the incidence of postoperative delirium and length of stay (LOS) in hospital.

Results: We randomised 40 participants (20 to TMH and 20 to TN]). The median [IQR] $PaCO_2$ in the TMH group was 51.5 mmHg [46.9 to 60.9] vs. 34.8 mmHg [32.8 to 38.1] in the TN group ($P<0.001$). The absolute difference between two groups in percentage change in rSO_2 from baseline to completion of surgery was 19.0% higher in both hemispheres with TMH ($P<0.001$). On the random-effect repeated measures analysis, the difference in $\%\Delta rSO_2$ on both left and right between the two groups diverged with time with the TMH group exhibiting smaller percentage decrease over time compared to the TN group. Postoperative delirium was higher in the TN group (risk difference 0.3, 95% CI [0.1 to 0.5], $P=0.02$). Length of stay was similar between groups (5 days vs. 5 days; $P=0.99$).

Conclusions: This study provides preliminary evidence that in patients undergoing major surgery, TMH is associated with a larger increase in rSO_2 from baseline on both the left and right cerebral cortex. Our findings provide the rationale for larger studies of TMH during surgery.

Clinical trial registration: The Australian New Zealand Clinical Trials Registry, unique identification number: ACTRN12616000320459

Keywords: Hypercapnia; Oximetry; Spectroscopy, Near-Infrared; Respiration, Artificial; Delirium

Article Summary

Strengths of this study

- High internal validity due to blinding and random allocation to groups
- Frequent sampling of oximetry data throughout monitoring period
- Robust statistical analysis without any data distortion and misrepresentation
- Non-invasive nature of near-infrared spectroscopy (NIRS) derived regional cerebral oxygen saturation (rSO_2)

Limitations of this study

- Study findings do not apply to emergency surgeries, intra-cranial surgeries, or surgeries requiring one lung ventilation
- rSO_2 measurements rely on the assumption that rSO_2 is homogenous in the brain
- Not statistically powered to investigate post-operative delirium
- Attending anaesthetists cannot be blinded due to the nature of the intervention

Acknowledgement

Funding Statement

Masimo provided the oximetry sensors used for this trial. This study conception, design, trial management, data collection, data analyses, and the writing of the manuscript, have been executed completely independently of Masimo and any other external organizations. This work was supported by the Deparment of Anaesthesia Research Fund, Austin Hospital, Heidelberg, Victoria, Australia

Declaration of interest

All authors declare no conflict of interest.

Presentation

Findings of this study were presented as a poster presentation at the PostGraduate Assembly in Anesthesiology, 8-12 December 2018, New York, USA

Introduction

In patients undergoing major surgery, the effects of mild hypercapnia on regional cerebral oxygen saturation (rSO_2) have not been fully examined, and any beneficial or harmful effects of hypercapnia as a therapeutic ventilation strategy to improve cerebral oxygenation are unknown. In animal models, CO_2 is a well-known vasodilator improving cerebral blood flow.[1-3] The neuroprotective mechanisms of mild hypercapnia, whilst not completely understood, have been postulated to be a result of increase in cerebral blood flow, enhancement of oxygen delivery, improvements in cerebral glucose utilisation and oxidative metabolism,[4,5] and activation of ATP-sensitive potassium channels to maintain normal neuronal activity in the setting of ischemia.[6]

The recent emergence of near-infrared spectroscopy (NIRS) based cerebral oximetry has provided a practical method to measure rSO_2 continuously and non-invasively. This technology has gained substantial supportive evidence in resuscitation, critical care, and surgical applications.[7-9] Numerous studies have shown that NIRS can be applied clinically in the resuscitation and cardiac surgery settings where cerebral desaturation events can be both effectively monitored and managed.[10-13] However, the relationship between mild hypercapnia and rSO_2 in patients undergoing surgery without pre-existing cerebral desaturation events remains unclear.

Accordingly, we conducted a randomised controlled trial to test the hypothesis that targeted mild hypercapnia (TMH) during elective major surgery would increase cerebral oxygen saturation compared to targeted normocapnia (TN). As a secondary aim, we evaluated if TMH would affect the development of postoperative delirium, a commonly reported complication in the immediately peri-operative setting.[14-16]

Methods

Ethics approval and clinical trial registration

The study was approved by the Austin Health Research and Ethics Committee on 6th January 2016 (HREC/15/Austin/488) and all participants gave written informed consent. The study was prospectively registered on 10th March 2016 with the Australian New Zealand Clinical Trials Registry (ACTRN12616000320459). The study was reported in accordance with the CONSORT Guidelines for reporting randomised trials.[17]

Trial design, setting, and population

Between March 2016 and March 2017, we conducted the randomised controlled trial at the Austin Hospital, a university teaching tertiary metropolitan hospital at Heidelberg, Victoria. Following pre-operative assessment at the anaesthesia pre-admissions clinic and the receipt of written informed consent, eligible patients undergoing elective major surgery were identified. Inclusion criteria included the following: adult patients (age greater than 18 years), surgery of greater than 2 hours expected duration requiring at least one overnight admission, a clinical indication for continuous blood pressure monitoring via an invasive arterial line, and intermittent positive pressure ventilation via an endotracheal tube as part of standard anesthesia care. Exclusion criteria included patients undergoing cardiac surgery, procedures requiring one lung isolation liver transplantation, intracranial surgery, GCS less than 15, known cognitive impairment, intellectual disability or a mental illness, moderate pulmonary hypertension (mean pulmonary arterial pressure greater than 40 mmHg), and American Society of Anesthesiology status V.

Randomisation and blinding

An independent statistician generated a computerised sequence of 40 allocation codes, 20 for each group. A research nurse sealed the allocation codes into sequentially numbered opaque envelopes. Study participants, surgeons, and all peri-operative staff were blinded to treatment allocation. However, it was not possible to blind the attending anaesthetist who was responsible for delivery of the intervention. Immediately after induction of anesthesia, patients were randomised to either targeted mild hypercapnia ($PaCO_2$ 45-55 mmHg) or

targeted normocapnia ($PaCO_2$ 35-40 mmHg). The end-tidal carbon dioxide ($EtCO_2$) was titrated accordingly in order to achieve the desired intervention but the anaesthetist did not have a rSO_2 goal to titrate to. Data collection for all the trial outcomes was collected by an independent researcher blinded to treatment allocation. The sequence was decoded after the data was analysed.

Outcomes and data collection

The primary endpoint was the absolute difference between the TMH and TN groups in percentage change in rSO_2 from baseline to completion of surgery. Secondary endpoints evaluated the effects of mild hypercapnia on the incidence of postoperative delirium, intra-operative pH, bicarbonate, base excess, serum potassium, and length of hospital stay (LOS).

Measurement of rSO_2

Regional cerebral oxygen saturation was collected using the Masimo O_3™ regional oximetry component of the Root™ Patient Monitor platform (O_3™ Masimo, Irvine, CA). This regional oximetry device uses NIRS and reflectance oximetry to monitor rSO_2 in the brain, capturing both absolute and trend rSO_2 data. Absolute oximetry data is defined as the regional oxygen saturation value measured by the oximetry probes calibrated by a fixed ratio between arterial to venous blood, whereas the trend oximetry data is defined as the change in regional oxygen saturation value measured by the oximetry probes. The measurement errors for absolute and trend data are reported to be approximately 4% and 3% respectively when tested against reference blood samples taken from the radial artery and internal jugular bulb vein.[18] Following manufacturer instructions, two NIRS sensors were attached to patient's left and right forehead, recording both absolute and trend data bilaterally. After the recording of baseline cerebral oximetry, only absolute oximetry data were extracted and analysed. Regional cerebral oxygen saturation was collected before commencing any premedication and before induction of anesthesia. Measurements were recorded every two seconds until the last surgical suture was sited. Data were exported as comma separated values files after surgery and processed using manually written R scripts on RStudio v. 1.0.136 (**Supplementary File 1)**. Data from the left and right forehead were analysed separately.

Measurement of delirium

Delirium was assessed using a validated and widely utilized Confusion Assessment Method (CAM) rating scale, adapted from Inouye *et al.*, immediately on arrival to hospital, then within 18-24 hours after surgery.[19,20] Diagnosis of delirium requires the presence of both acute onset with fluctuating course and inattention, together with either disorganised thinking or altered level of consciousness. A single trained interviewer, blinded to randomisation, and proficient and trained in the Confusion Assessment Method, conducted all the assessments pre-operatively when patient arrived at the hospital and at 8am on the next day after surgery in the ward (within 18-24 hours postoperatively). The baseline cognitive function was not formally assessed with collateral history from family or carers.

Measurement of $PaCO_2$ and intra-operative adherence to group allocation

Immediately after tracheal intubation with a cuffed endotracheal tube, minute ventilation was adjusted to achieve an $EtCO_2$ concentration of 45-55 mmHg in the TMH group or 35-40 mmHg in the TN group. Due to presence of alveolar dead space, $EtCO_2$ can be lower than $PaCO_2$ by up to 5 mmHg. Therefore, an arterial blood gas was obtained to check $PaCO_2$ and ventilation was further adjusted accordingly to achieve the desired $PaCO_2$ target ranges. The $PaCO_2$-$EtCO_2$ gradient was then maintained throughout the surgery, with the assumption that the $PaCO_2$ would remain constant. Additional ABG were sampled at the discretion of the anaesthetist if the gradient required re-evaluation e.g. requirements for adjustment of ventilation setting. Finally, at completion of surgery, an ABG was sampled to accurately document the $PaCO_2$ value, and to assess whether $PaCO_2$ was being maintained within target values. All arterial blood gas variables were collected by ABL80 FLEX Blood Gas Analyzer (Radiometer, Copenhagen, Denmark).

Standardisation of care

All patients underwent pre-operative multidisciplinary team assessment including a haematology led multimodal peri-operative haemoglobin optimisation program based on the National Blood Authority of Australia's patient blood management initiatives to optimise pre-operative red cell mass, minimise peri-operative blood loss and tolerate postoperative anaemia.[21] All participants were fasted two hours for clear fluids and six hours for solids according to standard hospital fasting protocols. All participants received a general anaesthetic with propofol for induction, an inhalational agent for maintenance of anaesthesia, with 50% oxygen:air mixture to maintain oxygen saturations above 97%. Routine monitoring for all participants included continuous ECG, pulse oximetry, temperature, bispectral index

(BIS) monitoring, and neuromuscular monitoring. Adequate depth of anaesthesia was ensured by targeting BIS reading between 40 and 60. Conduct of anaesthesia, including the use of additional invasive monitoring, intra-operative medications, fluids intervention, and use of vasoactive medications, were entirely at the discretion of the attending anaesthetist. In keeping with hospital protocol, we transfused blood if haemoglobin concentration was less than 75 g dL^{-1}, or less than 80 g dL^{-1} in the presence of ongoing bleeding.

Sample size calculations

Based on our institution's pilot data and reported figures, normal rSO_2 values for awake patients could range from 60% to 80% [22], which we assumed to be the case at the baseline (beginning of surgery). We assumed no change in rSO_2 in the control group and considered an absolute difference between the groups in percentage change in rSO_2 value from the baseline to completion of surgery of 15% to be clinically important. Thus, the absolute changes in rSO_2 from the baseline to the end of surgery were hypothesised to be 0% in control group and 12% (15% percentage change from the baseline of 80% rSO_2) in the intervention group. Assuming two-tailed threshold for statistical significance of 0.05 and common standard deviation of the absolute change of 10%, the total sample size of 40 patients (equally distributed between two groups) will yield the 0.9 power to observe large treatment effect (Cohen's d=1.1 or higher).

Statistical Analyses

The study was reported in accordance with the Statistical Analyses and Methods in the Published Literature (SAMPL) Guidelines.[23] Statistical analysis was performed using commercial statistical software STATA/IC v.13 with a *P* value of 0.05 to indicate statistical significance. Figures and tables were created by manually written R scripts on RStudio v. 1.0.136 (**Supplementary File 2)**. Normality was determined by the Shapiro–Wilk test, further confirmed by manual inspection of the skewness and kurtosis of the data. Parametric continuous data were compared by the Student's t-test, and non-parametric continuous data were compared by the Kruskal Wallis rank sum test. For normally distributed data, results were presented as mean (standard deviation); and for non-parametric data, results were presented as median [inter-quartile range] unless otherwise stated. Fisher's exact test was used in the analysis of all categorical variables. For the primary outcome we compared the absolute difference between the TMH and TN groups in percentage change in rSO_2 from

baseline to completion of surgery using an unpaired, two-tailed t-test. A more detailed longitudinal analysis of time-by-treatment interaction was also conducted using a random effect generalised least squares regression model (due to the repeated measures nature of the data) with percentage change in rSO_2 at a given time point throughout the surgery as the output, the treatment group and the time (minutes from start of surgery), as well as the time-by-treatment interaction term as inputs. The duration of surgery varied between different patients and therefore, in order to compare $\%\Delta rSO_2$ at different time points across all the patients, the time was measured using "minutes from the start of surgery" metric. For robustness analyses, similar models adjusted for age, baseline oximetry values, and pre-operative haemoglobin levels were implemented, as well as models where time was measured not in minutes, but as a percentage of total surgery duration.

Results

Seventy-seven participants were screened for eligibility. Thirty-seven patients were excluded because they did not meet the inclusion criteria (*n*=6), declined to participate (*n*=30), or due to anaesthetist objection to intervention (*n*=1). For logistical reasons, recruitment could only be performed when the interviewer conducting the CAM testing was available. The Consort diagram is presented in **Figure 1**. There were no violations or breaches of the study protocol, however two participants in the hypercapnic group had failure of bilateral probe attachment and lead connection problem that were unable to be rescued. These patients were subsequently excluded from the analyses of oxygenation as no rSO_2 data were captured and were included in the analysis of all other variables and endpoints. In the hypercapnic group, three participants had unilateral discontinuous oximetry readings due to intermittent signal dropout. In the normocapnic group, signal dropout occurred in two patients on the left side. The corresponding data were excluded.

The baseline participant characteristics are summarised in **Table 1**. Both groups were similar in terms of gender, age, weight, body mass index, ASA physical status, and type of surgery performed. In terms of co-morbidities, both groups were similar except for the presence of chronic obstructive pulmonary disease. There was 100% compliance to the designated $PaCO_2$ intra-operative targets. The median [IQR] $PaCO_2$ in the TMH group and TN groups were 51.5 mmHg [46.9 to 60.9] and 34.8 mmHg [32.8 to 38.1] respectively (P<0.001). With regards to surgical characteristics, both groups had similar median [IQR] duration of surgery: 219 min [124 to 304] in the TMH group and 144 min [108 to 218] in the TN group (P=0.121). PaO_2 was similar between the two groups: 156.8 mmHg [146.3 to 217.2] in the TMH group and 142.5 mmHg [122.5 to 199.1] in the TN group (P=0.380). Oxygen saturation was similar: 98.5% in the TMH group [98.1 to 99.0], and 98.5% in the TN group [97.9 to 99.0] (P=0.834). Both groups also had similar mean arterial pressure intra-operatively (repeated measure ANOVA P=0.128) and similar total dose of intra-operative opioid received, 21.67 mg in the TMH group [13.75 to 32.50] and 16.67 mg in the TN group [10.00 to 22.50] (P=0.22).

Primary endpoint

On the left hemisphere, the median [IQR] baseline oximetry was 68.7% [63.9 to 72.2] in the TMH group vs. 63.4% [57.3 to 69.6] in the TN group (P=0.233). On the right hemisphere the median [IQR] baseline oximetry was 67.9% [64.6 to 70.3] in the TMH group vs. 64.0% [59.4 to 69.9] TN group (P=0.286). On both sides, the $\%\Delta rSO_2$ was greater in the TMH group than the TN group throughout the duration of surgery (**Figure 2**). The average percentage changes in rSO_2 from the baseline to the conclusion of the surgery in TMH group were +8.56% (±SD 18.90%) on the left and +13.86% (±SD 18.17%) on the right, and in TN group they were -6.18% (±SD 17.24%) on the left and -5.48% (±SD 18.94%) on the right. The resulting treatment effects were 19% (95% CI [9.2 to 28.8]; P<0.001) on the left and 19% (95% CI [10.9 to 27.0]; P<0.001) on the right (**Table 2**).

On the longitudinal time-by-treatment interaction analysis, the difference in $\%\Delta rSO_2$ on both left and right between the two groups diverged with time with the intervention group exhibiting smaller percentage decrease over time compared to the control group (time-by-treatment interaction P<0.001 for both left and right hemispheres). We obtained very similar results on robustness analyses when the above model was adjusted for age, baseline oximetry and pre-operative haemoglobin levels, as well as when percentage of total duration of surgery instead of minutes from the start of surgery were included.

Secondary outcomes

Postoperative delirium was statistically significantly less common in the TMH group. Postoperative delirium was present in 0/20 (0%) participants in the TMH group and 6/20 (30%) participants in the TN group (risk difference 0.3, 95% CI [0.1 to 0.5], Fisher's exact P=0.02) (**Table 3).** In terms of acid base variables, median intra-operative pH was statistically significantly lower (7.31 vs. 7.46; P<0.001) and intra-operative bicarbonate was statistically significantly higher (25.00 vs. 24.00 mEq L^{-1}; P=0.020) in the TMH. No statistically significant differences in base excess (-1.00 vs. 1.00 mmol L^{-1}; P=0.069), potassium (3.98 vs. 4.03 mEq L^{-1}; P=0.759) and total haemoglobin (130.50 vs. 122.25 g L^{-1}; P=0.132) were observed intra-operatively. Length of hospital stay was also similar between the two groups without statistically significant difference (5 vs. 5 days; P=0.988). These results are summarized in **Table 4.**

Discussion

We conducted a prospective, single centre, single blinded, randomised controlled trial evaluating the effects of targeted mild hypercapnia (TMH) and targeted normocapnia (TN) on regional cerebral oxygen saturation (rSO_2) in patients undergoing major surgery. TMH led to a significantly larger increase in both left and right NIRS-derived regional cerebral oxygen saturation from baseline values, an effect sustained throughout surgery, and becoming more pronounced with the passage of time. TMH was associated with a lower incidence of postoperative delirium within 24 hours after surgery.

Whilst the relationship between elevated $PaCO_2$ and cerebral blood flow is well described,[24-26] the associations between hypercapnia and higher rSO_2 are poorly understood. Numerous factors, for instance, cardiac output, oxygen affinity of haemoglobin, and the ratio of cerebral arterial to venous blood volume, affect rSO_2 in the setting of hypercapnia, but changes in $PaCO_2$ and CBF, in turn, have direct influence on these factors. To complicate the subject further, the duration of effect of hypercapnia on rSO_2 is unknown. In our study, confounding variables, such as MAP, PaO_2, and Hb were similar between the TMH and TN groups. However, pH, which directly affects the oxygen affinity of haemoglobin via the Bohr Effect, was significantly different. Since we cannot measure the ratio of arterial to venous blood volume, it would be impetuous to comment on the mechanism behind the observed higher rSO_2 values in TMH. Clinically, similar observations have been reported previously. Eastwood *et al.* found that mild hypercapnia resulted in higher rSO_2 values in post-cardiac arrest patients when rSO_2 values at the end of the normocapnic period and the end of the hypercapnic period were compared.[27] Similarly rSO_2 remained higher in hypercapnic patients throughout shoulder surgery, and less cerebral desaturation events were observed by Murphy *et al*.[28] Giardino *et al.* reviewed how changes in respiratory alternations in patients with anxiety alter CBF and found that changes in CBF over time in acute hypercapnia or hypocapnia have high individual variability and CBF might never attain a true steady-state period with time.[29] Our study is one of the few randomised-controlled trials that investigate rSO_2 change over time in the setting of hypercapnia, and the sustained difference in rSO_2 over time observed is novel.

Interestingly, the incidence of postoperative delirium after surgery was lower in the TMH group while LOS remained similar between the groups. There has been conflicting evidence

in the literature regarding the relationship between rSO_2 and LOS or postoperative cognitive performance. Murkin *et al.* found that monitoring and reacting to cerebral desaturation during coronary artery bypass surgery was associated with clinical benefits.[13] Patients with shorter LOS (<10 days) had higher mean rSO_2. Intra-operative NIRS rSO_2 monitoring led to a significant reduction in postoperative cognitive disturbance confirmed by Trafidlo *et al.* [30] but not Deschamps *et al*. [31] Casati *et al.* also reported that higher rSO_2 led to shorter LOS and improved Mini-Mental State Examination scores in elderly patients undergoing major abdominal surgery,[32] and Schoen *et al.* found that low pre-operative rSO_2 was associated with higher incidence of postoperative delirium. Among patients who started at a normal saturation level, those who developed delirium had a larger intra-operative drop in rSO_2.[33] Our findings were consistant with Schoen *et al.*, however, they need to be interpreted with caution as the ASA scores and age were slightly higher in the TN group, and our study was not designed to quantitatively investgate postoperative cognitive performance in hypercapnia.

Implications of our findings demonstrate that TMH can be delivered reliably during major surgery and its effects on rSO_2 can be monitored with NIRS in most patients. Its delivery is reliably associated with increased levels of rSO_2, and the relatively higher rSO_2 is sustained over the duration of surgery, an observation that has not been reported in the literature. Furthermore, TMH may reduce the incidence of the development of immediate postoperative delirium. A clinical concern of mild hypercapnia is hypercapnic-induced acidosis and the subsequent development of hyperkalemia. Whilst a linear correlation between arterial carbon dioxide and plasma pH is well reported,[34] the relationship between acute hypercarbia, respiratory acidosis and plasma potassium is also poorly understood.[35] In the present study, we found no association between hypercarbia and serum potassium concentrations, a finding also supported by others.[36] We did not observe any other deleterious or adverse effects from hypercapnic-induced acidosis such as cardiac arrhythmias in our study. Finally, we have shown that NIRS-based cerebral oximetry is a non-invasive and practical method of measuring rSO_2, easily incorporated into the existing collection of routine monitoring variables, findings that are in agreement with other research groups.[18,37-39]

Our study has multiple strengths. Our findings have high internal validity because the study was a randomised controlled trial with concealed allocation and blinded assessment,

minimising selection and ascertainment bias. rSO_2 data were exported directly to RStudio, and ABG data were analysed by the ABL Blood Gas Analyzer, rendering sampling error from data entry unlikely, thereby increasing the robustness of our findings. Sampling of continuous oximetry data resulted in a stream of oximetry data throughout the monitoring periods, maximizing the details of our assessment. Although the duration of surgery was different for individual patients, oximetry data were not normalised to another time scale, enabling a fair comparison of data across the study groups. NIRS-derived rSO_2 has been criticised for potential extra-cranial contamination that would confound true rSO_2.[40] However, there is sufficient evidence to support the accuracy of NIRS-derived rSO_2,[18,37] particularly in the case of hypercapnia, where extra-cranial signal interference has been shown to be insignificant, justifying its reliability.[41] Moreover, as the technology was the same in both groups, any inaccuracy should not have been a source of bias.

Our study also has a number of limitations. The attending anaesthetists were not blinded due to the nature of the intervention. Nevertheless, bias was mitigated by the fact that measurements were taken directly from the cerebral oximetry machine and assessment of delirium was conducted by an independent researcher blinded to the intervention. The external validity of our findings was restricted by the small sample size from one single centre. Our findings were not applicable to patients undergoing emergency surgery, intracranial surgery, or surgery requiring one lung ventilation. The cerebral oximetry probes were only attached to the forehead, measuring rSO_2 within the frontal cortex region, which carries the assumption that rSO_2 was homogenous across every area of the brain. This assumption will need to be tested for the posterior circulation in future studies. Quantification of device failure rate, despite being a critical consideration, cannot be described by our study design. Finally, our findings of a greater incidence of early postoperative delirium in the TN group need to be interpreted with caution as confounders of postoperative delirium were not controlled, our study was not powered to investigation postoperative delirium, and mental state was only accessed by CAM, once pre-operatively and once postoperatively. Accordingly, our findings for delirium should be viewed as hypothesis generating. Nevertheless, if we were to consider that our effect size observed (i.e. 0.13) could be due to chance and a smaller effect would be observed in a larger study, an appropriate powered RCT for this outcome would be very feasible. If the proportion of patients with delirium in the

intervention group is 10%, to achieve 90% power, the required sample size for each group would be ninty two.

Conclusion

In summary, in patients undergoing elective major surgery, mild hypercapnia was associated with a larger increase in regional cerebral oxygen saturation from baseline on both the left and the right cerebral cortex. This effect was sustained and became more marked with the passage of time intra-operatively, resulting in a clear separation in the percentage change of regional cerebral oxygen saturation between the TMH and TN over time. These preliminary findings provide the rationale and justification for larger investigations of this intervention.

Author Contributions

Clarence Wong: This author contributed to data collection, data analysis, and writing up of manuscript

Leonid Churilov: This author contributed to data analysis and writing up of manuscript

Dean Cowie: This author contributed to patient recruitment, data collection, and writing up of manuscript

Chong Tan: This author contributed to patient recruitment and writing up of manuscript

Raymond Hu: This author contributed to patient recruitment and writing up of manuscript

David Tremewen: This author contributed to patient recruitment and writing up of manuscript

Brett Pearce: This author contributed to patient recruitment and writing up of manuscript

Param Pillai: This author contributed to data collection and writing up of manuscript

Dharshi Karalipillai: This author contributed to data collection and writing up of manuscript

Rinaldo Bellomo: This author contributed to study design and writing up of manuscript

Laurence Weinberg: This author designed the study, contributed to patient recruitment, data collection, data analysis and writing up of manuscript

References

1. Brosnan RJ, Steffey EP, LeCouteur RA, Imai A, Farver TB, Kortz GD. Effects of ventilation and isoflurane end-tidal concentration on intracranial and cerebral perfusion pressures in horses. *American journal of veterinary research.* 2003;64(1):21-25.
2. Faraci FM, Breese KR, Heistad DD. Cerebral vasodilation during hypercapnia. Role of glibenclamide-sensitive potassium channels and nitric oxide. *Stroke.* 1994;25(8):1679-1683.
3. Hino JK, Short BL, Rais-Bahrami K, Seale WR. Cerebral blood flow and metabolism during and after prolonged hypercapnia in newborn lambs. *Critical care medicine.* 2000;28(10):3505-3510.
4. Nakahata MDK, Kinoshita MDPDH, Hirano MDY, Kimoto MDY, Iranami MDH, Hatano MDPDY. Mild Hypercapnia Induces Vasodilation via Adenosine Triphosphate-sensitive K^+ Channels in Parenchymal Microvessels of the Rat Cerebral Cortex. *Anesthesiology.* 2003;99(6):1333-1339.
5. Kaku DA, Giffard RG, Choi DW. Neuroprotective effects of glutamate antagonists and extracellular acidity. *Science (New York, NY).* 1993;260(5113):1516-1518.
6. Vannucci RC, Brucklacher RM, Vannucci SJ. Effect of Carbon Dioxide on Cerebral Metabolism during Hypoxia-Ischemia in the Immature Rat. *Pediatr Res.* 1997;42(1):24-29.
7. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *British journal of anaesthesia.* 2009;103 Suppl 1:i3-13.
8. Elizabeth A, Frost M. Cerebral oximetry: emerging applications for an established technology. *Anesthesiol News.* 2012;38:10.
9. Steppan J, Hogue CW, Jr. Cerebral and tissue oximetry. *Best Pract Res Clin Anaesthesiol.* 2014;28(4):429-439.
10. Ahn A, Yang J, Inigo-Santiago L, Parnia S. A feasibility study of cerebral oximetry monitoring during the post-resuscitation period in comatose patients following cardiac arrest. *Resuscitation.* 2014;85(4):522-526.
11. Storm C, Leithner C, Krannich A, et al. Regional cerebral oxygen saturation after cardiac arrest in 60 patients--a prospective outcome study. *Resuscitation.* 2014;85(8):1037-1041.

12. Ito N, Nishiyama K, Callaway CW, et al. Noninvasive regional cerebral oxygen saturation for neurological prognostication of patients with out-of-hospital cardiac arrest: a prospective multicenter observational study. *Resuscitation.* 2014;85(6):778-784.
13. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomised, prospective study. *Anesth Analg.* 2007;104(1):51-58.
14. Robinson TN, Eiseman B. Postoperative delirium in the elderly: diagnosis and management. *Clinical Interventions in Aging.* 2008;3(2):351-355.
15. Liu LL, Leung JM. Predicting adverse postoperative outcomes in patients aged 80 years or older. *Journal of the American Geriatrics Society.* 2000;48(4):405-412.
16. Inouye SK. Delirium in older persons. *The New England journal of medicine.* 2006;354(11):1157-1165.
17. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340.
18. Redford D, Paidy S, Kashif F. Absolute and trend accuracy of a new regional oximeter in healthy volunteers during controlled hypoxia. *Anesth Analg.* 2014;119(6):1315-1319.
19. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Annals of internal medicine.* 1990;113(12):941-948.
20. Sharon K, Inouye MD, MPH. Confusion Assessment Method: Training Manual and Coding Guide, Copyright 2003.
21. National Blood Authority. Blood Management Guidelines: Module 2 Perioperative. 2012; http://www.nba.gov.au/guidelines/module2/po-mod2.pdf2.
22. Vretzakis G, Georgopoulou S, Stamoulis K, et al. Cerebral oximetry in cardiac anesthesia. *Journal of thoracic disease.* 2014;6 Suppl 1:S60-69.
23. Lang TA, Altman DG. Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines. *International journal of nursing studies.* 2015;52(1):5-9.
24. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. *Critical care (London, England).* 2010;14(2):220.

25. Yokoyama I, Inoue Y, Kinoshita T, Itoh H, Kanno I, Iida H. Heart and brain circulation and CO2 in healthy men. *Acta physiologica (Oxford, England).* 2008;193(3):303-308.

26. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. *J Physiol.* 2011;589(Pt 12):3039-3048.

27. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early cardiac arrest survivors: The impact of hypercapnia. *Resuscitation.* 2016;102:11-16.

28. Murphy GS, Szokol JW, Avram MJ, et al. Effect of ventilation on cerebral oxygenation in patients undergoing surgery in the beach chair position: a randomised controlled trial. *British journal of anaesthesia.* 2014;113(4):618-627.

29. Giardino ND, Friedman SD, Dager SR. Anxiety, respiration, and cerebral blood flow: implications for functional brain imaging. *Comprehensive psychiatry.* 2007;48(2):103-112.

30. Trafidlo T, Gaszynski T, Gaszynski W, Nowakowska-Domagala K. Intra-operative monitoring of cerebral NIRS oximetry leads to better postoperative cognitive performance: a pilot study. *International journal of surgery (London, England).* 2015;16(Pt A):23-30.

31. Deschamps A, Hall R, Grocott H, et al. Cerebral Oximetry Monitoring to Maintain Normal Cerebral Oxygen Saturation during High-risk Cardiac Surgery: A Randomised Controlled Feasibility Trial. *Anesthesiology.* 2016;124(4):826-836.

32. Casati A, Fanelli G, Pietropaoli P, et al. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth Analg.* 2005;101(3):740-747, table of contents.

33. Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger K-U. Pre-operative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. *Critical Care.* 2011;15(5):R218-R218.

34. Finsterer U, Luhr HG, Wirth AE. Effects of acute hypercapnia and hypocapnia on plasma and red cell potassium, blood lactate and base excess in man during anesthesia. *Acta anaesthesiologica Scandinavica.* 1978;22(4):353-366.

35. Adrogue HJ, Madias NE. Changes in plasma potassium concentration during acute acid-base disturbances. *The American journal of medicine.* 1981;71(3):456-467.

36. Natalini G, Seramondi V, Fassini P, et al. Acute respiratory acidosis does not increase plasma potassium in normokalaemic anaesthetized patients. A controlled randomised trial. *European Journal of Anaesthesiology.* 2006;18(6):394-400.

37. MacLeod DB, Ikeda K, Vacchiano C, Lobbestael A, Wahr JA, Shaw AD. Development and validation of a cerebral oximeter capable of absolute accuracy. *Journal of cardiothoracic and vascular anesthesia.* 2012;26(6):1007-1014.

38. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. *Anesthesiology.* 2000;93(4):947-953.

39. Brady K, Joshi B, Zweifel C, et al. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke.* 2010;41(9):1951-1956.

40. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology.* 2012;116(4):834-840.

41. Akça O, Sessler DI, DeLong D, Keijner R, Ganzel B, Doufas AG. Tissue Oxygenation Response to Mild Hypercapnia during Cardiopulmonary Bypass with Constant Pump Output. *British journal of anaesthesia.* 2006;96(6):708-714.

Tables and Figures

Table 1. Baseline patient characteristics and surgical characteristics.[a]

	TMH group[b] (*n*=20)	TN group[b] (*n*=20)	
Patient characteristics			
Gender (Male : Female)	11:9	12:8	
Age (years) [a]	63.7 [32 to 81]	65.4 [31 to 81]	
Weight (kg)	83.7 [56.8 to 110.6]	81.2 [67.9 to 94.5]	
BMI (kg m^{-2})[c]	33.6 [20.7 to 46.5]	32.8 [26.8 to 38.8]	
ASA Status[d]			
1	3 (16.7)	2 (10.0)	
2	6 (33.3)	4 (20.0)	
3	7 (38.9)	10 (50.0)	
4	2 (11.1)	4 (20.0)	
Diabetes	4 (22.2)	5 (25.0)	
COPD[e]	5 (27.8)	0 (0.0)	
Malignancy	11 (61.1)	7 (35.0)	
Other co-morbidities	11 (61.1)	16 (80.0)	
Surgical Characteristics			
Duration of surgery (mins)	219.0 [123.8 to 303.8]	144.0 [107.8 to 218.2]	(*P*=0.121)
Left baseline oximetry (%)	68.7 [63.9 to 72.2]	63.4 [57.3 to 69.6]	(*P*=0.233)
Right baseline oximetry (%)	67.9 [64.6 to 70.3]	64.0 [59.4 to 69.0]	(*P*=0.286)
O_2 Sats (%)[f]	98.5 [98.1 to 99.0]	98.5 [97.9 to 99.0]	(*P*=0.834)
LOS (days)[g]	5 [2.0 to 12.0]	5 [1.8 to 11.5]	(*P*=0.988)
Type of surgery			
colorectal	2 (11.1)	1 (5.0)	
endocrine	2 (11.1)	2 (10.0)	
ear nose & throat	0 (0.0)	1 (5.0)	
hepatobiliary	6 (33.3)	9 (45.0)	
neurosurgery[h]	1 (5.6)	1 (5.0)	
orthopedic	2 (11.1)	1 (5.0)	

thoracic[i]	4 (22.2)	1 (5.0)
urology	1 (5.6)	3 (15.0)
vascular	0 (0.0)	1 (5.0)

[a] data reported as number (%) or median [inter-quartile range], except for age, which is reported as median [range]

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

[c] BMI: body mass index

[d] ASA: American Society of Anesthesiologists

[e] COPD: chronic obstructive pulmonary disease

[f] O_2 Sats: peripheral oxygen saturation measured by pulse oximetry

[g] LOS: length of hospital stay

[h] includes non-intracranial procedures, e.g. complex spinal surgery

[i] includes procedures not requiring one lung ventilation, e.g. mediastinoscopy with nodal dissection

Table 2. Percentage change in cerebral oximetry (%ΔrSO_2) from baseline.[a]

Time from start of surgery (mins)		15	30	45	60	75	90	105	120
Left	**TMH**[b]	0.8 (12.9) {15}	5.8 (12.3) {15}	9.0 (15.9) {15}	7.0 (14.6) {15}	8.5 (15.4) {14}	7.3 (14.7) {13}	7.7 (17.4) {13}	8.1 (14.8) {13}
	TN[b]	4.7 (10.5) {18}	3.2 (15.4) {18}	-1.9 (14.1) {17}	-5.6 (12.7) {17}	-5.3 (15.2) {17}	-5.5 (15.8) {17}	-6.0 (15.2) {17}	-3.6 (15.8) {14}
Right	**TMH**	6.0 (12.9) {17}	9.8 (13.2) {17}	10.4 (18.1) {17}	11.1 (17.4) {17}	13.0 (16.4) {16}	15.6 (17.3) {15}	14.4 (17.5) {14}	14.1 (13.6) {14}
	TN	5.2 (12.6) {20}	3.9 (11.7) {20}	-3.3 (13.2) {19}	-5.2 (12.1) {19}	-5.4 (12.3) {19}	-4.7 (14.1) {19}	-3.8 (13.7) {18}	-1.3 (13.9) {15}

Time from start of surgery (mins)		120	240	360	480	600	720	Mean % difference from start to completion of surgery	95% confidence interval	*P* value (treatment)
Left	**TMH**	8.1 (14.8) {13}	6.8 (20.6) {7}	6.4 (32.5) {4}	-8.6 (21.1) {3}	-6.1 (14.1) {3}	6.9 (NA) {1}	19.0	9.2 -28.8	<0.001
	TN	-3.6 (15.8) {14}	-10.4 (39.5) {5}	-43.4 (34.9) {2}	-27.8 (NA) {1}					
Right	**TMH**	14.1 (13.6) {14}	18.4 (23.5) {8}	16.8 (36.8) {4}	1.5 (14.9) {3}	3.0 (8.7) {3}	2.0 (NA) {1}	19.0	10.9- 27.0	<0.001
	TN	-1.3 (13.9) {15}	-5.3 (32.6) {5}	-35.4 (26.9) {2}	-37.8 (NA) {1}					

[a] Data are presented every 15 minutes for the first 2 hours and every 2 hours afterwards, and are reported as mean (standard deviation) {sample size}.

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

Table 3. Postoperative delirium and opioid doses [a]

	TMH group[b] (*n*=20)	TN group[b] (*n*=20)	
Pre-medication			
Number of patients	0 (0)	2 (10.0)	
Mean midazolam dose (mg)	0	1.75	
Intra-operative opioid [c]			
Total dose (mg) [d]	21.67 [13.75 to 32.50]	16.67 [10.00 to 22.50]	(*P*=0.22)
Received i.v. morphine (%)	2 (10)	1 (5)	
Received i.v. fentanyl (%)	10 (50)	14 (70)	
Received i.v. oxycodone (%)	9 (45)	7 (35)	
Received i.v. tramadol (%)	4 (20)	0 (0)	
Received i.v. clonidine (%)	0 (0)	2 (10)	
Intrathecal morphine			
Number of patients	5	2	
Mean dose (mcg)	220	350	
Blood glucose level			
Glucose (mmol L-1)	7.1 [7.0 to 7.1]	6.6 [6.4 to 6.7]	(*P*=0.33)
Pre-op CAM [e]	0 [0 to 0]	0 [0 to 0]	
Post-op CAM [e]	0 [0 to 0]	1.5 [0 to 3]	
Presence of post-operative delirium	0 (0.0)	6 (30.0)	(*P*=0.02)

[a] Data reported as median [inter-quartile range] or number (%)

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

[c] Note some patients received 2 or more different opioids

[d] Total dose normalised to i.v. morphine equivalent

[e] CAM: Confusion Assessment Method

Table 4. Average arterial blood gas values [a]

	TMH group[b] (*n*=20)	**TN group[b] (*n*=20)**	*P*-value
pH	7.31 [7.27 to 7.33]	7.46 [7.43 to 7.47]	<0.001
PaO_2 (mmHg)[c]	156.8 [146.3 to 217.2]	142.5 [122.5 to 199.1]	0.380
$PaCO_2$ (mmHg)[d]	51.50 [46.88 to 60.88]	34.75 [32.75 to 38.12]	<0.001
Bicarbonate (mEq L^{-1})	25.00 [24.00 to 27.75]	24.00 [22.00 to 24.62]	0.020
Base excess (mmol L^{-1})	-1.00 [-2.50 to 0.25]	1.00 [-0.88 to 2.00]	0.069
Potassium (mEq L^{-1})	3.98 [3.73 to 4.38]	4.03 [3.58 to 4.31]	0.759
Total Hb (g L^{-1})[e]	130.50 [118.12 to 140.62]	122.25 [106.88 to 131.25]	0.132

[a] Data reported as median [inter-quartile range] or number (%)

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

[c] PaO_2: partial pressure of oxygen in arterial blood

[d] $PaCO_2$: partial pressure of carbon dioxide in arterial blood

[e] Hb: haemoglobin concentration

Figure 1. CONSORT flow diagram

(Please refer to the attached diagram)

Figure 2. Percentage change in cerebral oximetry from baseline (%ΔrSO_2) over time

(Please refer to the attached diagram)

Captions

Figure 1:

The progress of all participants through the trial displayed by the Consolidated Standards Of Reporting Trials (CONSORT) flow diagram.

Figure 2:

The solid lines represent mean percentage change, the shaded areas represent standard deviation, red represents the targeted mild hypercapnia (TMH) group, and blue represents the targeted normocapnia (TN) group.

Left: average percentage change of regional cerebral oxygen saturation from baseline on the left hemisphere

Right: average percentage change of regional cerebral oxygen saturation from baseline on the right hemisphere

Tables

Table 1. Baseline patient characteristics and surgical characteristics.[a]

	TMH group[b] (*n*=20)	TN group[b] (*n*=20)	
Patient characteristics			
Gender (Male : Female)	11:9	12:8	
Age (years) [a]	63.7 [32 to 81]	65.4 [31 to 81]	
Weight (kg)	83.7 [56.8 to 110.6]	81.2 [67.9 to 94.5]	
BMI (kg m^{-2})[c]	33.6 [20.7 to 46.5]	32.8 [26.8 to 38.8]	
ASA Status[d]			
1	3 (16.7)	2 (10.0)	
2	6 (33.3)	4 (20.0)	
3	7 (38.9)	10 (50.0)	
4	2 (11.1)	4 (20.0)	
Diabetes	4 (22.2)	5 (25.0)	
COPD[e]	5 (27.8)	0 (0.0)	
Malignancy	11 (61.1)	7 (35.0)	
Other co-morbidities	11 (61.1)	16 (80.0)	
Surgical Characteristics			
Duration of surgery (mins)	219.0 [123.8 to 303.8]	144.0 [107.8 to 218.2]	(*P*=0.121)
Left baseline oximetry (%)	68.7 [63.9 to 72.2]	63.4 [57.3 to 69.6]	(*P*=0.233)
Right baseline oximetry (%)	67.9 [64.6 to 70.3]	64.0 [59.4 to 69.0]	(*P*=0.286)
O_2 Sats (%)[f]	98.5 [98.1 to 99.0]	98.5 [97.9 to 99.0]	(*P*=0.834)

LOS (days)[g]	5 [2.0 to 12.0]	5 [1.8 to 11.5]	(*P*=0.988)
Type of surgery			
colorectal	2 (11.1)	1 (5.0)	
endocrine	2 (11.1)	2 (10.0)	
ear nose & throat	0 (0.0)	1 (5.0)	
hepatobiliary	6 (33.3)	9 (45.0)	
neurosurgery[h]	1 (5.6)	1 (5.0)	
orthopedic	2 (11.1)	1 (5.0)	
thoracic[i]	4 (22.2)	1 (5.0)	
urology	1 (5.6)	3 (15.0)	
vascular	0 (0.0)	1 (5.0)	

[a] data reported as number (%) or median [inter-quartile range], except for age, which is reported as median [range]

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

[c] BMI: body mass index

[d] ASA: American Society of Anesthesiologists

[e] COPD: chronic obstructive pulmonary disease

[f] O_2 Sats: peripheral oxygen saturation measured by pulse oximetry

[g] LOS: length of hospital stay

[h] includes non-intracranial procedures, e.g. complex spinal surgery

[i] includes procedures not requiring one lung ventilation, e.g. mediastinoscopy with nodal dissection

Table 2. Percentage change in cerebral oximetry (%ΔrSO_2) from baseline.[a]

Time from start of surgery (mins)		15	30	45	60	75	90	105	120
Left	**TMH**[b]	0.8 (12.9) {15}	5.8 (12.3) {15}	9.0 (15.9) {15}	7.0 (14.6) {15}	8.5 (15.4) {14}	7.3 (14.7) {13}	7.7 (17.4) {13}	8.1 (14.8) {13}
	TN[b]	4.7 (10.5) {18}	3.2 (15.4) {18}	-1.9 (14.1) {17}	-5.6 (12.7) {17}	-5.3 (15.2) {17}	-5.5 (15.8) {17}	-6.0 (15.2) {17}	-3.6 (15.8) {14}
Right	**TMH**	6.0 (12.9) {17}	9.8 (13.2) {17}	10.4 (18.1) {17}	11.1 (17.4) {17}	13.0 (16.4) {16}	15.6 (17.3) {15}	14.4 (17.5) {14}	14.1 (13.6) {14}
	TN	5.2 (12.6) {20}	3.9 (11.7) {20}	-3.3 (13.2) {19}	-5.2 (12.1) {19}	-5.4 (12.3) {19}	-4.7 (14.1) {19}	-3.8 (13.7) {18}	-1.3 (13.9) {15}

Time from start of surgery (mins)		120	240	360	480	600	720	Mean % difference from start to completion of surgery	95% confidence interval	*P* value (treatment)
Left	**TMH**	8.1 (14.8) {13}	6.8 (20.6) {7}	6.4 (32.5) {4}	-8.6 (21.1) {3}	-6.1 (14.1) {3}	6.9 (NA) {1}	19.0	9.2 -28.8	<0.001
	TN	-3.6 (15.8) {14}	-10.4 (39.5) {5}	-43.4 (34.9) {2}	-27.8 (NA) {1}					
Right	**TMH**	14.1 (13.6) {14}	18.4 (23.5) {8}	16.8 (36.8) {4}	1.5 (14.9) {3}	3.0 (8.7) {3}	2.0 (NA) {1}	19.0	10.9- 27.0	<0.001
	TN	-1.3 (13.9) {15}	-5.3 (32.6) {5}	-35.4 (26.9) {2}	-37.8 (NA) {1}					

[a] Data are presented every 15 minutes for the first 2 hours and every 2 hours afterwards, and are reported as mean (standard deviation) {sample size}.

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

Table 3. Postoperative delirium and opioid doses [a]

	TMH group[b] (*n*=20)	TN group[b] (*n*=20)	
Pre-medication			
Number of patients	0 (0)	2 (10.0)	
Mean midazolam dose (mg)	0	1.75	
Intra-operative opioid [c]			
Total dose (mg) [d]	21.67 [13.75 to 32.50]	16.67 [10.00 to 22.50]	(*P*=0.22)
Received i.v. morphine (%)	2 (10)	1 (5)	
Received i.v. fentanyl (%)	10 (50)	14 (70)	
Received i.v. oxycodone (%)	9 (45)	7 (35)	
Received i.v. tramadol (%)	4 (20)	0 (0)	
Received i.v. clonidine (%)	0 (0)	2 (10)	
Intrathecal morphine			
Number of patients	5	2	
Mean dose (mcg)	220	350	
Blood glucose level			
Glucose (mmol L-1)	7.1 [7.0 to 7.1]	6.6 [6.4 to 6.7]	(*P*=0.33)
Pre-op CAM [e]	0 [0 to 0]	0 [0 to 0]	
Post-op CAM [e]	0 [0 to 0]	1.5 [0 to 3]	
Presence of post-operative delirium	0 (0.0)	6 (30.0)	(*P*=0.02)

[a] Data reported as median [inter-quartile range] or number (%)

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

[c] Note some patients received 2 or more different opioids

[d] Total dose normalized to i.v. morphine equivalent

[e] CAM: Confusion Assessment Method

Table 4. Average arterial blood gas values [a]

	TMH group[b] (*n*=20)	**TN group[b] (*n*=20)**	*P*-value
pH	7.31 [7.27 to 7.33]	7.46 [7.43 to 7.47]	<0.001
PaO_2 (mmHg)[c]	156.8 [146.3 to 217.2]	142.5 [122.5 to 199.1]	0.380
$PaCO_2$ (mmHg)[d]	51.50 [46.88 to 60.88]	34.75 [32.75 to 38.12]	<0.001
Bicarbonate (mEq L^{-1})	25.00 [24.00 to 27.75]	24.00 [22.00 to 24.62]	0.020
Base excess (mmol L^{-1})	-1.00 [-2.50 to 0.25]	1.00 [-0.88 to 2.00]	0.069
Potassium (mEq L^{-1})	3.98 [3.73 to 4.38]	4.03 [3.58 to 4.31]	0.759
Total Hb (g L^{-1})[e]	130.50 [118.12 to 140.62]	122.25 [106.88 to 131.25]	0.132

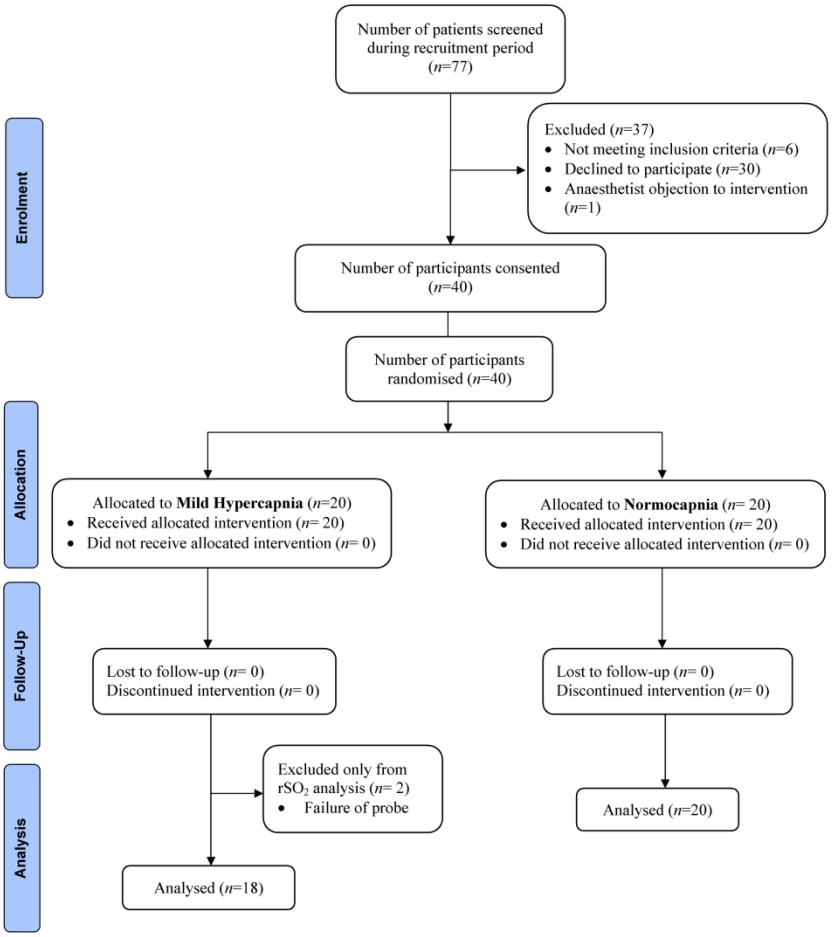
[a] Data reported as median [inter-quartile range] or number (%)

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

[c] PaO_2: partial pressure of oxygen in arterial blood

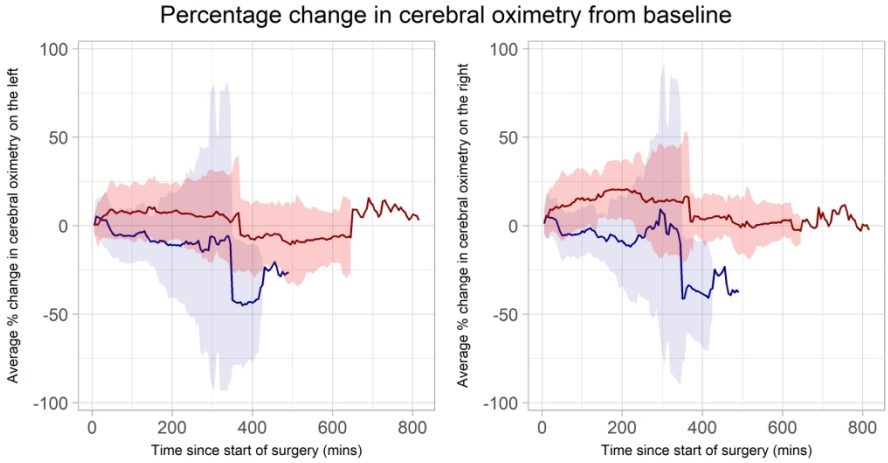
[d] $PaCO_2$: partial pressure of carbon dioxide in arterial blood

[e] Hb: hemoglobin concentration



The progress of all participants through the trial displayed by the Consolidated Standards Of Reporting Trials (CONSORT) flow diagram.

203x287mm (300 x 300 DPI)



The solid lines represent mean percentage change, the shaded areas represent standard deviation, red represents the targeted mild hypercapnia (TMH) group, and blue represents the targeted normocapnia (TN) group.
Left: average percentage change of regional cerebral oxygen saturation from baseline on the left hemisphere
Right: average percentage change of regional cerebral oxygen saturation from baseline on the right hemisphere

177x93mm (300 x 300 DPI)

Supplementary File 1

```
#-------------------------------------------------------------------------------------------------------------
--
# TITLE: Create oximetry database from raw data files
# Author: Clarence Wong
# Last updated: 2/7/2017
# RStudio v. 1.0.136
#-------------------------------------------------------------------------------------------------------------
--

library(readr)
require(lubridate)
require(TTR)
require(xts)
require(zoo)
library(reshape2)

#-------------------------------------------------------------------------------------------------------------
--
# Read all data files and save as R object
#-------------------------------------------------------------------------------------------------------------
--

master<-0
for (i in 1:8)
{
  file <-
read.csv(paste("D:/SS/R_data/FINAL_oximetry_data/",as.character(i),".csv",sep=""))
  master <- rbind(master,file)
}
master$date_time <- paste(master$Date, master$Time..GMT.)
master$date_time <- mdy_hms(master$date_time)
converted_master <- master[,c(58,3:57)]

save(converted_master,file = "converted_master.RData")

database_times <- read_csv("D:/SS/R_data/database_times.csv")
date_vector <- database_times[,c(1,5,6,7,11,12)]

date_vector$start_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Monitoring Start`))
date_vector$end_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Monitoring End`))
```

```
date_vector$surg_start_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Start Time`))
date_vector$surg_end_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Finish Time`))

converted_date_vector <- date_vector[,c(1,7,8,9,10)]

save(converted_date_vector,file = "converted_date_vector.RData")

rm(master,date_vector,file)

#-----------------------------------------------------------------------------------------------------
--
# 1.  Convert data types and locate monitoring periods
# 2.  Identify oximettry values at various time points
# 3.  Compute percentage change from baseline
# 4.  Identify and locate problematic data
#-----------------------------------------------------------------------------------------------------
--

minutes_taken_as_baseline <- 2.5
minutes_interval <- 5

secs_taken_as_baseline <- minutes_taken_as_baseline*60
secs_interval <- minutes_interval*60

load("converted_master.RData")
load("converted_date_vector.RData")
print("data loaded. check data version")

oximetry_L <-
as.numeric(levels(converted_master$RSO2_A1)[converted_master$RSO2_A1])
oximetry_R <-
as.numeric(levels(converted_master$RSO2_A2)[converted_master$RSO2_A2])
PSI <- as.numeric(levels(converted_master$PSI)[converted_master$PSI])

# monitoring duration
duration_mins <-
difftime(converted_date_vector$end_date_time,converted_date_vector$start_date_time,uni
ts = "mins")
duration_secs <-
difftime(converted_date_vector$end_date_time,converted_date_vector$start_date_time,uni
ts = "secs")

locate_start = seq(-1,-1,length.out = dim(converted_date_vector)[1])
```

```
for (i in 1:dim(converted_date_vector)[1]){
if(length(which(converted_date_vector$start_date_time[i]==converted_master$date_time))
==1)
  {
   locate_start[i] <-
which(converted_date_vector$start_date_time[i]==converted_master$date_time)
  }
}

# create final_oximetry data frame
final_oximetry <- data.frame()
baseline_L_mu<-baseline_L_std<-baseline_L_N<-baseline_R_mu<-baseline_R_std<-
baseline_R_N<-rep(9999,dim(converted_date_vector)[1])
num_time_pts <- rep(1,40)

for(j in 1:dim(converted_date_vector)[1])
{
 # for each patient
 if(locate_start[j]==-1)
 {
  p_id <- j
  time_id<-minute_from_baseline<-percentage_total_monitoring_period<-L_delta<-
L_mu<-L_sig<-L_N<-R_delta<-R_mu<-R_sig<-R_N<-PSI_mu<-9999

 } else{

  locate_baseline <- locate_start[j]+secs_taken_as_baseline/2
  locate_times <- seq(0,0)
  num_measurements <- (as.numeric(duration_secs)[j]-
secs_taken_as_baseline)%/%secs_interval +1
  num_time_pts[j] <- num_measurements
  locate_times[1] <- locate_baseline
  locate_times[2] <- locate_times[1] + secs_interval/2
  locate_times[2:num_measurements]<-
seq(locate_times[2],locate_start[j]+as.numeric(duration_secs[j])/2,by=secs_interval/2)
  locate_times[num_measurements+1]<-locate_start[j]+as.numeric(duration_secs[j])/2

  baseline_L_mu[j] <- mean(oximetry_L[locate_start[j]:(locate_baseline-1)],na.rm =
TRUE)
  baseline_L_std[j] <- sd(oximetry_L[locate_start[j]:(locate_baseline-1)],na.rm = TRUE)
  baseline_L_N[j] <- length(oximetry_L[locate_start[j]:(locate_baseline-1)])-
sum(is.na(oximetry_L[locate_start[j]:(locate_baseline-1)]))
```

```
   baseline_R_mu[j] <- mean(oximetry_R[locate_start[j]:(locate_baseline-1)],na.rm =
TRUE)
   baseline_R_std[j] <- sd(oximetry_R[locate_start[j]:(locate_baseline-1)],na.rm = TRUE)
   baseline_R_N[j] <- length(oximetry_R[locate_start[j]:(locate_baseline-1)])-
sum(is.na(oximetry_R[locate_start[j]:(locate_baseline-1)]))

   L_delta <- L_mu <- L_sig <- L_N <- R_delta <- R_mu <- R_sig <- R_N <- PSI_mu <-
seq(0,0)

   for (k in 1:num_measurements)
   {
    L_mu[k] <- mean(oximetry_L[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    L_sig[k] <- sd(oximetry_L[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    L_N[k] <- length(oximetry_L[locate_times[k]:(locate_times[k+1]-1)])-
sum(is.na(oximetry_L[locate_times[k]:(locate_times[k+1]-1)]))

    R_mu[k] <- mean(oximetry_R[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    R_sig[k] <- sd(oximetry_R[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    R_N[k] <- length(oximetry_R[locate_times[k]:(locate_times[k+1]-1)])-
sum(is.na(oximetry_R[locate_times[k]:(locate_times[k+1]-1)]))

    PSI_mu[k] <- mean(PSI[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
   }

   L_delta <- (L_mu/baseline_L_mu[j] -1)*100
   R_delta <- (R_mu/baseline_R_mu[j] -1)*100

   time_id <- 1:num_measurements
   minute_from_baseline <- c(seq(minutes_interval,minutes_interval*(num_measurements-
1), by = minutes_interval),as.numeric(duration_mins[j]-minutes_taken_as_baseline))
   p_id <- rep(j,num_measurements)
   percentage_total_monitoring_period <-
((minute_from_baseline*60+secs_taken_as_baseline)/as.numeric(duration_secs[j]))*100

  }

  temp_df <-
data.frame(p_id,time_id,minute_from_baseline,percentage_total_monitoring_period,L_delt
a,L_mu,L_sig,L_N,R_delta,R_mu,R_sig,R_N,PSI_mu)
  final_oximetry <- rbind(final_oximetry,temp_df)
  rm(temp_df)

}

missing_L <- unique(final_oximetry$p_id[is.na(final_oximetry$L_delta)])
```

```
missing_R <- unique(final_oximetry$p_id[is.na(final_oximetry$R_delta)])
percentage_total_missing_L <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$L_delta)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$L_delta)])])
percentage_total_missing_R <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$R_delta)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$R_delta)])])
missing_data <- unique(final_oximetry$p_id[(final_oximetry$L_delta==9999)])
missing_data <- missing_data[!is.na(missing_data)]
missing_PSI <- unique(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])
percentage_total_missing_PSI <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])])

print("there are missing delta oximetry values in the following patients")
print(missing_L)
print(percentage_total_missing_L)

print(missing_R)
print(percentage_total_missing_R)

print(missing_data)

print("there are missing PSI values in the following patients")
print(missing_PSI)
print(percentage_total_missing_PSI)

other_data <-
data.frame(num_time_pts,baseline_L_mu,baseline_L_std,baseline_L_N,baseline_R_mu,
baseline_R_std,baseline_R_N)
other_data[is.na(other_data)]<-9999
save(other_data, file="other_data.RData")

final_oximetry[is.na(final_oximetry)]<-9999
save(final_oximetry,file = "final_oximetry.RData")


#-----------------------------------------------------------------------------------------------------------
--
# 1.  Convert baseline characteristic database from wide to long format
# 2.  Incorporating oximetry data in the database with time as a nested data in the hierarchy
# 3.  Create final database
#-----------------------------------------------------------------------------------------------------------
--
```

```
load("final_oximetry.RData")
load("other_data.RData")
print("check if final oximetry is latest")

baseline_results <- read.csv("D:/SS/R_data/FINAL_oximetry_data/all_baseline.csv",
sep=",", stringsAsFactors=FALSE)

baseline_results$baseline_L_mu <- other_data$baseline_L_mu
baseline_results$baseline_L_std <- other_data$baseline_L_std
baseline_results$baseline_L_N <- other_data$baseline_L_N
baseline_results$baseline_R_mu <- other_data$baseline_R_mu
baseline_results$baseline_R_std <- other_data$baseline_R_std
baseline_results$baseline_R_N <- other_data$baseline_R_N

baseline_results$P_id <- index(baseline_results)

baseline_results[baseline_results == "#N/A"]<-9999

#generate baseline_results with the same number of rows as final oximetry
baseline_results <- baseline_results[rep(seq_len((40)),num_time_pts),]


all_results <- cbind(baseline_results,final_oximetry)
if (sum(1*(all_results$P_id != all_results$p_id))==0)
{
  all_results <- all_results[,c(which(colnames(all_results)=="p_id"),1:109,112:122)]
}

save(all_results,file = "all_results.RData")

#UNCOMMENT TO WRITE CSV
#-------------------------------------------------
write.csv(all_results, file="all_results.csv")
```

Supplementary File 2

```
#-----------------------------------------------------------------------------------------------------------
-------
# TITLE: Create baseline patient and surgical characteristics table, oximetry table, and
oximetry graphs
# Author: Clarence Wong
# Last updated: 2/7/2017
# RStudio v. 1.0.136
#-----------------------------------------------------------------------------------------------------------
-------

library(readr)
require(lubridate)
require(TTR)
require(xts)
require(zoo)
require(tableone)
require(ggplot2)
library(grid)
require(gridExtra)
require(quantreg)

#-----------------------------------------------------------------------------------------------------------
-------
# 1.  Create summary statistics for baseline characteristics
# 2.  Perform statistical analysis on secondary outcomes. e.g post-operative delirium
# 3.  Export tables in csv files
# Requires baseline characteristic and baseline oximetry data.
#-----------------------------------------------------------------------------------------------------------
-------

baseline_db <- read.csv("D:/SS/R_data/baseline/all_baseline.csv", sep=",",
stringsAsFactors=TRUE)
load("other_data.RData")

other_data <- other_data[-c(1,2),]

baseline_db$baseline_L_mu <- other_data$baseline_L_mu
baseline_db$baseline_L_std <- other_data$baseline_L_std
baseline_db$baseline_L_N <- other_data$baseline_L_N
baseline_db$baseline_R_mu <- other_data$baseline_R_mu
baseline_db$baseline_R_std <- other_data$baseline_R_std
baseline_db$baseline_R_N <- other_data$baseline_R_N

baseline_db$P_id <- index(baseline_db)
```

```
baseline_db[baseline_db == "#N/A"]<-NA
baseline_db[baseline_db == 9999]<-NA
baseline_db$pCO2_2<-
as.numeric(levels(baseline_db$pCO2_2))[baseline_db$pCO2_2]
baseline_db$BMI<-as.numeric(levels(baseline_db$BMI))[baseline_db$BMI]
vars <-
c("Gender","Age","Weight","BMI","ASA","Diabetes","COPD","Maligancy","Other_C
omorbidities",

"Surgery_type","Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu")
factorVars <- c("ASA","Diabetes","COPD","Maligancy","Other_Comorbidities")
Tableone <- CreateTableOne(vars,"Group",baseline_db,factorVars)


baseline_db$LOS<-as.numeric(levels(baseline_db$LOS))[baseline_db$LOS]
baseline_db$pH_2<-as.numeric(levels(baseline_db$pH_2))[baseline_db$pH_2]
baseline_db$HCO3._2<-
as.numeric(levels(baseline_db$HCO3._2))[baseline_db$HCO3._2]
baseline_db$Base_excess_2<-
as.numeric(levels(baseline_db$Base_excess_2))[baseline_db$Base_excess_2]
baseline_db$Potassium_2<-
as.numeric(levels(baseline_db$Potassium_2))[baseline_db$Potassium_2]
baseline_db$Total_Hb_2<-
as.numeric(levels(baseline_db$Total_Hb_2))[baseline_db$Total_Hb_2]

baseline_db$pH<-apply(baseline_db[,c("pH_1","pH_2")],1,mean,na.rm=TRUE)
baseline_db$pCO2<-
apply(baseline_db[,c("pCO2_1","pCO2_2")],1,mean,na.rm=TRUE)
baseline_db$HCO3.<-
apply(baseline_db[,c("HCO3._1","HCO3._2")],1,mean,na.rm=TRUE)
baseline_db$Base_excess<-
apply(baseline_db[,c("Base_excess_1","Base_excess_2")],1,mean,na.rm=TRUE)
baseline_db$Potassium<-
apply(baseline_db[,c("Potassium_1","Potassium_2")],1,mean,na.rm=TRUE)
baseline_db$Total_Hb<-
apply(baseline_db[,c("Total_Hb_1","Total_Hb_2")],1,mean,na.rm=TRUE)

vars_2 <-
c("Surgery_type","Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu","L
OS",

"pH","pCO2","HCO3.","Base_excess","Potassium","Total_Hb","post_op_delirium")
factorVars_2 <- c("post_op_delirium")
Tabletwo <- CreateTableOne(vars_2,"Group",baseline_db,factorVars_2,argsExact =
"post_op_delirium")

print(Tabletwo,exact = "post_op_delirium",nonnormal =
c("Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu",
```

```
"LOS","pH","pCO2","HCO3.","Base_excess","Potassium","Total_Hb"))


write.csv(print(Tabletwo,exact = "post_op_delirium",nonnormal =
c("Duration_Surgery_Minutes","baseline_L_mu",

"baseline_R_mu","LOS","pH","pCO2","HCO3.",
                                                    "Base_excess","Potassium","Total_Hb")),
"Table_Two.csv")

#-----------------------------------------------------------------------------------------------------
-------
# 1.  Create summary statistics for percentage change of regional cerebral oxygen
saturation
# 2.  Create plots for regional cerebral oxygen saturation over time
# 3.  Export oximetry tables in csv files
# Requires baseline characteristic and baseline oximetry data.
#-----------------------------------------------------------------------------------------------------
-------

#-----------------------------------------------------------------------------------------------------
-------
# Normocapnic group

plot_db <- read.csv("D:/SS/R_data/oximetry/MASTER_results_deleted_missing.csv",
sep=",", stringsAsFactors=TRUE)

plot_db[plot_db == "#N/A"]<-NA
plot_db[plot_db == 9999]<-NA

normocapnia <- subset(plot_db, Group %in% 0)
hypercapnia <- subset(plot_db, Group %in% 1)

normo_plot <- ggplot(normocapnia, aes(x=minute_from_baseline, y=L_delta,
group=p_id)) + geom_line() +geom_point()+
  ggtitle("normocapnia: L delta")+ xlab("Time since start of operation (mins)")+
ylab("% change in oximetry from baseline")

hyper_plot <- ggplot(hypercapnia, aes(x=minute_from_baseline, y=L_delta,
group=p_id)) + geom_line() +geom_point()+
  ggtitle("hypercapnia: L delta")+ xlab("Time since start of operation (mins)")+ ylab("%
change in oximetry from baseline")

means <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x) sd(x, na.rm =
TRUE))
```

```
N <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x)
length(x[!is.na(x)]))

normo_df_L <- data.frame(means,stdevs)
times<- index(normo_df_L)*5
normo_df_L <- data.frame(means,stdevs,N, times)
total_normo_L <- ggplot(normo_df_L, aes(x=times, y=means)) +
geom_line(colour="blue4") +
  geom_ribbon(normo_df_L,mapping = aes(x=times,
ymax=means+stdevs,ymin=means-stdevs),fill="blue4",alpha=0.1)

means <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x) mean(x,
na.rm = TRUE))
stdevs <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x)
length(x[!is.na(x)]))

normo_df_R <- data.frame(means,stdevs)
times<- index(normo_df_R)*5
normo_df_R <- data.frame(means,stdevs,N, times)
total_normo_R <- ggplot(normo_df_R, aes(x=times, y=means)) +
geom_line(colour="blue4") +
  geom_ribbon(normo_df_R,mapping = aes(x=times,
ymax=means+stdevs,ymin=means-stdevs),fill="blue4",alpha=0.1)

#-----------------------------------------------------------------------------------------------
-------
# Hypercapnic group

means <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) length(x[!is.na(x)]))

hyper_df_L <- data.frame(means,stdevs)
times<- index(hyper_df_L)*5
hyper_df_L <- data.frame(means,stdevs,N, times)
total_hyper_L <- ggplot(hyper_df_L, aes(x=times, y=means))

means <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) length(x[!is.na(x)]))

hyper_df_R <- data.frame(means,stdevs)
```

```
times<- index(hyper_df_R)*5
hyper_df_R <- data.frame(means,stdevs,N, times)
total_hyper_R <- ggplot(hyper_df_R, aes(x=times, y=means))

total_L <- total_normo_L +
  geom_ribbon(hyper_df_L,mapping = aes(x=times, ymax=means+stdevs,ymin=means-
stdevs),fill="red2",alpha=0.2) +
  geom_line(hyper_df_L,mapping = aes(x=times, y=means),colour="red4") +
  theme_light() +
  xlab("Time since start of surgery (mins)")+ ylab("Average % change in cerebral
oximetry on the left") +
  theme(axis.title.y = element_text(size = rel(0.65), angle = 90)) +
  theme(axis.title.x = element_text(size = rel(0.65), angle = 00))

total_R <- total_normo_R +
  geom_ribbon(hyper_df_R,mapping = aes(x=times, ymax=means+stdevs,ymin=means-
stdevs),fill="red2",alpha=0.2) +
  geom_line(hyper_df_R,mapping = aes(x=times, y=means),colour="red4")+
  theme_light() +
  xlab("Time since start of surgery (mins)")+ ylab("Average % change in cerebral
oximetry on the right") +
  scale_color_manual(values=c("red4","blue4"))+
  theme(axis.title.y = element_text(size = rel(0.65), angle = 90)) +
  theme(axis.title.x = element_text(size = rel(0.65), angle = 00))

#tiff('oximetry_graph_high_res.tiff', units="in", width=7, height=3.6667, res=600,
compression = 'lzw')

grid.arrange(total_L, total_R, ncol = 2, top=textGrob("Percentage change in cerebral
oximetry from baseline",
                                        gp=gpar(fontsize=11,fontfamily="Times")),
          vp=viewport(width=0.9, height=0.9))

#insert ggplot code
#dev.off()

temp_hyper_L <- t(paste(round(hyper_df_L$mean,1)," (",
round(hyper_df_L$stdev,1),")"," {", hyper_df_L$N,"}", sep = ""))
temp_normo_L <- t(paste(round(normo_df_L$mean,1)," (",
round(normo_df_L$stdev,1),")"," {", normo_df_L$N,"}", sep = ""))

temp_hyper_R <- t(paste(round(hyper_df_R$mean,1)," (",
round(hyper_df_R$stdev,1),")"," {", hyper_df_R$N,"}", sep = ""))
temp_normo_R <- t(paste(round(normo_df_R$mean,1)," (",
round(normo_df_R$stdev,1),")"," {", normo_df_R$N,"}", sep = ""))

write.csv( temp_normo_L , "normo_df_L.csv")
write.csv( temp_normo_R , "normo_df_R.csv")
```

```
write.csv( temp_hyper_L , "hyper_df_L.csv")
write.csv( temp_hyper_R , "hyper_df_R.csv")
```

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5-6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5-6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8-9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8-9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	10
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	20
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-13
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	3

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A randomised controlled trial to investigate the relationship between mild hypercapnia and cerebral oxygen saturation in patients undergoing major surgery

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029159.R1
Article Type:	Original research
Date Submitted by the Author:	03-Sep-2019
Complete List of Authors:	Wong, Clarence; Austin Hospital, Department of Anaesthesia Churilov, Leonid; The Florey Institute of Neuroscience and Mental Health; University of Melbourne Cowie, Dean; Austin Hospital, Department of Anaesthesia Tan, Chong; Austin Hospital, Department of Anaesthesia Hu, Raymond; Austin Hospital, Department of Anaesthesia Tremewen, David; Austin Hospital, Department of Anaesthesia Pearce, Brett; Austin Hospital, Department of Anaesthesia Pillai, Param; Austin Hospital, Department of Anaesthesia Karalipillai, Dharshi; Austin Hospital, Department of Anaesthesia Bellomo, Rinaldo; Austin Hospital, Department of Intensive Care; University of Melbourne Weinberg, Laurence; Austin Hospital, Department of Anaesthesia; University of Melbourne
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Evidence based practice, Health informatics
Keywords:	hypercapnia, oximetry, Spectroscopy, Near-Infrared, Respiration, Artificial, Delirium

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A randomised controlled trial to investigate the relationship between mild hypercapnia and cerebral oxygen saturation in patients undergoing major surgery

Authors: Clarence Wong[1,2], Leonid Churilov[2,3], Dean Cowie[1], Chong Tan[1], Raymond Hu[1], David Tremewen[1], Brett Pearce[1], Param Pillai[1], Dharshi Karalipillai[1], Rinaldo Bellomo[1,2], Laurence Weinberg[1,2]

1. Department of Anaesthesia, Austin Hospital, Heidelberg, Victoria, Australia;

2. University of Melbourne, Parkville, Victoria, Australia;

3. The Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia

Correspondence

A/Prof Laurence Weinberg

Department of Anaesthesia, Austin Hospital

145 Studley Road, Heidelberg, Victoria 3084, Australia

Phone number: (61) 03 94965000

Email: laurence.weinberg@austin.org.au

Word Count

Abstract: 300

Introduction: 304

Methods: 2017

Results: 743

Discussion: 1718

Conclusion: 91

Body text: 4873

Abstract

Objectives: The effects of hypercapnia on regional cerebral oxygen saturation (rSO_2) during surgery are unclear. We conducted a randomised controlled trial to investigate the relationship between mild hypercapnia and rSO_2. We hypothesized that, compared with targeted normocapnia (TN), targeted mild hypercapnia (TMH) during major surgery would increase rSO_2.

Design: A prospective, randomised controlled trial in adult participants undergoing elective major surgery.

Setting: A single tertiary centre in Heidelberg, Victoria, Australia.

Participants: 40 participants were randomised to either TMN or TN group (20 to each).

Interventions: TMH (partial pressure of carbon dioxide in arterial blood, $PaCO_2$, 45-55 mmHg) or TN ($PaCO_2$ 35-40 mmHg) was delivered via controlled ventilation throughout surgery.

Primary and secondary outcome measures: The primary endpoint was the absolute difference between two groups in percentage change in rSO_2 from baseline to completion of surgery. Secondary endpoints included intra-operative pH, bicarbonate concentration, base excess, serum potassium concentration, incidence of postoperative delirium and length of stay (LOS) in hospital.

Results: The absolute difference between two groups in percentage change in rSO_2 from baseline to completion of surgery was 19.0% higher in both hemispheres with TMH ($P<0.001$). The difference in $\%\Delta rSO_2$ on both hemispheres between the two groups diverged with time with TMH exhibiting smaller percentage decrease over time compared to TN. Postoperative delirium was higher in the TN group (risk difference 0.3, 95% CI [0.1 to 0.5], $P=0.02$). Length of stay was similar between groups (5 days vs. 5 days; $P=0.99$).

Conclusions: TMH was associated with a stable increase in rSO_2 from baseline while TN was associated with a decrease in rSO_2 in both hemispheres in patients undergoing major

surgery. This resulted in a clear separation of percentage change in rSO_2 from baseline between TMH and TN over time. Our findings provide the rationale for larger studies of TMH during surgery.

Clinical trial registration: The Australian New Zealand Clinical Trials Registry, unique identification number: ACTRN12616000320459

Keywords: Hypercapnia; Oximetry; Spectroscopy, Near-Infrared; Respiration, Artificial; Delirium

Article Summary

Strengths of this study

- High internal validity due to blinding and random allocation to groups
- Frequent sampling of oximetry data throughout monitoring period
- Non-invasive nature of near-infrared spectroscopy (NIRS) derived regional cerebral oxygen saturation (rSO_2)

Limitations of this study

- Study findings do not apply to emergency surgeries, intra-cranial surgeries, or surgeries requiring one lung ventilation
- rSO_2 measurements rely on the assumption that rSO_2 is homogenous in the brain

Acknowledgement

Funding Statement

Masimo provided the oximetry sensors used for this trial. This study conception, design, trial management, data collection, data analyses, and the writing of the manuscript, have been executed completely independently of Masimo and any other external organizations. This work was supported by the Deparment of Anaesthesia Research Fund, Austin Hospital, Heidelberg, Victoria, Australia

Declaration of interest

All authors declare no conflict of interest.

Presentation

Findings of this study were presented as a poster presentation at the PostGraduate Assembly in Anesthesiology, 8-12 December 2018, New York, USA

Data sharing statement

De-identified participant data are available upon reasonable request.

Introduction

In patients undergoing major surgery, the effects of mild hypercapnia on regional cerebral oxygen saturation (rSO_2) have not been fully examined, and any beneficial or harmful effects of hypercapnia as a therapeutic ventilation strategy to improve cerebral oxygenation are unknown. In animal models, CO_2 is a well-known vasodilator improving cerebral blood flow.[1-3] The neuroprotective mechanisms of mild hypercapnia, whilst not completely understood, have been postulated to be a result of increase in cerebral blood flow, enhancement of oxygen delivery, improvements in cerebral glucose utilisation and oxidative metabolism,[4,5] and activation of ATP-sensitive potassium channels to maintain normal neuronal activity in the setting of ischemia.[6]

The recent emergence of near-infrared spectroscopy (NIRS) based cerebral oximetry has provided a practical method to measure rSO_2 continuously and non-invasively. This technology has gained substantial supportive evidence in resuscitation, critical care, and surgical applications.[7-9] Numerous studies have shown that NIRS can be applied clinically in the resuscitation and cardiac surgery settings where cerebral desaturation events can be both effectively monitored and managed.[10-13] However, whilst absolute and relative saturation thresholds theoretically requiring prompt interventions have been proposed, [14] these thresholds have not been validated and there is a lack of consensus on the indication and timing of interventions. In patients undergoing surgery, rSO_2 was reported to be higher with mild hypercapnia but the intra-operative temporal relationship between rSO_2 and mild hypercapnia remains unclear.[15]

Accordingly, we conducted a randomised controlled trial to test the hypothesis that targeted mild hypercapnia (TMH), defined as partial pressure of carbon dioxide in arterial blood ($PaCO_2$) between 45 and 55 mmHg, during elective major surgery would increase cerebral oxygen saturation compared to targeted normocapnia (TN), defined as $PaCO_2$ between 35 and 40 mmHg. As a secondary aim, we evaluated if TMH would affect the development of postoperative delirium, a commonly reported complication in the immediately peri-operative setting.[16-18]

Methods

Ethics approval and clinical trial registration

The study was approved by the Austin Health Research and Ethics Committee on 6th January 2016 (HREC/15/Austin/488) and all participants gave written informed consent. The study was prospectively registered on 10th March 2016 with the Australian New Zealand Clinical Trials Registry (ACTRN12616000320459). The study was reported in accordance with the CONSORT Guidelines for reporting randomised trials.[19]

Trial design, setting, and population

Between March 2016 and March 2017, we conducted the randomised controlled trial at the Austin Hospital, a university teaching tertiary metropolitan hospital at Heidelberg, Victoria. Following pre-operative assessment at the anaesthesia pre-admissions clinic and the receipt of written informed consent, eligible patients undergoing elective major surgery were identified. Inclusion criteria included the following: adult patients (age over 18 years), surgery of greater than 2 hours expected duration requiring at least one overnight admission, a clinical indication for continuous blood pressure monitoring via an invasive arterial line, and intermittent positive pressure ventilation via an endotracheal tube as part of standard anaesthesia care. Exclusion criteria included patients undergoing cardiac surgery, procedures requiring one lung isolation, liver transplantation, intracranial surgery, GCS less than 15, known cognitive impairment, intellectual disability or a mental illness, moderate pulmonary hypertension (mean pulmonary arterial pressure greater than 40 mmHg), and American Society of Anesthesiology status V.

Randomisation and blinding

An independent statistician generated a computerised sequence of 40 allocation codes, 20 for each group. A research nurse sealed the allocation codes into sequentially numbered opaque envelopes. Study participants, surgeons, and all peri-operative staff were blinded to treatment allocation. However, it was not possible to blind the attending anaesthetist who was responsible for delivery of the intervention. Immediately after induction of anaesthesia, patients were randomised to either targeted mild hypercapnia ($PaCO_2$ 45-55 mmHg) or targeted normocapnia ($PaCO_2$ 35-40 mmHg). The end-tidal carbon dioxide ($EtCO_2$) was

titrated accordingly in order to achieve the desired intervention but the anaesthetist did not have a rSO_2 goal to titrate to. Data collection for all the trial outcomes was collected by an independent researcher blinded to treatment allocation. The sequence was decoded after the data was analysed. The anaesthetist delivering the intervention did not participate in the assessment of postoperative delirium.

Outcomes and data collection

The primary endpoint was the absolute difference between the TMH and TN groups in percentage change in rSO_2 from baseline to completion of surgery. Secondary endpoints evaluated the effects of mild hypercapnia on the incidence of postoperative delirium, intra-operative pH, bicarbonate, base excess, serum potassium, and length of hospital stay (LOS).

Measurement of rSO_2

Regional cerebral oxygen saturation was collected using the Masimo O_3™ regional oximetry component of the Root™ Patient Monitor platform (O_3™ Masimo, Irvine, CA). This regional oximetry device uses NIRS and reflectance oximetry to monitor rSO_2 in the brain, capturing both absolute and trend rSO_2 data. Absolute oximetry data is defined as the regional oxygen saturation value measured by the oximetry probes calibrated by a fixed ratio between arterial to venous blood, whereas the trend oximetry data is defined as the change in regional oxygen saturation value measured by the oximetry probes. The measurement errors for absolute and trend data are reported to be approximately 4% and 3% respectively when tested against reference blood samples taken from the radial artery and internal jugular bulb vein.[20] rSO_2 was measured in the two hemispheres separately. Following manufacturer instructions, two NIRS sensors were attached to patient's left and right forehead, recording both absolute and trend data bilaterally. After the recording of baseline cerebral oximetry, only absolute oximetry data were extracted and analysed. Regional cerebral oxygen saturation was collected before commencing any premedication and before induction of anaesthesia. Measurements were recorded every two seconds until the last surgical suture was sited. Data were exported as comma separated values files after surgery and processed using manually written R scripts on RStudio v. 1.0.136 (**Supplementary File 1)**. Data from the left and right forehead were analysed separately.

Measurement of delirium

Delirium was assessed using a validated and widely utilized Confusion Assessment Method (CAM) rating scale, adapted from Inouye *et al.*, immediately on arrival to hospital, then within 18-24 hours after surgery.[21,22] Diagnosis of delirium requires the presence of both acute onset with fluctuating course and inattention, together with either disorganised thinking or altered level of consciousness. A single trained interviewer, blinded to randomisation, and proficient and trained in the Confusion Assessment Method, conducted all the assessments pre-operatively when patient arrived at the hospital and at 8am on the next day after surgery in the ward (within 18-24 hours postoperatively). The baseline cognitive function was not formally assessed with collateral history from family or carers.

Measurement of $PaCO_2$ and intra-operative adherence to group allocation

Immediately after tracheal intubation with a cuffed endotracheal tube, minute ventilation was adjusted to achieve an $EtCO_2$ concentration of 45-55 mmHg in the TMH group or 35-40 mmHg in the TN group. Due to presence of alveolar dead space, $EtCO_2$ can be lower than $PaCO_2$ by up to 5 mmHg. Therefore, an arterial blood gas (ABG) was obtained to check $PaCO_2$ and ventilation was further adjusted accordingly to achieve the desired $PaCO_2$ target ranges. The $PaCO_2$-$EtCO_2$ gradient was then maintained throughout the surgery, with the assumption that the $PaCO_2$ would remain constant. Additional ABG were sampled at the discretion of the anaesthetist if the gradient required re-evaluation e.g. requirements for adjustment of ventilation setting. Finally, at completion of surgery, an ABG was sampled to accurately document the $PaCO_2$ value, and to assess whether $PaCO_2$ was being maintained within target values.

Arterial blood gas analysis

All arterial blood gas variables were collected by ABL80 FLEX Blood Gas Analyzer (Radiometer, Copenhagen, Denmark) with a fully automated micromode eliminating risk of user-induced bias or loss of accuracy with very small samples, and an interference-protected lactate analyses. ABG variables include partial pressure of oxygen, partial pressure of carbon dioxide, pH, bicarbonate concentration, base excess, lactate, haemoglobin concentration (Hb) and electrolytes such as sodium and potassium ion concentration. The machine calculates the bicarbonate concentration using the Henderson-Hasselbalch equation and the standard base excess (SBE) using the Van Slyke equation with the following reference points pH = 7.40, $PaCO_2$ = 40mmHg, and temperature = 37°C to determine changes in bicarbonate, protein anion, and phosphate concentrations, and therefore SBE. Two or more ABG samples were

measured intra-operatively as described previously. The mean values of pH, bicarbonate concentration, base excess, and serum potassium concentration from the first and the last ABG sample were considered as some of the secondary outcomes for the study. Intra-operative pH, bicarbonate, and base excess are important variables that inform acid-base status of a patient, in particular, bicarbonate and base excess are useful when determining the extent of metabolic contributions or compensation. Potassium concentration is a key physiological parameter that affects cardiac action potential conduction, and its relevance in the study is paramount as hyperkalaemia from hypercapnic-induce acidosis is a potential complication of the intervention. Potential confounders to rSO_2 measurements such as Haemoglobin concentration and partial pressure of oxygen were recorded. Other variables such as lactate and sodium concentration were collected for routine clinical care and they were not considered as part of the outcome measures.

Standardisation of care

All patients underwent pre-operative multidisciplinary team assessment including a haematology led multimodal peri-operative haemoglobin optimisation program based on the National Blood Authority of Australia's patient blood management initiatives to optimise pre-operative red cell mass, minimise peri-operative blood loss and tolerate postoperative anaemia.[23] All participants were fasted two hours for clear fluids and six hours for solids according to standard hospital fasting protocols. All participants received a general anaesthetic with propofol for induction, an inhalational agent for maintenance of anaesthesia, with 50% oxygen to air mixture to maintain oxygen saturations above 97%. Routine monitoring for all participants included continuous ECG, pulse oximetry, temperature, bispectral index (BIS) monitoring, and neuromuscular monitoring. Adequate depth of anaesthesia was ensured by targeting BIS reading between 40 and 60. Conduct of anaesthesia, including the use of additional invasive monitoring, intra-operative medications, fluids intervention, and use of vasoactive medications, regional anaesthesia and use of intraoperative opioids were entirely at the discretion of the attending anaesthetist. In keeping with hospital protocol, we transfused blood if haemoglobin concentration was less than 75 g dL^{-1}, or less than 80 g dL^{-1} in the presence of ongoing bleeding.

Sample size calculations

Based on our institution's pilot data and reported figures, normal rSO_2 values for awake patients could range from 60% to 80% [24], which we assumed to be the case at the baseline (beginning of surgery). We assumed no change in rSO_2 in the control group and considered an absolute difference between the groups in percentage change in rSO_2 value from the baseline to completion of surgery of 15% to be clinically important. Thus, the absolute changes in rSO_2 from the baseline to the end of surgery were hypothesised to be 0% in control group and 12% (15% percentage change from the baseline of 80% rSO_2) in the intervention group. Assuming two-tailed threshold for statistical significance of 0.05 and common standard deviation of the absolute change of 10%, the total sample size of 40 patients (equally distributed between two groups) will yield the 0.9 power to observe large treatment effect (Cohen's d=1.1 or higher).

Statistical Analyses

The study was reported in accordance with the Statistical Analyses and Methods in the Published Literature (SAMPL) Guidelines.[25] Statistical analysis was performed using commercial statistical software STATA/IC v.13 with a *P* value of 0.05 to indicate statistical significance. Figures and tables were created by manually written R scripts on RStudio v. 1.0.136 (**Supplementary File 2)**. Normality was determined by the Shapiro–Wilk test, further confirmed by manual inspection of the skewness and kurtosis of the data. Parametric continuous data were compared by the Student's t-test, and non-parametric continuous data were compared by the Mann-Whitney U test. For normally distributed data, results were presented as mean (standard deviation); and for non-parametric data, results were presented as median [inter-quartile range] unless otherwise stated. Fisher's exact test was used in the analysis of all categorical variables. For the primary outcome we compared the absolute difference between the TMH and TN groups in percentage change in rSO_2 from baseline to completion of surgery using an unpaired, two-tailed t-test. A more detailed longitudinal analysis of time-by-treatment interaction was also conducted using a random effect generalised least squares regression model (due to the repeated measures nature of the data) with percentage change in rSO_2 at a given time point throughout the surgery as the output, the treatment group and the time (minutes from start of surgery), as well as the time-by-treatment interaction term as inputs. The duration of surgery varied between different patients and therefore, in order to compare $\%\Delta rSO_2$ at different time points across all the patients, the time

was measured using "minutes from the start of surgery" metric. For robustness analyses, similar models adjusted for age, baseline oximetry values, and pre-operative haemoglobin levels were implemented, as well as models where time was measured not in minutes, but as a percentage of total surgery duration.

Patient and Public Involvement

The study was designed to investigation the relationship between TMH and rSO_2, and the incidence of postoperative delirium was one of the secondary outcomes. As mentioned previously, postoperative delirium is a commonly reported postoperative complication and it is linked to functional decline, institutionalisation, and higher mortality. [16,18] Our study involved minimal invasive monitoring and interventions, thereby causing minimal inconvenience or physical discomfort to patients. The study implications, however, could potentially inform standard anaesthesia practice to smoothen patients' postoperative course of recovery and minimise length of stay. Patients were involved in the study from the initial pre-admission consultation appointment where the rationale of the study, potential applications of the study outcomes, data privacy and management, and potential harmful effects were explained in detail. Study participants were not directly involved in the design and conduct of the study. Potential burden of the intervention was not rated by patients themselves, rather, potential harmful effects were monitored by the attending anaesthetist as part of routine clinical care. Study results and outcomes, once finalised, will be posted to study participants.

Results

Seventy-seven participants were screened for eligibility. Thirty-seven patients were excluded because they did not meet the inclusion criteria (*n*=6), declined to participate (*n*=30), or due to anaesthetist objection to intervention (*n*=1). For logistical reasons, recruitment could only be performed when the interviewer conducting the CAM testing was available. The Consort diagram is presented in **Figure 1**. There were no violations or breaches of the study protocol, however two participants in the hypercapnic group had failure of bilateral probe attachment and lead connection problem that were unable to be rescued. These patients were subsequently excluded from the analyses of oxygenation as no rSO_2 data were captured and were included in the analysis of all other variables and endpoints. In the hypercapnic group, three participants had unilateral discontinuous oximetry readings due to intermittent signal dropout. In the normocapnic group, signal dropout occurred in two patients on the left side. The corresponding data were excluded.

The baseline participant characteristics are summarised in **Table 1**.

Table 1. Baseline patient characteristics and surgical characteristics.[a]

	TMH group[b] (*n*=20)	**TN group[b] (*n*=20)**
Patient characteristics		
Gender (Male : Female)	11:9	12:8
Age (years) [a]	63.7 [32 to 81]	65.4 [31 to 81]
Weight (kg)	83.7 [56.8 to 110.6]	81.2 [67.9 to 94.5]
BMI (kg m^{-2})[c]	33.6 [20.7 to 46.5]	32.8 [26.8 to 38.8]
ASA Status[d]		
1	3 (16.7)	2 (10.0)
2	6 (33.3)	4 (20.0)
3	7 (38.9)	10 (50.0)
4	2 (11.1)	4 (20.0)
Diabetes	4 (22.2)	5 (25.0)
COPD[e]	5 (27.8)	0 (0.0)

Malignancy	11 (61.1)	7 (35.0)	
Other co-morbidities	11 (61.1)	16 (80.0)	
Surgical Characteristics			
Duration of surgery (mins)	219.0 [123.8 to 303.8]	144.0 [107.8 to 218.2]	(*P*=0.121)
Left baseline oximetry (%)	68.7 [63.9 to 72.2]	63.4 [57.3 to 69.6]	(*P*=0.233)
Right baseline oximetry (%)	67.9 [64.6 to 70.3]	64.0 [59.4 to 69.0]	(*P*=0.286)
Pulse oximetry (%)[f]	98.5 [98.1 to 99.0]	98.5 [97.9 to 99.0]	(*P*=0.834)
LOS (days)[g]	5 [2.0 to 12.0]	5 [1.8 to 11.5]	(*P*=0.988)
Type of surgery			
colorectal	2 (11.1)	1 (5.0)	
endocrine	2 (11.1)	2 (10.0)	
ear nose & throat	0 (0.0)	1 (5.0)	
hepatobiliary	6 (33.3)	9 (45.0)	
spinal surgery[h]	1 (5.6)	1 (5.0)	
orthopedic	2 (11.1)	1 (5.0)	
thoracic[i]	4 (22.2)	1 (5.0)	
urology	1 (5.6)	3 (15.0)	
vascular	0 (0.0)	1 (5.0)	

[a] data reported as number (%) or median [inter-quartile range], except for age, which is reported as median [range]

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

[c] BMI: body mass index

[d] ASA: American Society of Anesthesiologists

[e] COPD: chronic obstructive pulmonary disease

[f] peripheral oxygen saturation measured by pulse oximetry

[g] LOS: length of hospital stay

[h] non-intracranial procedures, e.g. complex spinal surgery

[i] includes procedures not requiring one lung ventilation, e.g. mediastinoscopy with nodal dissection

Both groups were similar in terms of gender, age, weight, body mass index, ASA physical status, and type of surgery performed. In terms of co-morbidities, both groups were similar except for the presence of chronic obstructive pulmonary disease. There was 100% compliance to the designated $PaCO_2$ intra-operative targets. The median [inter-quartile range, IQR] $PaCO_2$ in the TMH group and TN groups were 51.5 mmHg [46.9 to 60.9] and 34.8

mmHg [32.8 to 38.1] respectively (P<0.001). With regards to surgical characteristics, median duration of surgery was longer in the TMN group with median [IQR] duration of 219 min [124 to 304] versus 144 min [108 to 218] in the TN group (P=0.121). PaO_2 was similar between the two groups: 156.8 mmHg [146.3 to 217.2] in the TMH group and 142.5 mmHg [122.5 to 199.1] in the TN group (P=0.380). Oxygen saturation was similar: 98.5% in the TMH group [98.1 to 99.0], and 98.5% in the TN group [97.9 to 99.0] (P=0.834). Both groups also had similar mean arterial pressure intra-operatively (P=0.307), similar total haemoglobin (130.50 vs. 122.25 g L^{-1}; P=0.132), and similar total dose of intra-operative opioid received, 21.67 mg in the TMH group [13.75 to 32.50] and 16.67 mg in the TN group [10.00 to 22.50] (P=0.22).

Primary endpoint

On the left hemisphere, the median [IQR] baseline oximetry was 68.7% [63.9 to 72.2] in the TMH group vs. 63.4% [57.3 to 69.6] in the TN group (P=0.233). On the right hemisphere the median [IQR] baseline oximetry was 67.9% [64.6 to 70.3] in the TMH group vs. 64.0% [59.4 to 69.9] TN group (P=0.286). On both sides, the $\%\Delta rSO_2$ was greater in the TMH group than the TN group throughout the duration of surgery (**Figure 2**). The average (standard deviation, SD) percentage changes in rSO_2 from the baseline to the conclusion of the surgery in TMH group were +8.56% (18.90%) on the left and +13.86% (18.17%) on the right, and in TN group they were -6.18% (17.24%) on the left and -5.48% (18.94%) on the right. The resulting treatment effects were 19% (95% CI [9.2 to 28.8]; P<0.001) on the left and 19% (95% CI [10.9 to 27.0]; P<0.001) on the right (**Table 2**).

Table 2. Percentage change in cerebral oximetry (%ΔrSO_2) from baseline.[a]

Time from start of surgery (mins)		15	30	45	60	75	90	105	120
Left	**TMH**[b]	0.8 (12.9) {15}	5.8 (12.3) {15}	9.0 (15.9) {15}	7.0 (14.6) {15}	8.5 (15.4) {14}	7.3 (14.7) {13}	7.7 (17.4) {13}	8.1 (14.8) {13}
	TN[b]	4.7 (10.5) {18}	3.2 (15.4) {18}	-1.9 (14.1) {17}	-5.6 (12.7) {17}	-5.3 (15.2) {17}	-5.5 (15.8) {17}	-6.0 (15.2) {17}	-3.6 (15.8) {14}
Right	**TMH**	6.0 (12.9) {17}	9.8 (13.2) {17}	10.4 (18.1) {17}	11.1 (17.4) {17}	13.0 (16.4) {16}	15.6 (17.3) {15}	14.4 (17.5) {14}	14.1 (13.6) {14}
	TN	5.2 (12.6) {20}	3.9 (11.7) {20}	-3.3 (13.2) {19}	-5.2 (12.1) {19}	-5.4 (12.3) {19}	-4.7 (14.1) {19}	-3.8 (13.7) {18}	-1.3 (13.9) {15}

Time from start of surgery (mins)		120	240	360	480	600	720	Mean % difference from start to completion of surgery	95% confidence interval	*P* value (treatment)
Left	**TMH**	8.1 (14.8) {13}	6.8 (20.6) {7}	6.4 (32.5) {4}	-8.6 (21.1) {3}	-6.1 (14.1) {3}	6.9 (NA) {1}	19.0	9.2 -28.8	<0.001
	TN	-3.6 (15.8) {14}	-10.4 (39.5) {5}	-43.4 (34.9) {2}	-27.8 (NA) {1}					
Right	**TMH**	14.1 (13.6) {14}	18.4 (23.5) {8}	16.8 (36.8) {4}	1.5 (14.9) {3}	3.0 (8.7) {3}	2.0 (NA) {1}	19.0	10.9- 27.0	<0.001
	TN	-1.3 (13.9) {15}	-5.3 (32.6) {5}	-35.4 (26.9) {2}	-37.8 (NA) {1}					

[a] Data are presented every 15 minutes for the first 2 hours and every 2 hours afterwards, and are reported as mean (standard deviation) {sample size}.

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

On the longitudinal time-by-treatment interaction analysis, the difference in $\%\Delta rSO_2$ on both left and right between the two groups diverged with time with the intervention group exhibiting smaller percentage decrease over time compared to the control group (time-by-treatment interaction $P<0.001$ for both left and right hemispheres). We obtained very similar results on robustness analyses when the above model was adjusted for age, baseline oximetry and pre-operative haemoglobin levels, as well as when percentage of total duration of surgery instead of minutes from the start of surgery were included.

Secondary outcomes

Postoperative delirium was statistically significantly less common in the TMH group. Postoperative delirium was present in 0/20 (0%) participants in the TMH group and 6/20 (30%) participants in the TN group (risk difference 0.3, 95% CI [0.1 to 0.5], Fisher's exact P=0.02) (**Table 3).**

Table 3. Postoperative delirium and opioid doses [a]

	TMH group[b] (*n*=20)	**TN group[b] (*n*=20)**	
Pre-medication			
Number of patients	0 (0)	2 (10.0)	
Mean midazolam dose (mg)	0	1.75	
Intra-operative opioid [c]			
Total dose (mg) [d]	21.67 [13.75 to 32.50]	16.67 [10.00 to 22.50]	(P=0.22)
Received i.v. morphine (%)	2 (10)	1 (5)	
Received i.v. fentanyl (%)	10 (50)	14 (70)	
Received i.v. oxycodone (%)	9 (45)	7 (35)	
Received i.v. tramadol (%)	4 (20)	0 (0)	
Received i.v. clonidine (%)	0 (0)	2 (10)	
Intrathecal morphine			
Number of patients	5	2	
Mean dose (mcg)	220	350	

Epidural analgesia			
Number of patients	0	0	
Blood glucose level			
Glucose (mmol L-1)	7.1 [7.0 to 7.1]	6.6 [6.4 to 6.7]	(*P*=0.33)
Pre-operative CAM [e]	0 [0 to 0]	0 [0 to 0]	
Postoperative CAM [e]	0 [0 to 0]	1.5 [0 to 3]	
Presence of postoperative delirium	0 (0.0)	6 (30.0)	(*P*=0.02)

[a] Data reported as median [inter-quartile range] or number (%)

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

[c] Note some patients received 2 or more different opioids

[d] Total dose normalised to i.v. morphine equivalent

[e] CAM: Confusion Assessment Method

In terms of acid base variables, median intra-operative pH was statistically significantly lower (7.31 vs. 7.46; *P*<0.001) and intra-operative bicarbonate was statistically significantly higher (25.00 vs. 24.00 mEq L^{-1}; *P*=0.020) in the TMH. No statistically significant differences in base excess (-1.00 vs. 1.00 mmol L^{-1}; *P*=0.069) and potassium (3.98 vs. 4.03 mEq L^{-1}; *P*=0.759) were observed intra-operatively. Length of hospital stay was also similar between the two groups without statistically significant difference (5 vs. 5 days; *P*=0.988). These results are summarized in **Table 4.**

Table 4. Average arterial blood gas values [a] and corresponding end-tidal carbon dioxide

	TMH group[b] (*n*=20)	**TN group[b] (*n*=20)**	*P*-value
pH	7.31 [7.27 to 7.33]	7.46 [7.43 to 7.47]	<0.001
PaO_2 (mmHg)[c]	156.8 [146.3 to 217.2]	142.5 [122.5 to 199.1]	0.380
$PaCO_2$ (mmHg)[d]	51.50 [46.88 to 60.88]	34.75 [32.75 to 38.12]	<0.001
$EtCO_2$ (mmHg)[e]	46.40 [39.80 to 50.20]	30.40 [28.50 to 32.00]	<0.001
Bicarbonate (mEq L^{-1})	25.00 [24.00 to 27.75]	24.00 [22.00 to 24.62]	0.020
Base excess (mmol L^{-1})	-1.00 [-2.50 to 0.25]	1.00 [-0.88 to 2.00]	0.069
Potassium (mEq L^{-1})	3.98 [3.73 to 4.38]	4.03 [3.58 to 4.31]	0.759
Total Hb (g L^{-1})[f]	130.50 [118.12 to 140.62]	122.25 [106.88 to 131.25]	0.132

[a] Data reported as median [inter-quartile range] or number (%)

[b] TMH: targeted mild hypercapnia, TN: targeted normocapnia

[c] PaO_2: partial pressure of oxygen in arterial blood

[d] $PaCO_2$: partial pressure of carbon dioxide in arterial blood

[e] $EtCO_2$: end tidal carbon dioxide

[f] Hb: haemoglobin concentration

Discussion

We conducted a prospective, single centre, single blinded, randomised controlled trial evaluating the effects of targeted mild hypercapnia (TMH) and targeted normocapnia (TN) on regional cerebral oxygen saturation (rSO_2) in patients undergoing major surgery. TMH led to a stable increase in both left and right NIRS-derived regional cerebral oxygen saturation from baseline values while TN led to a decrease in rSO_2. This effect sustained throughout surgery and became more pronounced with the passage of time. Furthermore, TMH was associated with a lower incidence of postoperative delirium within 24 hours after surgery.

Whilst the relationship between elevated $PaCO_2$ and cerebral blood flow is well described,[26-28] the associations between hypercapnia and higher rSO_2 are poorly understood. Numerous factors, for instance, cardiac output, oxygen affinity of haemoglobin, cerebral autoregulation, and the ratio of cerebral arterial to venous blood volume, affect rSO_2 in the setting of hypercapnia, but changes in $PaCO_2$ and CBF, in turn, have direct influence on these factors. [29] To complicate the subject further, the duration of effect of hypercapnia on rSO_2 is unknown. In our study, confounding variables, such as MAP, PaO_2, and Hb were similar between the TMH and TN groups. However, pH, which directly affects the oxygen affinity of haemoglobin via the Bohr Effect, was significantly different. Since we cannot measure the ratio of arterial to venous blood volume, it would be impetuous to comment on the mechanism behind the observed higher rSO_2 values in TMH. Clinically, similar observations have been reported previously. Eastwood *et al.* found that mild hypercapnia resulted in higher rSO_2 values in post-cardiac arrest patients when rSO_2 values at the end of the normocapnic period and the end of the hypercapnic period were compared.[30] When Akca *et al.* delivered mild hypercapnia intra-operatively to investigate tissue oxygenation and its relationship with wound infection risk after surgery, cerebral oxygen saturation was found to be higher in mild hypercapnic group. [15] Similarly rSO_2 remained higher in hypercapnic patients throughout shoulder surgery, and less cerebral desaturation events were observed by Murphy *et al*.[31] Giardino *et al.* reviewed how changes in respiratory alternations in patients with anxiety alter CBF and found that changes in CBF over time in acute hypercapnia or hypocapnia have high individual

variability and CBF might never attain a true steady-state period with time.[32] Our study is one of the few randomised-controlled trials that investigated rSO_2 change over time. We found that the sustained difference in rSO_2 over time was a combined effect of stable increase in rSO_2 from baseline in the TMH group and a stable decrease in rSO_2 from baseline in the TN group. In the literature, the association between normocapnia and reduced CBF and lower levels of rSO_2 were reported briefly. [33] Normocapnia was also found to be superior in preserving cerebral autoregulation, [34] however, the exact mechanism and associations between normocapnia and variations in rSO_2 values are not entirely clear. Whilst theoretical absolute and relative saturation thresholds requiring prompt interventions have been proposed, [14] these thresholds have not been validated and there is a lack of consensus on the indication and timing of interventions. In our study, reduction in rSO_2 from baseline was small in the majority of patients in the TN group and the attending anaesthetists had no rSO_2 target to titrate to. Comparing the TMH and TN groups, the sustained difference in percentage change in rSO_2 over time is a novel finding.

Interestingly, the incidence of postoperative delirium after surgery was lower in the TMH group while LOS remained similar between the groups. Patients who suffered from postoperative delirium were all in the TN group but they were also older (median [IQR] age 72 [59.5 to 77]) and had higher ASA scores (ASA scores of 3, 2, 1, 4 and 4). Their baseline medical co-morbidities and duration of surgery (median [IQR] duration of surgery 171 minutes [83.5 to 254.5]) were similar to other study participants. There has been conflicting evidence in the literature regarding the relationship between rSO_2 and LOS or postoperative cognitive performance. Cognitive outcomes were similar in groups with or without NIRS-based rSO_2 optimisation in a recent randomised controlled trial. [14,35] On the other hand, Murkin *et al.* found that monitoring and reacting to cerebral desaturation during coronary artery bypass surgery was associated with clinical benefits.[13] Patients with shorter LOS (<10 days) had higher mean rSO_2. Intra-operative NIRS rSO_2 monitoring led to a significant reduction in postoperative cognitive disturbance confirmed by Trafidlo *et al.*[36] Casati *et al.* also reported that higher rSO_2 led to shorter LOS and improved Mini-Mental State Examination scores in elderly patients undergoing major abdominal surgery,[37] and Schoen *et al.* found that low pre-operative

rSO_2 was associated with higher incidence of postoperative delirium. Among patients who started at a normal saturation level, those who developed delirium had a larger intra-operative drop in rSO_2.[38] Our findings were consistent with Schoen *et al.*, however, they need to be interpreted with caution as the ASA scores and age were slightly higher in the TN group, and our study was not designed to quantitatively investigate postoperative cognitive performance in hypercapnia.

Implications of our findings demonstrate that TMH can be delivered reliably during major surgery and its effects on rSO_2 can be monitored with NIRS in most patients. Its delivery is reliably associated with increased levels of rSO_2, and the relatively higher rSO_2 is sustained over the duration of surgery, an observation that has not been reported in the literature. Furthermore, TMH may reduce the incidence of the development of immediate postoperative delirium. A clinical concern of mild hypercapnia is hypercapnic-induced acidosis and the subsequent development of hyperkalaemia. Whilst a linear correlation between arterial carbon dioxide and plasma pH is well reported,[39] the relationship between acute hypercarbia, respiratory acidosis and plasma potassium is also poorly understood.[40] In the present study, we found no association between hypercarbia and serum potassium concentrations, a finding also supported by others.[41] We did not observe any other deleterious or adverse effects from hypercapnic-induced acidosis such as cardiac arrhythmias in our study. Interestingly, whilst our study was not designed to measure differences in analgesia and partial pressure of oxygen in arterial blood, we observed a 10% higher median PaO_2 level in the TMH group, and found that the median intraoperative analgesia requirements were also approximately 30% higher. Both arterial oxygen levels and pain have been reported to influence tissue oxygenation,[42] which was not directly measured in our study. The effect of pain on cerebral oxygenation is unclear, and has not be borne out in clinical studies;[43] further studies exploring this association are needed. Finally, we have shown that NIRS-based cerebral oximetry is a non-invasive and practical method of measuring rSO_2, easily incorporated into the existing collection of routine monitoring variables, findings that are in agreement with other research groups.[20,44-46]

Our study has multiple strengths. Our findings have high internal validity because the study was a randomised controlled trial with concealed allocation and blinded assessment, minimising selection and ascertainment bias. rSO_2 data were exported directly to RStudio, and ABG data were analysed by the ABL Blood Gas Analyzer, rendering sampling error from data entry unlikely, thereby increasing the robustness of our findings. Sampling of continuous oximetry data resulted in a stream of oximetry data throughout the monitoring periods, maximizing the details of our assessment. Although the duration of surgery was different for individual patients, oximetry data were not normalised to another time scale, enabling a fair comparison of data across the study groups. NIRS-derived rSO_2 has been criticised for potential extra-cranial contamination that would confound true rSO_2.[47] However, there is sufficient evidence to support the accuracy of NIRS-derived rSO_2,[20,44] particularly in the case of hypercapnia, where extra-cranial signal interference has been shown to be insignificant, justifying its reliability.[48] Moreover, as the technology was the same in both groups, any inaccuracy should not have been a source of bias.

Our study also has a number of limitations. The attending anaesthetists were not blinded due to the nature of the intervention. Nevertheless, bias was mitigated by the fact that measurements were taken directly from the cerebral oximetry machine and assessment of delirium was conducted by an independent researcher blinded to the intervention. The external validity of our findings was restricted by the small sample size from one single centre. Sample size calculation was based on the assumption that there were no changes in rSO_2 values from baseline in the TN group. The observed negative change can therefore impact the calculation. The strong nature of interaction between treatment and time for rSO_2 outcome should be treated with caution due to the potential minor departures of the data from the linear trend. Our findings were not applicable to patients undergoing emergency surgery, intracranial surgery, or surgery requiring one lung ventilation. The cerebral oximetry probes were only attached to the forehead, measuring rSO_2 within the frontal cortex region, which carries the assumption that rSO_2 was homogenous across every area of the brain. This assumption will need to be tested for the posterior circulation in future studies. Quantification of device failure rate, despite being a critical consideration, cannot be described by our study design.

We did not measure cardiac output, stroke volume and systemic vascular resistance. Therefore, the effects on changes in intrathoracic pressures on cardiac output are unknown. Changes in intrathoracic pressure may have adversely impacted cardiac output, which may in turn have affected the $EtCO_2$. However, given that the PEEP was held constant in both groups, and the changes in lung tidal volumes were relatively small, the impact of intrathoracic pressure on cardiac output is likely to be small. Finally, our findings of a greater incidence of early postoperative delirium in the TN group need to be interpreted with caution as confounders of postoperative delirium were not controlled, our study was not powered to investigation postoperative delirium, and mental state was only assessed by CAM, once pre-operatively and once postoperatively. Accordingly, our findings for delirium should be viewed as hypothesis generating. Nevertheless, if we were to consider that our effect size observed (i.e. 0.13) could be due to chance and a smaller effect would be observed in a larger study, an appropriate powered RCT for this outcome would be very feasible. If the proportion of patients with delirium in the intervention group is 10%, to achieve 90% power, the required sample size for each group would be ninety two.

Conclusion

In summary, in patients undergoing elective major surgery, targeted mild hypercapnia was associated with a stable increase in regional cerebral oxygen saturation from baseline while targeted normocapnia was associated with a decrease in regional cerebral oxygen saturation from baseline in both hemispheres. This effect was sustained and became more marked with the passage of time intra-operatively, resulting in a clear separation of the percentage change in regional cerebral oxygen saturation between TMH and TN groups over time. These preliminary findings provide the rationale and justification for larger investigations of this intervention.

Author Contributions

Clarence Wong: This author contributed to data collection, data analysis, and writing up of manuscript

Leonid Churilov: This author contributed to data analysis and writing up of manuscript

Dean Cowie: This author contributed to patient recruitment, data collection, and writing up of manuscript

Chong Tan: This author contributed to patient recruitment and writing up of manuscript

Raymond Hu: This author contributed to patient recruitment and writing up of manuscript

David Tremewen: This author contributed to patient recruitment and writing up of manuscript

Brett Pearce: This author contributed to patient recruitment and writing up of manuscript

Param Pillai: This author contributed to data collection and writing up of manuscript

Dharshi Karalipillai: This author contributed to data collection and writing up of manuscript

Rinaldo Bellomo: This author contributed to study design and writing up of manuscript

Laurence Weinberg: This author designed the study, contributed to patient recruitment, data collection, data analysis and writing up of manuscript

References

1. Brosnan RJ, Steffey EP, LeCouteur RA, Imai A, Farver TB, Kortz GD. Effects of ventilation and isoflurane end-tidal concentration on intracranial and cerebral perfusion pressures in horses. *American journal of veterinary research.* 2003;64(1):21-25.
2. Faraci FM, Breese KR, Heistad DD. Cerebral vasodilation during hypercapnia. Role of glibenclamide-sensitive potassium channels and nitric oxide. *Stroke.* 1994;25(8):1679-1683.
3. Hino JK, Short BL, Rais-Bahrami K, Seale WR. Cerebral blood flow and metabolism during and after prolonged hypercapnia in newborn lambs. *Critical care medicine.* 2000;28(10):3505-3510.
4. Nakahata MDK, Kinoshita MDPDH, Hirano MDY, Kimoto MDY, Iranami MDH, Hatano MDPDY. Mild Hypercapnia Induces Vasodilation via Adenosine Triphosphate-sensitive K+Channels in Parenchymal Microvessels of the Rat Cerebral Cortex. *Anesthesiology.* 2003;99(6):1333-1339.
5. Kaku DA, Giffard RG, Choi DW. Neuroprotective effects of glutamate antagonists and extracellular acidity. *Science (New York, NY).* 1993;260(5113):1516-1518.
6. Vannucci RC, Brucklacher RM, Vannucci SJ. Effect of Carbon Dioxide on Cerebral Metabolism during Hypoxia-Ischemia in the Immature Rat. *Pediatr Res.* 1997;42(1):24-29.
7. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *British journal of anaesthesia.* 2009;103 Suppl 1:i3-13.
8. Elizabeth A, Frost M. Cerebral oximetry: emerging applications for an established technology. *Anesthesiol News.* 2012;38:10.
9. Steppan J, Hogue CW, Jr. Cerebral and tissue oximetry. *Best Pract Res Clin Anaesthesiol.* 2014;28(4):429-439.
10. Ahn A, Yang J, Inigo-Santiago L, Parnia S. A feasibility study of cerebral oximetry monitoring during the post-resuscitation period in comatose patients following cardiac arrest. *Resuscitation.* 2014;85(4):522-526.

11. Storm C, Leithner C, Krannich A, et al. Regional cerebral oxygen saturation after cardiac arrest in 60 patients--a prospective outcome study. *Resuscitation.* 2014;85(8):1037-1041.
12. Ito N, Nishiyama K, Callaway CW, et al. Noninvasive regional cerebral oxygen saturation for neurological prognostication of patients with out-of-hospital cardiac arrest: a prospective multicenter observational study. *Resuscitation.* 2014;85(6):778-784.
13. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesthesia and analgesia.* 2007;104(1):51-58.
14. Deschamps A, Hall R, Grocott H, et al. Cerebral Oximetry Monitoring to Maintain Normal Cerebral Oxygen Saturation during High-risk Cardiac Surgery: A Randomized Controlled Feasibility Trial. *Anesthesiology.* 2016;124(4):826-836.
15. Akca O, Liem E, Suleman MI, Doufas AG, Galandiuk S, Sessler DI. Effect of intra-operative end-tidal carbon dioxide partial pressure on tissue oxygenation. *Anaesthesia.* 2003;58(6):536-542.
16. Robinson TN, Eiseman B. Postoperative delirium in the elderly: diagnosis and management. *Clinical Interventions in Aging.* 2008;3(2):351-355.
17. Liu LL, Leung JM. Predicting adverse postoperative outcomes in patients aged 80 years or older. *Journal of the American Geriatrics Society.* 2000;48(4):405-412.
18. Inouye SK. Delirium in older persons. *The New England journal of medicine.* 2006;354(11):1157-1165.
19. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340.
20. Redford D, Paidy S, Kashif F. Absolute and trend accuracy of a new regional oximeter in healthy volunteers during controlled hypoxia. *Anesth Analg.* 2014;119(6):1315-1319.
21. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Annals of internal medicine.* 1990;113(12):941-948.

22. Sharon K, Inouye MD, MPH. Confusion Assessment Method: Training Manual and Coding Guide, Copyright 2003.
23. National Blood Authority. Blood Management Guidelines: Module 2 Perioperative. 2012; http://www.nba.gov.au/guidelines/module2/po-mod2.pdf2.
24. Vretzakis G, Georgopoulou S, Stamoulis K, et al. Cerebral oximetry in cardiac anesthesia. *Journal of thoracic disease.* 2014;6 Suppl 1:S60-69.
25. Lang TA, Altman DG. Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines. *International journal of nursing studies.* 2015;52(1):5-9.
26. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. *Critical care (London, England).* 2010;14(2):220.
27. Yokoyama I, Inoue Y, Kinoshita T, Itoh H, Kanno I, Iida H. Heart and brain circulation and CO2 in healthy men. *Acta physiologica (Oxford, England).* 2008;193(3):303-308.
28. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. *J Physiol.* 2011;589(Pt 12):3039-3048.
29. Vranken NPA, Weerwind PW, Sutedja NA, Severdija EE, Barenbrug PJC, Maessen JG. Cerebral Oximetry and Autoregulation during Cardiopulmonary Bypass: A Review. *The journal of extra-corporeal technology.* 2017;49(3):182-191.
30. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early cardiac arrest survivors: The impact of hypercapnia. *Resuscitation.* 2016;102:11-16.
31. Murphy GS, Szokol JW, Avram MJ, et al. Effect of ventilation on cerebral oxygenation in patients undergoing surgery in the beach chair position: a randomized controlled trial. *British journal of anaesthesia.* 2014;113(4):618-627.
32. Giardino ND, Friedman SD, Dager SR. Anxiety, respiration, and cerebral blood flow: implications for functional brain imaging. *Comprehensive psychiatry.* 2007;48(2):103-112.

33. Brian Johnny E, MD. Carbon Dioxide and the Cerebral Circulation *Anesthesiology: The Journal of the American Society of Anesthesiologists.* 1998;88(5):1365-1386.

34. Severdija EE, Vranken NP, Simons AP, et al. Hemodilution Combined With Hypercapnia Impairs Cerebral Autoregulation During Normothermic Cardiopulmonary Bypass. *Journal of cardiothoracic and vascular anesthesia.* 2015;29(5):1194-1199.

35. Rogers CA, Stoica S, Ellis L, et al. Randomized trial of near-infrared spectroscopy for personalized optimization of cerebral tissue oxygenation during cardiac surgery. *Br J Anaesth.* 2017;119(3):384-393.

36. Trafidlo T, Gaszynski T, Gaszynski W, Nowakowska-Domagala K. Intraoperative monitoring of cerebral NIRS oximetry leads to better postoperative cognitive performance: a pilot study. *International journal of surgery (London, England).* 2015;16(Pt A):23-30.

37. Casati A, Fanelli G, Pietropaoli P, et al. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth Analg.* 2005;101(3):740-747, table of contents.

38. Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger K-U. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. *Critical Care.* 2011;15(5):R218-R218.

39. Finsterer U, Luhr HG, Wirth AE. Effects of acute hypercapnia and hypocapnia on plasma and red cell potassium, blood lactate and base excess in man during anesthesia. *Acta anaesthesiologica Scandinavica.* 1978;22(4):353-366.

40. Adrogue HJ, Madias NE. Changes in plasma potassium concentration during acute acid-base disturbances. *The American journal of medicine.* 1981;71(3):456-467.

41. Natalini G, Seramondi V, Fassini P, et al. Acute respiratory acidosis does not increase plasma potassium in normokalaemic anaesthetized patients. A controlled randomized trial. *European Journal of Anaesthesiology.* 2006;18(6):394-400.

42. Akca O. Pain and Tissue Oxygenation. *Critical care medicine.* 2015;43:e462-463.
43. Hoiseth LO, Hisdal J, Hoff IE, Hagen OA, Landsverk SA, Kirkeboen KA. Tissue oxygen saturation and finger perfusion index in central hypovolemia: influence of pain. *Crit Care Med.* 2015;43(4):747-756.
44. MacLeod DB, Ikeda K, Vacchiano C, Lobbestael A, Wahr JA, Shaw AD. Development and validation of a cerebral oximeter capable of absolute accuracy. *Journal of cardiothoracic and vascular anesthesia.* 2012;26(6):1007-1014.
45. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. *Anesthesiology.* 2000;93(4):947-953.
46. Brady K, Joshi B, Zweifel C, et al. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke.* 2010;41(9):1951-1956.
47. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology.* 2012;116(4):834-840.
48. Akça O, Sessler DI, DeLong D, Keijner R, Ganzel B, Doufas AG. Tissue Oxygenation Response to Mild Hypercapnia during Cardiopulmonary Bypass with Constant Pump Output. *British journal of anaesthesia.* 2006;96(6):708-714.

Figures

Figure 1. CONSORT flow diagram
(Please refer to the attached diagram)

Figure 2. Percentage change in cerebral oximetry from baseline (%ΔrSO_2) over time
(Please refer to the attached diagram)

Figure Captions

Figure 1:

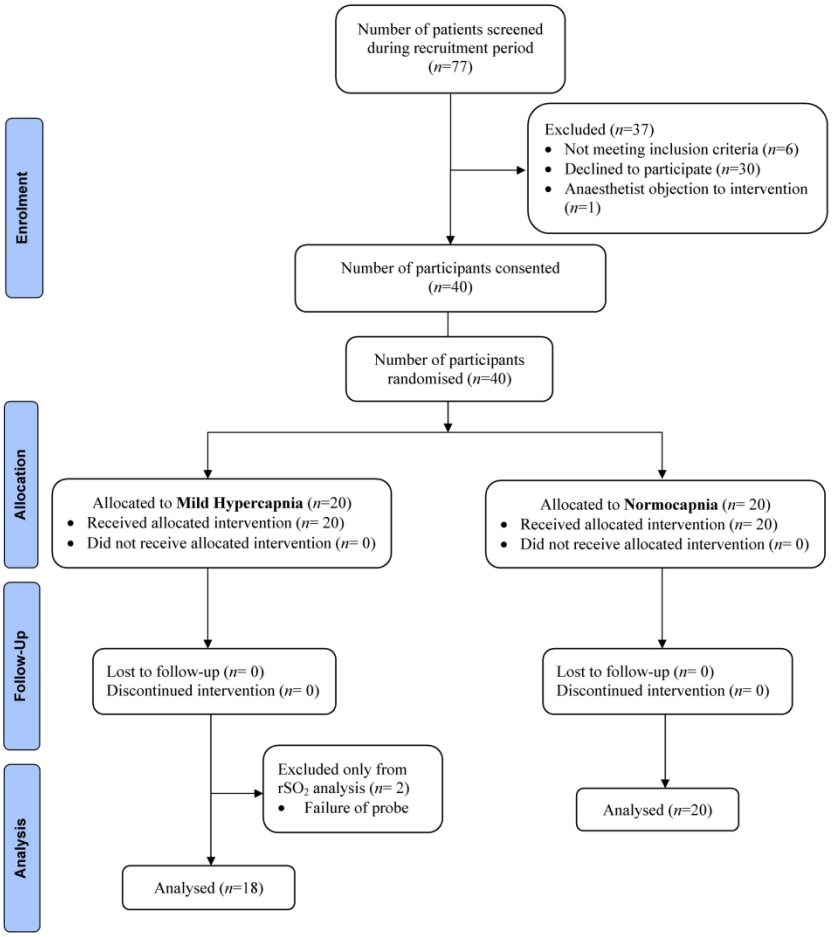
The progress of all participants through the trial displayed by the Consolidated Standards Of Reporting Trials (CONSORT) flow diagram.

Figure 2:

The solid lines represent mean percentage change, the shaded areas represent standard deviation, red represents the targeted mild hypercapnia (TMH) group, and blue represents the targeted normocapnia (TN) group.

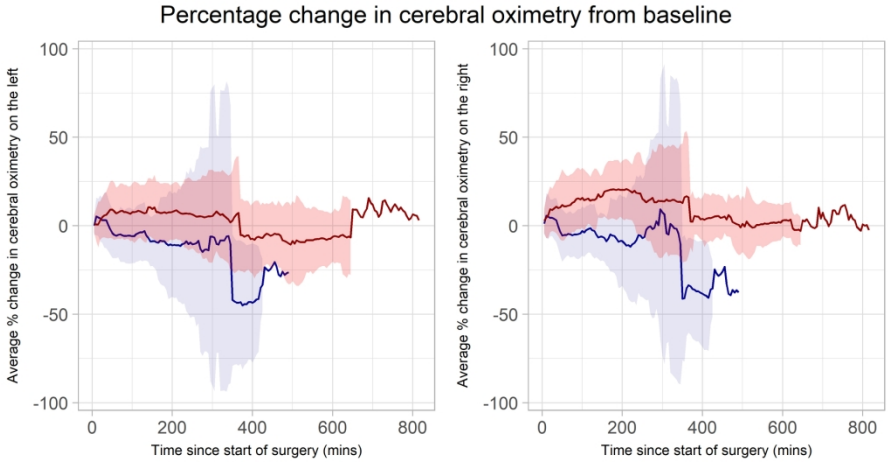
Left: average percentage change of regional cerebral oxygen saturation from baseline on the left hemisphere

Right: average percentage change of regional cerebral oxygen saturation from baseline on the right hemisphere



The progress of all participants through the trial displayed by the Consolidated Standards Of Reporting Trials (CONSORT) flow diagram.

203x287mm (300 x 300 DPI)



The solid lines represent mean percentage change, the shaded areas represent standard deviation, red represents the targeted mild hypercapnia (TMH) group, and blue represents the targeted normocapnia (TN) group.
Left: average percentage change of regional cerebral oxygen saturation from baseline on the left hemisphere
Right: average percentage change of regional cerebral oxygen saturation from baseline on the right hemisphere

177x93mm (300 x 300 DPI)

Supplementary File 1

```
#-----------------------------------------------------------------------------------------------------------
--
# TITLE: Create oximetry database from raw data files
# Author: Clarence Wong
# Last updated: 2/7/2017
# RStudio v. 1.0.136
#-----------------------------------------------------------------------------------------------------------
--

library(readr)
require(lubridate)
require(TTR)
require(xts)
require(zoo)
library(reshape2)

#-----------------------------------------------------------------------------------------------------------
--
# Read all data files and save as R object
#-----------------------------------------------------------------------------------------------------------
--

master<-0
for (i in 1:8)
{
  file <-
read.csv(paste("D:/SS/R_data/FINAL_oximetry_data/",as.character(i),".csv",sep=""))
  master <- rbind(master,file)
}
master$date_time <- paste(master$Date, master$Time..GMT.)
master$date_time <- mdy_hms(master$date_time)
converted_master <- master[,c(58,3:57)]

save(converted_master,file = "converted_master.RData")

database_times <- read_csv("D:/SS/R_data/database_times.csv")
date_vector <- database_times[,c(1,5,6,7,11,12)]

date_vector$start_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Monitoring Start`))
date_vector$end_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Monitoring End`))
```

```
date_vector$surg_start_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Start Time`))
date_vector$surg_end_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Finish Time`))

converted_date_vector <- date_vector[,c(1,7,8,9,10)]

save(converted_date_vector,file = "converted_date_vector.RData")

rm(master,date_vector,file)

#-----------------------------------------------------------------------------------------------------
--
# 1.  Convert data types and locate monitoring periods
# 2.  Identify oximettry values at various time points
# 3.  Compute percentage change from baseline
# 4.  Identify and locate problematic data
#-----------------------------------------------------------------------------------------------------
--

minutes_taken_as_baseline <- 2.5
minutes_interval <- 5

secs_taken_as_baseline <- minutes_taken_as_baseline*60
secs_interval <- minutes_interval*60

load("converted_master.RData")
load("converted_date_vector.RData")
print("data loaded. check data version")

oximetry_L <-
as.numeric(levels(converted_master$RSO2_A1)[converted_master$RSO2_A1])
oximetry_R <-
as.numeric(levels(converted_master$RSO2_A2)[converted_master$RSO2_A2])
PSI <- as.numeric(levels(converted_master$PSI)[converted_master$PSI])

# monitoring duration
duration_mins <-
difftime(converted_date_vector$end_date_time,converted_date_vector$start_date_time,uni
ts = "mins")
duration_secs <-
difftime(converted_date_vector$end_date_time,converted_date_vector$start_date_time,uni
ts = "secs")

locate_start = seq(-1,-1,length.out = dim(converted_date_vector)[1])
```

```
for (i in 1:dim(converted_date_vector)[1]){
if(length(which(converted_date_vector$start_date_time[i]==converted_master$date_time))
==1)
  {
    locate_start[i] <-
which(converted_date_vector$start_date_time[i]==converted_master$date_time)
  }
}

# create final_oximetry data frame
final_oximetry <- data.frame()
baseline_L_mu<-baseline_L_std<-baseline_L_N<-baseline_R_mu<-baseline_R_std<-
baseline_R_N<-rep(9999,dim(converted_date_vector)[1])
num_time_pts <- rep(1,40)

for(j in 1:dim(converted_date_vector)[1])
{
  # for each patient
  if(locate_start[j]==-1)
  {
    p_id <- j
    time_id<-minute_from_baseline<-percentage_total_monitoring_period<-L_delta<-
L_mu<-L_sig<-L_N<-R_delta<-R_mu<-R_sig<-R_N<-PSI_mu<-9999

  } else{

    locate_baseline <- locate_start[j]+secs_taken_as_baseline/2
    locate_times <- seq(0,0)
    num_measurements <- (as.numeric(duration_secs)[j]-
secs_taken_as_baseline)%/%secs_interval +1
    num_time_pts[j] <- num_measurements
    locate_times[1] <- locate_baseline
    locate_times[2] <- locate_times[1] + secs_interval/2
    locate_times[2:num_measurements]<-
seq(locate_times[2],locate_start[j]+as.numeric(duration_secs[j])/2,by=secs_interval/2)
    locate_times[num_measurements+1]<-locate_start[j]+as.numeric(duration_secs[j])/2

    baseline_L_mu[j] <- mean(oximetry_L[locate_start[j]:(locate_baseline-1)],na.rm =
TRUE)
    baseline_L_std[j] <- sd(oximetry_L[locate_start[j]:(locate_baseline-1)],na.rm = TRUE)
    baseline_L_N[j] <- length(oximetry_L[locate_start[j]:(locate_baseline-1)])-
sum(is.na(oximetry_L[locate_start[j]:(locate_baseline-1)]))
```

```
   baseline_R_mu[j] <- mean(oximetry_R[locate_start[j]:(locate_baseline-1)],na.rm =
TRUE)
   baseline_R_std[j] <- sd(oximetry_R[locate_start[j]:(locate_baseline-1)],na.rm = TRUE)
   baseline_R_N[j] <- length(oximetry_R[locate_start[j]:(locate_baseline-1)])-
sum(is.na(oximetry_R[locate_start[j]:(locate_baseline-1)]))

   L_delta <- L_mu <- L_sig <- L_N <- R_delta <- R_mu <- R_sig <- R_N <- PSI_mu <-
seq(0,0)

   for (k in 1:num_measurements)
   {
    L_mu[k] <- mean(oximetry_L[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    L_sig[k] <- sd(oximetry_L[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    L_N[k] <- length(oximetry_L[locate_times[k]:(locate_times[k+1]-1)])-
sum(is.na(oximetry_L[locate_times[k]:(locate_times[k+1]-1)]))

    R_mu[k] <- mean(oximetry_R[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    R_sig[k] <- sd(oximetry_R[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    R_N[k] <- length(oximetry_R[locate_times[k]:(locate_times[k+1]-1)])-
sum(is.na(oximetry_R[locate_times[k]:(locate_times[k+1]-1)]))

    PSI_mu[k] <- mean(PSI[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
   }

   L_delta <- (L_mu/baseline_L_mu[j] -1)*100
   R_delta <- (R_mu/baseline_R_mu[j] -1)*100

   time_id <- 1:num_measurements
   minute_from_baseline <- c(seq(minutes_interval,minutes_interval*(num_measurements-
1), by = minutes_interval),as.numeric(duration_mins[j]-minutes_taken_as_baseline))
   p_id <- rep(j,num_measurements)
   percentage_total_monitoring_period <-
((minute_from_baseline*60+secs_taken_as_baseline)/as.numeric(duration_secs[j]))*100

  }

  temp_df <-
data.frame(p_id,time_id,minute_from_baseline,percentage_total_monitoring_period,L_delt
a,L_mu,L_sig,L_N,R_delta,R_mu,R_sig,R_N,PSI_mu)
  final_oximetry <- rbind(final_oximetry,temp_df)
  rm(temp_df)

}

missing_L <- unique(final_oximetry$p_id[is.na(final_oximetry$L_delta)])
```

```
missing_R <- unique(final_oximetry$p_id[is.na(final_oximetry$R_delta)])
percentage_total_missing_L <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$L_delta)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$L_delta)])])
percentage_total_missing_R <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$R_delta)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$R_delta)])])
missing_data <- unique(final_oximetry$p_id[(final_oximetry$L_delta==9999)])
missing_data <- missing_data[!is.na(missing_data)]
missing_PSI <- unique(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])
percentage_total_missing_PSI <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])])

print("there are missing delta oximetry values in the following patients")
print(missing_L)
print(percentage_total_missing_L)

print(missing_R)
print(percentage_total_missing_R)

print(missing_data)

print("there are missing PSI values in the following patients")
print(missing_PSI)
print(percentage_total_missing_PSI)

other_data <-
data.frame(num_time_pts,baseline_L_mu,baseline_L_std,baseline_L_N,baseline_R_mu,
baseline_R_std,baseline_R_N)
other_data[is.na(other_data)]<-9999
save(other_data, file="other_data.RData")

final_oximetry[is.na(final_oximetry)]<-9999
save(final_oximetry,file = "final_oximetry.RData")


#-----------------------------------------------------------------------------------------------------------
--
# 1.  Convert baseline characteristic database from wide to long format
# 2.  Incorporating oximetry data in the database with time as a nested data in the hierarchy
# 3.  Create final database
#-----------------------------------------------------------------------------------------------------------
--
```

```
load("final_oximetry.RData")
load("other_data.RData")
print("check if final oximetry is latest")

baseline_results <- read.csv("D:/SS/R_data/FINAL_oximetry_data/all_baseline.csv",
sep=",", stringsAsFactors=FALSE)

baseline_results$baseline_L_mu <- other_data$baseline_L_mu
baseline_results$baseline_L_std <- other_data$baseline_L_std
baseline_results$baseline_L_N <- other_data$baseline_L_N
baseline_results$baseline_R_mu <- other_data$baseline_R_mu
baseline_results$baseline_R_std <- other_data$baseline_R_std
baseline_results$baseline_R_N <- other_data$baseline_R_N

baseline_results$P_id <- index(baseline_results)

baseline_results[baseline_results == "#N/A"]<-9999

#generate baseline_results with the same number of rows as final oximetry
baseline_results <- baseline_results[rep(seq_len((40)),num_time_pts),]


all_results <- cbind(baseline_results,final_oximetry)
if (sum(1*(all_results$P_id != all_results$p_id))==0)
{
  all_results <- all_results[,c(which(colnames(all_results)=="p_id"),1:109,112:122)]
}

save(all_results,file = "all_results.RData")

#UNCOMMENT TO WRITE CSV
#-------------------------------------------------
write.csv(all_results, file="all_results.csv")
```

Supplementary File 2

```
#-------------------------------------------------------------------------------------------------------
-------
# TITLE: Create baseline patient and surgical characteristics table, oximetry table, and
oximetry graphs
# Author: Clarence Wong
# Last updated: 2/7/2017
# RStudio v. 1.0.136
#-------------------------------------------------------------------------------------------------------
-------

library(readr)
require(lubridate)
require(TTR)
require(xts)
require(zoo)
require(tableone)
require(ggplot2)
library(grid)
require(gridExtra)
require(quantreg)

#-------------------------------------------------------------------------------------------------------
-------
# 1.  Create summary statistics for baseline characteristics
# 2.  Perform statistical analysis on secondary outcomes. e.g post-operative delirium
# 3.  Export tables in csv files
# Requires baseline characteristic and baseline oximetry data.
#-------------------------------------------------------------------------------------------------------
-------

baseline_db <- read.csv("D:/SS/R_data/baseline/all_baseline.csv", sep=",",
stringsAsFactors=TRUE)
load("other_data.RData")

other_data <- other_data[-c(1,2),]

baseline_db$baseline_L_mu <- other_data$baseline_L_mu
baseline_db$baseline_L_std <- other_data$baseline_L_std
baseline_db$baseline_L_N <- other_data$baseline_L_N
baseline_db$baseline_R_mu <- other_data$baseline_R_mu
baseline_db$baseline_R_std <- other_data$baseline_R_std
baseline_db$baseline_R_N <- other_data$baseline_R_N

baseline_db$P_id <- index(baseline_db)
```

```
baseline_db[baseline_db == "#N/A"]<-NA
baseline_db[baseline_db == 9999]<-NA
baseline_db$pCO2_2<-
as.numeric(levels(baseline_db$pCO2_2))[baseline_db$pCO2_2]
baseline_db$BMI<-as.numeric(levels(baseline_db$BMI))[baseline_db$BMI]
vars <-
c("Gender","Age","Weight","BMI","ASA","Diabetes","COPD","Maligancy","Other_C
omorbidities",

"Surgery_type","Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu")
factorVars <- c("ASA","Diabetes","COPD","Maligancy","Other_Comorbidities")
Tableone <- CreateTableOne(vars,"Group",baseline_db,factorVars)


baseline_db$LOS<-as.numeric(levels(baseline_db$LOS))[baseline_db$LOS]
baseline_db$pH_2<-as.numeric(levels(baseline_db$pH_2))[baseline_db$pH_2]
baseline_db$HCO3._2<-
as.numeric(levels(baseline_db$HCO3._2))[baseline_db$HCO3._2]
baseline_db$Base_excess_2<-
as.numeric(levels(baseline_db$Base_excess_2))[baseline_db$Base_excess_2]
baseline_db$Potassium_2<-
as.numeric(levels(baseline_db$Potassium_2))[baseline_db$Potassium_2]
baseline_db$Total_Hb_2<-
as.numeric(levels(baseline_db$Total_Hb_2))[baseline_db$Total_Hb_2]

baseline_db$pH<-apply(baseline_db[,c("pH_1","pH_2")],1,mean,na.rm=TRUE)
baseline_db$pCO2<-
apply(baseline_db[,c("pCO2_1","pCO2_2")],1,mean,na.rm=TRUE)
baseline_db$HCO3.<-
apply(baseline_db[,c("HCO3._1","HCO3._2")],1,mean,na.rm=TRUE)
baseline_db$Base_excess<-
apply(baseline_db[,c("Base_excess_1","Base_excess_2")],1,mean,na.rm=TRUE)
baseline_db$Potassium<-
apply(baseline_db[,c("Potassium_1","Potassium_2")],1,mean,na.rm=TRUE)
baseline_db$Total_Hb<-
apply(baseline_db[,c("Total_Hb_1","Total_Hb_2")],1,mean,na.rm=TRUE)

vars_2 <-
c("Surgery_type","Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu","L
OS",

"pH","pCO2","HCO3.","Base_excess","Potassium","Total_Hb","post_op_delirium")
factorVars_2 <- c("post_op_delirium")
Tabletwo <- CreateTableOne(vars_2,"Group",baseline_db,factorVars_2,argsExact =
"post_op_delirium")

print(Tabletwo,exact = "post_op_delirium",nonnormal =
c("Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu",
```

```
"LOS","pH","pCO2","HCO3.","Base_excess","Potassium","Total_Hb"))


write.csv(print(Tabletwo,exact = "post_op_delirium",nonnormal =
c("Duration_Surgery_Minutes","baseline_L_mu",

"baseline_R_mu","LOS","pH","pCO2","HCO3.",
                                                    "Base_excess","Potassium","Total_Hb")),
"Table_Two.csv")

#-----------------------------------------------------------------------------------------------------
-------
# 1.  Create summary statistics for percentage change of regional cerebral oxygen
saturation
# 2.  Create plots for regional cerebral oxygen saturation over time
# 3.  Export oximetry tables in csv files
# Requires baseline characteristic and baseline oximetry data.
#-----------------------------------------------------------------------------------------------------
-------

#-----------------------------------------------------------------------------------------------------
-------
# Normocapnic group

plot_db <- read.csv("D:/SS/R_data/oximetry/MASTER_results_deleted_missing.csv",
sep=",", stringsAsFactors=TRUE)

plot_db[plot_db == "#N/A"]<-NA
plot_db[plot_db == 9999]<-NA

normocapnia <- subset(plot_db, Group %in% 0)
hypercapnia <- subset(plot_db, Group %in% 1)

normo_plot <- ggplot(normocapnia, aes(x=minute_from_baseline, y=L_delta,
group=p_id)) + geom_line() +geom_point()+
  ggtitle("normocapnia: L delta")+ xlab("Time since start of operation (mins)")+
ylab("% change in oximetry from baseline")

hyper_plot <- ggplot(hypercapnia, aes(x=minute_from_baseline, y=L_delta,
group=p_id)) + geom_line() +geom_point()+
  ggtitle("hypercapnia: L delta")+ xlab("Time since start of operation (mins)")+ ylab("%
change in oximetry from baseline")

means <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x) sd(x, na.rm =
TRUE))
```

```
N <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x)
length(x[!is.na(x)]))

normo_df_L <- data.frame(means,stdevs)
times<- index(normo_df_L)*5
normo_df_L <- data.frame(means,stdevs,N, times)
total_normo_L <- ggplot(normo_df_L, aes(x=times, y=means)) +
geom_line(colour="blue4") +
  geom_ribbon(normo_df_L,mapping = aes(x=times,
ymax=means+stdevs,ymin=means-stdevs),fill="blue4",alpha=0.1)

means <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x) mean(x,
na.rm = TRUE))
stdevs <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x)
length(x[!is.na(x)]))

normo_df_R <- data.frame(means,stdevs)
times<- index(normo_df_R)*5
normo_df_R <- data.frame(means,stdevs,N, times)
total_normo_R <- ggplot(normo_df_R, aes(x=times, y=means)) +
geom_line(colour="blue4") +
  geom_ribbon(normo_df_R,mapping = aes(x=times,
ymax=means+stdevs,ymin=means-stdevs),fill="blue4",alpha=0.1)

#-----------------------------------------------------------------------------------------------
-------
# Hypercapnic group

means <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) length(x[!is.na(x)]))

hyper_df_L <- data.frame(means,stdevs)
times<- index(hyper_df_L)*5
hyper_df_L <- data.frame(means,stdevs,N, times)
total_hyper_L <- ggplot(hyper_df_L, aes(x=times, y=means))

means <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) length(x[!is.na(x)]))

hyper_df_R <- data.frame(means,stdevs)
```

```
times<- index(hyper_df_R)*5
hyper_df_R <- data.frame(means,stdevs,N, times)
total_hyper_R <- ggplot(hyper_df_R, aes(x=times, y=means))

total_L <- total_normo_L +
  geom_ribbon(hyper_df_L,mapping = aes(x=times, ymax=means+stdevs,ymin=means-
stdevs),fill="red2",alpha=0.2) +
  geom_line(hyper_df_L,mapping = aes(x=times, y=means),colour="red4") +
  theme_light() +
  xlab("Time since start of surgery (mins)")+ ylab("Average % change in cerebral
oximetry on the left") +
  theme(axis.title.y = element_text(size = rel(0.65), angle = 90)) +
  theme(axis.title.x = element_text(size = rel(0.65), angle = 00))

total_R <- total_normo_R +
  geom_ribbon(hyper_df_R,mapping = aes(x=times, ymax=means+stdevs,ymin=means-
stdevs),fill="red2",alpha=0.2) +
  geom_line(hyper_df_R,mapping = aes(x=times, y=means),colour="red4")+
  theme_light() +
  xlab("Time since start of surgery (mins)")+ ylab("Average % change in cerebral
oximetry on the right") +
  scale_color_manual(values=c("red4","blue4"))+
  theme(axis.title.y = element_text(size = rel(0.65), angle = 90)) +
  theme(axis.title.x = element_text(size = rel(0.65), angle = 00))

#tiff('oximetry_graph_high_res.tiff', units="in", width=7, height=3.6667, res=600,
compression = 'lzw')

grid.arrange(total_L, total_R, ncol = 2, top=textGrob("Percentage change in cerebral
oximetry from baseline",
                                        gp=gpar(fontsize=11,fontfamily="Times")),
          vp=viewport(width=0.9, height=0.9))

#insert ggplot code
#dev.off()

temp_hyper_L <- t(paste(round(hyper_df_L$mean,1)," (",
round(hyper_df_L$stdev,1),")"," {", hyper_df_L$N,"}", sep = ""))
temp_normo_L <- t(paste(round(normo_df_L$mean,1)," (",
round(normo_df_L$stdev,1),")"," {", normo_df_L$N,"}", sep = ""))

temp_hyper_R <- t(paste(round(hyper_df_R$mean,1)," (",
round(hyper_df_R$stdev,1),")"," {", hyper_df_R$N,"}", sep = ""))
temp_normo_R <- t(paste(round(normo_df_R$mean,1)," (",
round(normo_df_R$stdev,1),")"," {", normo_df_R$N,"}", sep = ""))

write.csv( temp_normo_L , "normo_df_L.csv")
write.csv( temp_normo_R , "normo_df_R.csv")
```

```
write.csv( temp_hyper_L , "hyper_df_L.csv")
write.csv( temp_hyper_R , "hyper_df_R.csv")
```

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6-7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6-7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	9
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12-13
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14,16,17
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	14
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	21
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	22-23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	21-22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19-21
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	4

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A randomised controlled trial to investigate the relationship between mild hypercapnia and cerebral oxygen saturation in patients undergoing major surgery

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029159.R2
Article Type:	Original research
Date Submitted by the Author:	04-Nov-2019
Complete List of Authors:	Wong, Clarence; Austin Hospital, Department of Anaesthesia Churilov, Leonid; The Florey Institute of Neuroscience and Mental Health; University of Melbourne Cowie, Dean; Austin Hospital, Department of Anaesthesia Tan, Chong; Austin Hospital, Department of Anaesthesia Hu, Raymond; Austin Hospital, Department of Anaesthesia Tremewen, David; Austin Hospital, Department of Anaesthesia Pearce, Brett; Austin Hospital, Department of Anaesthesia Pillai, Param; Austin Hospital, Department of Anaesthesia Karalipillai, Dharshi; Austin Hospital, Department of Anaesthesia Bellomo, Rinaldo; Austin Hospital, Department of Intensive Care; University of Melbourne Weinberg, Laurence; Austin Hospital, Department of Anaesthesia; University of Melbourne
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Evidence based practice, Health informatics
Keywords:	hypercapnia, oximetry, Spectroscopy, Near-Infrared, Respiration, Artificial, Delirium

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A randomised controlled trial to investigate the relationship between mild hypercapnia and cerebral oxygen saturation in patients undergoing major surgery

Authors: Clarence Wong[1,2], Leonid Churilov[2,3], Dean Cowie[1], Chong Tan[1], Raymond Hu[1], David Tremewen[1], Brett Pearce[1], Param Pillai[1], Dharshi Karalipillai[1], Rinaldo Bellomo[1,2], Laurence Weinberg[1,2]

1. Department of Anaesthesia, Austin Hospital, Heidelberg, Victoria, Australia;

2. University of Melbourne, Parkville, Victoria, Australia;

3. The Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia

Correspondence

A/Prof Laurence Weinberg

Department of Anaesthesia, Austin Hospital

145 Studley Road, Heidelberg, Victoria 3084, Australia

Phone number: (61) 03 94965000

Email: laurence.weinberg@austin.org.au

Word Count

Abstract: 304

Introduction: 307

Methods: 2035

Results: 802

Discussion: 1671

Conclusion: 43

Body text: 4858

Abstract

Objectives: The effects of hypercapnia on regional cerebral oxygen saturation (rSO_2) during surgery are unclear. We conducted a randomised controlled trial to investigate the relationship between mild hypercapnia and rSO_2. We hypothesised that, compared with targeted normocapnia (TN), targeted mild hypercapnia (TMH) during major surgery would increase rSO_2.

Design: A prospective, randomised, controlled trial in adult participants undergoing elective major surgery.

Setting: A single tertiary centre in Heidelberg, Victoria, Australia.

Participants: 40 participants were randomised to either a TMH or TN group (20 to each).

Interventions: TMH (partial pressure of carbon dioxide in arterial blood, $PaCO_2$, 45-55 mmHg) or TN ($PaCO_2$ 35-40 mmHg) was delivered via controlled ventilation throughout surgery.

Primary and secondary outcome measures: The primary endpoint was the absolute difference between the two groups in percentage change in rSO_2 from baseline to completion of surgery. Secondary endpoints included intra-operative pH, bicarbonate concentration, base excess, serum potassium concentration, incidence of postoperative delirium, and length of stay (LOS) in hospital.

Results: The absolute difference between the two groups in percentage change in rSO_2 from the baseline to the completion of surgery was 19.0% higher in both hemispheres with TMH ($P<0.001$). On both sides, the percentage change in rSO_2 was greater in the TMH group than the TN group throughout the duration of surgery. The difference between the groups became more noticeable over time. Furthermore, postoperative delirium was higher in the TN group (risk difference 0.3, 95% CI [0.1 to 0.5], $P=0.02$). Length of stay was similar between groups (5 days vs. 5 days; $P=0.99$).

Conclusion: TMH was associated with a stable increase in rSO_2 from the baseline, while TN was associated with a decrease in rSO_2 in both hemispheres in patients undergoing major surgery. This resulted in a clear separation of percentage change in rSO_2 from the baseline between TMH and TN over time. Our findings provide the rationale for larger studies on TMH during surgery.

Clinical trial registration: The Australian New Zealand Clinical Trials Registry, unique identification number: ACTRN12616000320459

Keywords: Hypercapnia; Oximetry; Spectroscopy, Near-Infrared; Respiration, Artificial; Delirium

Article Summary

Strengths of this study

- High internal validity due to blinding and random allocation to groups
- Frequent sampling of oximetry data throughout monitoring period
- Non-invasive nature of near-infrared spectroscopy (NIRS) cerebral oximetry for regional cerebral oxygen saturation (rSO_2) measurements

Limitations of this study

- Study findings do not apply to emergency surgeries, intra-cranial surgeries, or surgeries requiring one lung ventilation.
- Interpretation of rSO_2 depends on an assumption that rSO_2 is the same in different regions of the brain.

Acknowledgement

Funding Statement

Masimo provided the oximetry sensors used for this trial. This study conception, design, trial management, data collection, data analysis, and the writing of the manuscript, have been executed completely independently of Masimo and any other external organisations. This work was supported by the Deparment of Anaesthesia Research Fund, Austin Hospital, Heidelberg, Victoria, Australia.

Declaration of interest

All authors declare no conflict of interest.

Presentation

Findings of this study were presented as a poster presentation at the PostGraduate Assembly in Anesthesiology held during 8-12th December 2018 at New York, United States of America.

Data sharing statement

De-identified participant data are available upon reasonable request.

Introduction

In patients undergoing major surgery, the effects of mild hypercapnia on regional cerebral oxygen saturation (rSO_2) have not been fully examined, and any beneficial or harmful effects of hypercapnia as a therapeutic ventilation strategy to improve cerebral oxygenation are unknown. In animal models, CO_2 is a well-known vasodilator, improving cerebral blood flow.[1-3] The neuroprotective mechanisms of mild hypercapnia, whilst not completely understood, have been postulated to be a result of an increase in cerebral blood flow, enhancement of oxygen delivery, improvements in cerebral glucose utilisation and oxidative metabolism,[4,5] and activation of adenosine triphosphate (ATP)-sensitive potassium channels to maintain normal neuronal activity in the setting of ischemia.[6]

The recent emergence of near-infrared spectroscopy (NIRS) cerebral oximetry has provided a practical method to measure rSO_2 continuously and non-invasively. This technology has gained substantial supportive evidence in resuscitation, critical care, and surgical applications.[7-9] Numerous studies have shown that NIRS can be applied clinically in the resuscitation and cardiac surgery settings, where cerebral desaturation events can be both effectively monitored and managed.[10-13] However, whilst absolute and relative saturation thresholds theoretically requiring prompt interventions have been proposed,[14] these thresholds have not been validated, and there is a lack of consensus on the indication and timing of interventions. In patients undergoing surgery, rSO_2 was reported to be higher with mild hypercapnia, however, the intra-operative temporal relationship between rSO_2 and mild hypercapnia remains unclear.[15]

Accordingly, we conducted a randomised controlled trial to test the hypothesis that targeted mild hypercapnia (TMH), defined as the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) between 45 and 55 mmHg, during elective major surgery would increase cerebral oxygen saturation compared to targeted normocapnia (TN), defined as $PaCO_2$ between 35 and 40 mmHg. As a secondary aim, we evaluated whether TMH would affect the development of postoperative delirium, a commonly reported complication in the immediately peri-operative setting.[16-18]

Methods

Ethics approval and clinical trial registration

The study was approved by the Austin Health Research and Ethics Committee on 6th January 2016 (HREC/15/Austin/488), and all participants gave written informed consent. The study was prospectively registered on 10th March 2016 with the Australian New Zealand Clinical Trials Registry (ACTRN12616000320459). The study was reported in accordance with the CONSORT Guidelines for reporting randomised trials.[19]

Trial design, setting, and population

Between March 2016 and March 2017, we conducted the randomised controlled trial at the Austin Hospital, a university teaching, tertiary, metropolitan hospital at Heidelberg, Victoria. Following a pre-operative assessment at the anaesthesia pre-admissions clinic and the receipt of written informed consent, eligible patients undergoing elective major surgery were identified. Inclusion criteria included the following: adult patients (age over 18 years), surgery of greater than 2 hours' expected duration requiring at least one overnight admission, a clinical indication for continuous blood pressure monitoring via an invasive arterial line, and intermittent positive pressure ventilation via an endotracheal tube as part of standard anaesthesia care. Age criterion was modified from the previous criterion (age over 65 years) to age over 18 years in order to recruit patients who represent the intended study population. Exclusion criteria included patients undergoing cardiac surgery, procedures requiring one lung isolation, liver transplantation, intracranial surgery, GCS less than 15, known cognitive impairment, intellectual disability or a mental illness, moderate pulmonary hypertension (mean pulmonary arterial pressure greater than 40 mmHg), and American Society of Anesthesiology (ASA) status V.

Randomisation and blinding

An independent statistician generated a computerised sequence of 40 allocation codes, 20 for each group. A research nurse sealed the allocation codes into sequentially numbered opaque envelopes. The study participants, surgeons, and all peri-operative staff were blinded to treatment allocation. However, it was not possible to blind the attending anaesthetist who was responsible for the delivery of the intervention. Immediately after induction of anaesthesia,

patients were randomised to either targeted mild hypercapnia ($PaCO_2$ 45-55 mmHg) or targeted normocapnia ($PaCO_2$ 35-40 mmHg). The end-tidal carbon dioxide ($EtCO_2$) was titrated accordingly in order to achieve the desired intervention, but the anaesthetist did not have an rSO_2 goal to titrate to. Data collection for all the trial outcomes was collected by an independent researcher blinded to treatment allocation. The sequence was decoded after the data were analysed. The anaesthetist delivering the intervention did not participate in the assessment of postoperative delirium.

Outcomes and data collection

The primary endpoint was the absolute difference between the TMH and TN groups in percentage change in rSO_2 from baseline to completion of surgery. Secondary endpoints evaluated the effects of mild hypercapnia on the incidence of postoperative delirium, intra-operative pH, bicarbonate, base excess, serum potassium, and length of hospital stay (LOS).

Measurement of rSO_2

Regional cerebral oxygen saturation was collected using the Masimo O_3™ regional oximetry component of the Root™ Patient Monitor platform (O_3™ Masimo, Irvine, CA). This regional oximetry device uses NIRS and reflectance oximetry to monitor rSO_2 in the brain, displaying both absolute and trend rSO_2 values. The absolute oximetry value is defined as the rSO_2 value measured by the oximetry probe calibrated by a fixed ratio of arterial to venous blood, whereas the trend oximetry value is defined as the change in rSO_2 from a user-specified value (usually the baseline rSO_2). The measurement errors for absolute and trend data are reported to be approximately 4% and 3% respectively when checked against reference blood samples taken from the radial artery and internal jugular bulb vein.[20] Regional cerebral oxygen saturation was measured in the two hemispheres separately, with a NIRS sensor attached to each side of patient's forehead. Only the absolute oximetry data were extracted and analysed. The baseline rSO_2 was recorded before commencing any premedication and before induction of anaesthesia. Subsequent rSO_2 measurements were recorded every two seconds until the last surgical suture was sited. Data were exported as comma separated values files after surgery and processed using manually written R scripts on RStudio v.1.0.136 (**Supplementary File 1)**. The percentage change in rSO_2 ($\%\Delta rSO_2$) was computed by subtracting the baseline rSO_2 value from the measured rSO_2 value at all timepoints

throughout surgery, multiplied by one hundred percent. Data from the left and right forehead were analysed separately.

Measurement of delirium

Delirium was assessed using a validated and widely utilised Confusion Assessment Method (CAM) rating scale, adapted from Inouye *et al.*, immediately on arrival to hospital, then within 18-24 hours after surgery.[21,22] Diagnosis of delirium requires the presence of both acute onset with fluctuating course and inattention, together with either disorganised thinking or altered level of consciousness. A single trained interviewer, blinded to randomisation and proficient and trained in CAM, conducted all the assessments pre-operatively when each patient arrived at the hospital and at 8am on the next day after surgery in the ward (within 18-24 hours postoperatively). The baseline cognitive function was not formally assessed with collateral history from family members or carers.

Measurement of $PaCO_2$ and intra-operative adherence to group allocation

Immediately after tracheal intubation with a cuffed endotracheal tube, minute ventilation was adjusted to achieve an $EtCO_2$ concentration of 45-55 mmHg in the TMH group or 35-40 mmHg in the TN group. Due to the presence of alveolar dead space, $EtCO_2$ can be lower than $PaCO_2$ by up to 5 mmHg. Therefore, an arterial blood gas (ABG) was obtained to check $PaCO_2$, and ventilation was further adjusted accordingly to achieve the desired $PaCO_2$ target ranges. The $PaCO_2$-$EtCO_2$ gradient was then maintained throughout surgery, with the assumption that the $PaCO_2$ would remain constant. Additional ABGs were sampled at the discretion of the anaesthetist if the gradient required re-evaluation, for example, requirements for an adjustment of the ventilation setting. Finally, at completion of surgery, an ABG was sampled to accurately document the $PaCO_2$ value and to assess whether $PaCO_2$ was being maintained within target values.

Arterial blood gas analysis

All arterial blood gas variables were collected by ABL80 FLEX Blood Gas Analyzer (Radiometer, Copenhagen, Denmark) with a fully automated micromode, eliminating the risk of user-induced bias or loss of accuracy with very small samples, and an interference-protected lactate analyser. ABG variables include partial pressure of oxygen (PaO_2), $PaCO_2$, pH, bicarbonate concentration, base excess, lactate, haemoglobin concentration (Hb), and electrolytes such as sodium and potassium ion concentrations. The machine calculates the

bicarbonate concentration using the Henderson-Hasselbalch equation and the standard base excess (SBE) using the Van Slyke equation by determining changes in bicarbonate, protein anion, and phosphate concentrations, with the reference points pH = 7.40, $PaCO_2$ = 40mmHg, and temperature = 37°C. Two or more ABG samples were measured intra-operatively, as described previously. The mean values of pH, bicarbonate concentration, base excess, and serum potassium concentration from the first and the last ABG samples were considered as some of the secondary outcomes for the study. Intra-operative pH, bicarbonate, and base excess are important variables that inform the acid–base status of a patient; in particular, bicarbonate and base excess are useful when determining the extent of metabolic contributions or compensation. Potassium concentration is a key physiological parameter that affects cardiac action potential conduction, and its relevance in the study is paramount, as hyperkalaemia from hypercapnic-induced acidosis is a potential complication of the intervention. Potential confounders to rSO_2 measurements, such as Hb and PaO_2, were recorded. Other variables, such as lactate and sodium concentration, were collected for routine clinical care, and they were not considered as part of the outcome measures.

Standardisation of care

All patients underwent a pre-operative multidisciplinary team assessment, including a haematology-led, multimodal peri-operative haemoglobin optimisation program based on the National Blood Authority of Australia's patient blood management initiatives to optimise pre-operative red cell mass, minimise peri-operative blood loss, and tolerate postoperative anaemia.[23] All participants were fasted two hours for clear fluids and six hours for solids, according to standard hospital fasting protocols. All participants received a general anaesthetic with propofol for induction, an inhalational agent for the maintenance of anaesthesia, with a 50% oxygen-to-air mixture to maintain oxygen saturations above 97%. Routine monitoring for all participants included continuous electrocardiogram (ECG), pulse oximetry, temperature, bispectral index (BIS) monitoring, and neuromuscular monitoring. Adequate depth of anaesthesia was ensured by targeting BIS readings between 40 and 60. Conduct of anaesthesia, including the use of additional invasive monitoring, intra-operative medications, intervention fluids, vasoactive medications, regional anaesthesia, and intraoperative opioids, were entirely at the discretion of the attending anaesthetist. In keeping with hospital protocol, we transfused blood if the haemoglobin concentration was less than 75 g dL^{-1} or less than 80 g dL^{-1} in the presence of ongoing bleeding.

Sample size calculations

Based on our institution's pilot data and reported figures, normal rSO_2 values for awake patients could range from 60% to 80%,[24] which we assumed to be the case at the baseline (beginning of surgery). We assumed no change in rSO_2 in the control group and considered an absolute difference between the groups in percentage change in rSO_2 value from the baseline to the completion of surgery of 15% to be clinically important. Thus, the absolute changes in rSO_2 from the baseline to the end of surgery were hypothesised to be 0% in the control group and 12% (15% percentage change from the baseline of 80% rSO_2) in the intervention group. Assuming a two-tailed threshold for statistical significance of 0.05 and standard deviation of the absolute change of 10%, the total sample size of 40 patients (equally distributed between two groups) will yield the 0.9 power to observe a large treatment effect (Cohen's d=1.1 or higher).

Statistical analysis

The study was reported in accordance with the Statistical Analyses and Methods in the Published Literature (SAMPL) Guidelines.[25] The statistical analysis was performed using commercial statistical software STATA/IC v.13 with a P value of 0.05 to indicate statistical significance. Figures and tables were created by manually written R scripts on RStudio v. 1.0.136 (**Supplementary File 2)**. Fisher's exact test was used in the analysis of all categorical variables. For continuous variables, normality was determined by the Shapiro–Wilk test and further confirmed by a manual inspection of the skewness and kurtosis of the data. Parametric continuous data were compared by the Student's t-test, and non-parametric continuous data were compared by the Mann-Whitney U test. For normally distributed data, the results were presented as the mean (standard deviation); and for non-parametric data, the results were presented as the median [inter-quartile range] unless otherwise stated. A more detailed longitudinal analysis of time-by-treatment interaction was also conducted using a random effect generalised least squares regression model (due to the repeated measures nature of the data) with percentage change in rSO_2 at a given time point throughout the surgery as the output, the treatment group, the time (minutes from start of surgery), as well as the time-by-treatment interaction term as inputs. The duration of surgery varied between different patients, and therefore, in order to compare $\%\Delta rSO_2$ at different time points across all the patients, the time was measured using the "minutes from the start of surgery" metric. For robustness analyses, similar models adjusted for age, baseline oximetry values, and pre-

operative Hb levels were implemented, as well as models where time was measured not in minutes, but as a percentage of total surgery duration.

Patient and public involvement

The study was designed to investigate the relationship between TMH and rSO_2, and the incidence of postoperative delirium was one of the secondary outcomes. As mentioned previously, postoperative delirium is a commonly reported postoperative complication, and it is linked to functional decline, institutionalisation, and higher mortality.[16,18] Our study involved minimal invasive monitoring and interventions, thereby causing minimal inconvenience or physical discomfort to patients. The study implications, however, could potentially inform standard anaesthesia practice to smoothen patients' postoperative course of recovery and minimise LOS. Patients were involved in the study from the initial pre-admission consultation appointment where the rationale of the study, potential applications of the study outcomes, data privacy and management, and potential harmful effects were explained in detail. Study participants were not directly involved in the design and conduct of the study. Potential burden of the intervention was not rated by the patients themselves; rather, potential harmful effects were monitored by the attending anaesthetist as part of routine clinical care. Study results and outcomes, once finalised, will be posted to study participants.

Results

Seventy-seven participants were screened for eligibility. Thirty-seven patients were excluded because they did not meet the inclusion criteria (*n*=6), they declined to participate (*n*=30), or the anaesthetist objected to the intervention (*n*=1). For logistical reasons, recruitment could only be performed when the interviewer conducting the CAM testing was available. The CONSORT diagram is presented in **Figure 1**. There were no violations or breaches of the study protocol; however, two participants in the hypercapnic group had a failure of bilateral probe attachment and lead connection problem that were unable to be rectified. These patients were subsequently excluded from the analyses of oxygenation, as no rSO_2 data were captured. They were included in the analysis of all other variables and endpoints. In the hypercapnic group, three participants had unilateral discontinuous oximetry readings due to intermittent signal dropout. In the normocapnic group, signal dropout occurred in two patients on the left side. The corresponding data were excluded.

The baseline participant and surgical characteristics are summarised in **Table 1**.

Table 1. Baseline patient characteristics and surgical characteristics

	TMH group (*n*=20)	**TN group (*n*=20)**
Patient characteristics		
Gender (Male : Female)	11:9	12:8
Age (years)	63.7 [32 to 81]	65.4 [31 to 81]
Age > 65 (years)	9 (45.0)	11 (55.0)
Weight (kg)	83.7 [56.8 to 110.6]	81.2 [67.9 to 94.5]
BMI (kg m^{-2})	33.6 [20.7 to 46.5]	32.8 [26.8 to 38.8]
ASA Status		
1	5 (25.0)	2 (10.0)
2	6 (30.0)	4 (20.0)
3	7 (35.0)	10 (50.0)
4	2 (10.0)	4 (20.0)
Diabetes	4 (22.2)	5 (25.0)

COPD	5 (27.8)	0 (0.0)	
Malignancy	11 (61.1)	7 (35.0)	
Other co-morbidities	11 (61.1)	16 (80.0)	
Surgical Characteristics			
Duration of surgery (mins)	219.0 [123.8 to 303.8]	144.0 [107.8 to 218.2]	(*P*=0.121)
Left baseline oximetry (%)	68.7 [63.9 to 72.2]	63.4 [57.3 to 69.6]	(*P*=0.233)
Right baseline oximetry (%)	67.9 [64.6 to 70.3]	64.0 [59.4 to 69.0]	(*P*=0.286)
Pulse oximetry (%)	98.5 [98.1 to 99.0]	98.5 [97.9 to 99.0]	(*P*=0.834)
LOS (days)	5 [2.0 to 12.0]	5 [1.8 to 11.5]	(*P*=0.988)
Type of surgery			
colorectal	2 (10.0)	1 (5.0)	
endocrine	2 (10.0)	2 (10.0)	
ear nose & throat	0 (0.0)	1 (5.0)	
hepatobiliary	6 (30.0)	9 (45.0)	
spinal surgery	1 (5.0)	1 (5.0)	
orthopedic	2 (10.0)	1 (5.0)	
thoracic	5 (25.0)	1 (5.0)	
urology	2 (10.0)	3 (15.0)	
vascular	0 (0.0)	1 (5.0)	

Data reported as number (%) or median [inter-quartile range], except for age, which is reported as mean [range]

ASA: American Society of Anesthesiologists

BMI: body mass index

COPD: chronic obstructive pulmonary disease

LOS: length of hospital stay

Other co-morbidities include any of the following, ischaemic heart disease, atrial fibrillation, hypertension, history of cerebral vascular disease, and chronic kidney impairment

Spinal surgery includes non-intracranial procedures

Thoracic surgery includes procedures not requiring one lung ventilation, e.g. mediastinoscopy with nodal dissection

TMH: targeted mild hypercapnia, TN: targeted normocapnia

Both groups were similar in terms of gender, age, weight, body mass index, ASA physical status, and type of surgery performed. In terms of co-morbidities, both groups were similar, except for the presence of chronic obstructive pulmonary disease. There was 100%

compliance to the designated $PaCO_2$ intra-operative targets. The median [inter-quartile range, IQR] $PaCO_2$ in the TMH group and TN groups were 51.5 mmHg [46.9 to 60.9] and 34.8 mmHg [32.8 to 38.1], respectively (P<0.001). With regards to surgical characteristics, the duration of surgery was longer in the TMN group, with a median [IQR] duration of 219 minutes [124 to 304] versus 144 minutes [108 to 218] in the TN group, although this was not significant at the 5% level (P=0.121). PaO_2 was similar between the two groups: 156.8 mmHg [146.3 to 217.2] in the TMH group and 142.5 mmHg [122.5 to 199.1] in the TN group (P=0.380). Oxygen saturation was similar: 98.5% in the TMH group [98.1 to 99.0] and 98.5% in the TN group [97.9 to 99.0] (P=0.834). Both groups also had similar mean arterial pressure (MAP) intra-operatively (P=0.307), similar total Hb (130.50 vs. 122.25 g L^{-1}; P=0.132), and similar total dose of intra-operative opioid received, 21.67 mg in the TMH group [13.75 to 32.50] and 16.67 mg in the TN group [10.00 to 22.50] (P=0.22). In terms of intra-operative positioning of patients, one patient from each group was positioned in steep reverse Trendelenburg with minimal tilt. All other patients were positioned in the supine position with a neutral head position.

Primary endpoint

On the left hemisphere, the median [IQR] baseline oximetry was 68.7% [63.9 to 72.2] in the TMH group vs. 63.4% [57.3 to 69.6] in the TN group (P=0.233). On the right hemisphere, the median [IQR] baseline oximetry was 67.9% [64.6 to 70.3] in the TMH group vs. 64.0% [59.4 to 69.9] in the TN group (P=0.286). On both sides, the $\%\Delta rSO_2$ was greater in the TMH group than the TN group throughout the duration of surgery (**Figure 2**). The mean (standard deviation, SD) percentage changes in rSO_2 from the baseline to the conclusion of the surgery in the TMH group were +8.56% (18.90%) on the left and +13.86% (18.17%) on the right; and in TN the group, they were -6.18% (17.24%) on the left and -5.48% (18.94%) on the right. The resulting treatment effects were 19% (95% CI [9.2 to 28.8]; P<0.001) on the left and 19% (95% CI [10.9 to 27.0]; P<0.001) on the right (**Table 2**).

Table 2. Percentage change in cerebral oximetry (%ΔrSO_2) from baseline

Time from start of surgery (mins)		15	30	45	60	75	90	105	120
Left	**TMH**	0.8 (12.9) {15}	5.8 (12.3) {15}	9.0 (15.9) {15}	7.0 (14.6) {15}	8.5 (15.4) {14}	7.3 (14.7) {13}	7.7 (17.4) {13}	8.1 (14.8) {13}
	TN	4.7 (10.5) {18}	3.2 (15.4) {18}	-1.9 (14.1) {17}	-5.6 (12.7) {17}	-5.3 (15.2) {17}	-5.5 (15.8) {17}	-6.0 (15.2) {17}	-3.6 (15.8) {14}
Right	**TMH**	6.0 (12.9) {17}	9.8 (13.2) {17}	10.4 (18.1) {17}	11.1 (17.4) {17}	13.0 (16.4) {16}	15.6 (17.3) {15}	14.4 (17.5) {14}	14.1 (13.6) {14}
	TN	5.2 (12.6) {20}	3.9 (11.7) {20}	-3.3 (13.2) {19}	-5.2 (12.1) {19}	-5.4 (12.3) {19}	-4.7 (14.1) {19}	-3.8 (13.7) {18}	-1.3 (13.9) {15}

Time from start of surgery (mins)		120	240	360	480	600	720	Mean % difference from start to completion of surgery	95% confidence interval	*P* value (treatment)
Left	**TMH**	8.1 (14.8) {13}	6.8 (20.6) {7}	6.4 (32.5) {4}	-8.6 (21.1) {3}	-6.1 (14.1) {3}	6.9 {1}	19.0	9.2 -28.8	<0.001
	TN	-3.6 (15.8) {14}	-10.4 (39.5) {5}	-43.4 (34.9) {2}	-27.8 {1}					
Right	**TMH**	14.1 (13.6) {14}	18.4 (23.5) {8}	16.8 (36.8) {4}	1.5 (14.9) {3}	3.0 (8.7) {3}	2.0 {1}	19.0	10.9- 27.0	<0.001
	TN	-1.3 (13.9) {15}	-5.3 (32.6) {5}	-35.4 (26.9) {2}	-37.8 {1}					

Data reported as mean (standard deviation) {sample size}, and presented every 15 minutes for the first 2 hours and every 2 hours afterwards

TMH: targeted mild hypercapnia, TN: targeted normocapnia

On the longitudinal time-by-treatment interaction analysis, the difference in $\%\Delta rSO_2$ on both left and right hemispheres between the two groups diverged with time, with the intervention group exhibiting a smaller percentage decrease over time compared to the control group (time-by-treatment interaction $P<0.001$ for both left and right hemispheres). We obtained very similar results on the robustness analyses when the above model was adjusted for age, baseline oximetry, and pre-operative Hb levels, as well as when the percentage of total duration of surgery, instead of minutes from the start of surgery, were included.

Secondary outcomes

Postoperative delirium was statistically significantly less common in the TMH group. Postoperative delirium was present in 0 out of 20 (0%) participants in the TMH group and 6 out of 20 (30%) participants in the TN group (risk difference 0.3, 95% CI [0.1 to 0.5], Fisher's exact $P=0.02$) (**Table 3).**

Table 3. Postoperative delirium and opioid doses

	TMH group (*n*=20)	**TN group (*n*=20)**	
Pre-medication			
Number of patients	0 (0.0)	2 (10.0)	
Mean midazolam dose (mg)	0	1.75	
Intra-operative opioid			
Total dose (mg)	21.67 [13.75 to 32.50]	16.67 [10.00 to 22.50]	(P=0.22)
Received i.v. morphine	2 (10.0)	1 (5.0)	
Received i.v. fentanyl	10 (50.0)	14 (70.0)	
Received i.v. oxycodone	9 (45.0)	7 (35.0)	
Received i.v. tramadol	4 (20.0)	0 (0.0)	
Received i.v. clonidine	0 (0.0)	2 (10.0)	
Intrathecal morphine			
Number of patients	5	2	
Mean dose (mcg)	220	350	

Epidural analgesia			
Number of patients	0	0	
Blood glucose level			
Glucose (mmol L-1)	7.1 [7.0 to 7.1]	6.6 [6.4 to 6.7]	(*P*=0.33)
Pre-operative CAM	0 [0.0 to 0.0]	0 [0.0 to 0.0]	
Postoperative CAM	0 [0.0 to 0.0]	1.5 [0.0 to 3.0]	
Presence of postoperative delirium	0 (0.0)	6 (30.0)	(*P*=0.02)

Data reported as median [inter-quartile range] or number (%)

CAM: Confusion Assessment Method

Note some patients received 2 or more different intra-operative opioids

Total dose of intra-operative opioid normalised to i.v. morphine equivalent

TMH: targeted mild hypercapnia, TN: targeted normocapnia

In terms of acid–base variables, median intra-operative pH was statistically significantly lower (7.31 vs. 7.46; *P*<0.001), and intra-operative bicarbonate was statistically significantly higher (25.00 vs. 24.00 mEq L^{-1}; *P*=0.020) in the TMH. No statistically significant differences in base excess (-1.00 vs. 1.00 mmol L^{-1}; *P*=0.069) and potassium (3.98 vs. 4.03 mEq L^{-1}; *P*=0.759) were observed intra-operatively. Length of hospital stay was also similar between the two groups (5 vs. 5 days; *P*=0.988). These results are summarised in **Table 4.**

Table 4. Arterial blood gas values and the corresponding $EtCO_2$

	TMH group (*n*=20)	**TN group (*n*=20)**	*P*-value
pH	7.31 [7.27 to 7.33]	7.46 [7.43 to 7.47]	<0.001
PaO_2 (mmHg)	156.8 [146.3 to 217.2]	142.5 [122.5 to 199.1]	0.380
$PaCO_2$ (mmHg)	51.50 [46.88 to 60.88]	34.75 [32.75 to 38.12]	<0.001
$EtCO_2$ (mmHg)	46.40 [39.80 to 50.20]	30.40 [28.50 to 32.00]	<0.001
Bicarbonate (mEq L^{-1})	25.00 [24.00 to 27.75]	24.00 [22.00 to 24.62]	0.020
Base excess (mmol L^{-1})	-1.00 [-2.50 to 0.25]	1.00 [-0.88 to 2.00]	0.069
Potassium (mEq L^{-1})	3.98 [3.73 to 4.38]	4.03 [3.58 to 4.31]	0.759
Total Hb (g L^{-1})	130.50 [118.12 to 140.62]	122.25 [106.88 to 131.25]	0.132

Data reported as median [inter-quartile range] or number (%)

$EtCO_2$: end tidal carbon dioxide

Hb: haemoglobin concentration

$PaCO_2$: partial pressure of carbon dioxide in arterial blood

PaO_2: partial pressure of oxygen in arterial blood

TMH: targeted mild hypercapnia, TN: targeted normocapnia

Discussion

We conducted a prospective, single centre, single blinded, randomised controlled trial evaluating the effects of TMH and TN on rSO_2 in patients undergoing major surgery. TMH led to a stable increase in both left and right NIRS-derived rSO_2 from the baseline values, while TN led to a decrease in rSO_2. This effect was sustained throughout surgery and became more pronounced with the passage of time. Furthermore, TMH was associated with a lower incidence of postoperative delirium within 24 hours after surgery.

Whilst the relationship between elevated $PaCO_2$ and cerebral blood flow (CBF) is well described,[26-29] the associations between hypercapnia and higher rSO_2 are poorly understood. Numerous factors, for instance, cardiac output, haemoglobin affinity for oxygen, cerebral autoregulation, and the ratio of cerebral arterial to venous blood volume, affect rSO_2 in the setting of hypercapnia, but changes in $PaCO_2$ and CBF, in turn, have a direct influence on these factors.[30] To complicate the subject further, the duration of effect of hypercapnia on rSO_2 is unknown. In our study, confounding variables, such as MAP, PaO_2, Hb, and intra-operative position, were similar between the TMH and TN groups. However, pH, which directly affects the haemoglobin affinity for oxygen via the Bohr Effect, was significantly different. Since we cannot measure the ratio of arterial to venous blood volume, it would be impetuous to comment on the mechanism behind the observed higher rSO_2 values in TMH. Clinically, similar observations have been reported previously. Eastwood *et al.* found that mild hypercapnia resulted in higher rSO_2 values in post-cardiac arrest patients when rSO_2 values at the end of the normocapnic period and the end of the hypercapnic period were compared.[31] When Akca *et al.* delivered mild hypercapnia intra-operatively to investigate tissue oxygenation and its relationship with wound infection risk after surgery, cerebral oxygen saturation was found to be higher in the mild hypercapnic group.[15] Similarly, rSO_2 remained higher in hypercapnic patients throughout shoulder surgery, and less cerebral desaturation events were observed by Murphy *et al*.[32] Our study is one of the few randomised controlled trials that investigated rSO_2 change over time. We found that the sustained difference in rSO_2 over time was a combined effect of a stable increase in rSO_2 from the baseline in the TMH group and a stable decrease in

rSO_2 from the baseline in the TN group. In the literature, the association between normocapnia and reduced CBF and lower levels of rSO_2 were reported briefly.[33] Normocapnia was also found to be superior in preserving cerebral autoregulation.[34] However, the exact mechanism and associations between normocapnia and variations in rSO_2 values are not entirely clear. Whilst theoretical absolute and relative saturation thresholds requiring prompt interventions have been proposed,[14] these thresholds have not been validated and there is a lack of consensus on the indication and timing of interventions. In our study, the reduction in rSO_2 from the baseline was small in the majority of patients in the TN group, and the attending anaesthetists had no rSO_2 target to titrate to. Comparing the TMH and TN groups, the sustained difference in percentage change in rSO_2 over time is a novel finding.

Interestingly, the incidence of postoperative delirium after surgery was lower in the TMH group, while LOS remained similar between the groups. Patients who suffered from postoperative delirium were all in the TN group, but they were also older (median [IQR] age = 72 [59.5 to 77]) and had higher ASA scores (ASA scores of 3, 2, 1, 4 and 4). Their baseline medical co-morbidities and duration of surgery (median [IQR] duration of surgery = 171 minutes [83.5 to 254.5]) were similar to other study participants. There has been conflicting evidence in the literature regarding the relationship between rSO_2 and LOS or postoperative cognitive performance. Cognitive outcomes were similar in groups with or without NIRS-based rSO_2 optimisation in a recent randomised controlled trial.[14,35] On the other hand, Murkin *et al.* found that monitoring and reacting to cerebral desaturation during coronary artery bypass surgery was associated with clinical benefits.[13] Patients with shorter LOS (<10 days) had a higher mean rSO_2. Intra-operative NIRS rSO_2 monitoring led to a significant reduction in postoperative cognitive disturbance, confirmed by Trafidlo *et al.*[36] Casati *et al.* also reported that higher rSO_2 led to shorter LOS and improved Mini-Mental State Examination scores in elderly patients undergoing major abdominal surgery,[37] and Schoen *et al.* found that low pre-operative rSO_2 was associated with a higher incidence of postoperative delirium. Among patients who started at a normal rSO_2 level, those who developed delirium had a larger intra-operative drop in rSO_2.[38] Our findings were consistent with those of Schoen *et al.*; however, they need to be interpreted with

caution, as the ASA scores and age were slightly higher in the TN group, and our study was not designed to quantitatively investigate postoperative cognitive performance in hypercapnia.

Implications of our findings demonstrate that TMH can be delivered reliably during major surgery, and its effects on rSO_2 can be monitored with NIRS in most patients. Its delivery is reliably associated with increased levels of rSO_2, and the relatively higher rSO_2 is sustained over the duration of surgery, an observation that has not been reported in the literature. Furthermore, TMH may reduce the incidence of the development of immediate postoperative delirium. A clinical concern of mild hypercapnia is hypercapnic-induced acidosis and the subsequent development of hyperkalaemia. Whilst a linear correlation between arterial carbon dioxide and plasma pH is well reported,[39] the relationship between acute hypercapnia, respiratory acidosis, and plasma potassium is also poorly understood.[40] In the present study, we found no association between hypercapnia and serum potassium concentration, a finding also supported by others.[41] We did not observe any other deleterious or adverse effects from hypercapnic-induced acidosis such as cardiac arrhythmias in our study. Interestingly, whilst our study was not designed to measure differences in analgesia and partial pressure of oxygen in arterial blood, we observed a 10% higher median PaO_2 level in the TMH group and found that the median intra-operative analgesia requirements were also approximately 30% higher. Both arterial oxygen levels and pain have been reported to influence tissue oxygenation,[42] which was not directly measured in our study. The effect of pain on cerebral oxygenation is unclear and has not been borne out in clinical studies;[43] further studies exploring this association are needed. Finally, we have shown that NIRS-based cerebral oximetry is a non-invasive and practical method of measuring rSO_2, easily incorporated into the existing collection of routine monitoring variables, findings that are in agreement with other research groups.[20,44-46]

Our study has multiple strengths. Our findings have high internal validity because the study was a randomised controlled trial with concealed allocation and blinded assessment, minimising selection and ascertainment bias. The rSO_2 data were exported

directly to RStudio, and ABG data were analysed by the ABL Blood Gas Analyzer, rendering sampling error from data entry unlikely, thereby increasing the robustness of our findings. Sampling of continuous oximetry data resulted in a stream of oximetry data throughout the monitoring periods, maximising the details of our assessment. Although the duration of surgery was different for individual patients, oximetry data were not normalised to another time scale, enabling a fair comparison of data across the study groups. NIRS-derived rSO_2 has been criticised for potential extra-cranial contamination that would confound true rSO_2.[47] However, there is sufficient evidence to support the accuracy of NIRS-derived rSO_2,[20,44] particularly in the case of hypercapnia, where extra-cranial signal interference has been shown to be insignificant, justifying its reliability.[48] Moreover, as the technology was the same in both groups, any inaccuracy should not have been a source of bias.

Our study also has a number of limitations. The attending anaesthetists were not blinded due to the nature of the intervention. Nevertheless, bias was mitigated by the fact that measurements were taken directly from the cerebral oximetry machine, and the assessment of delirium was conducted by an independent researcher blinded to the intervention. The external validity of our findings was restricted by the small sample size from one single centre. The sample size calculation was based on the assumption that there were no changes in rSO_2 values from the baseline in the TN group. The observed negative change can therefore impact the calculation. The strong nature of interaction between treatment and time for rSO_2 outcome should be treated with caution due to the potential minor departures of the data from the linear trend. Our findings were not applicable to patients undergoing emergency surgery, intracranial surgery, or surgery requiring one lung ventilation. The cerebral oximetry probes were only attached to the forehead, measuring rSO_2 within the frontal cortex region, which carries the assumption that rSO_2 was homogenous across every area of the brain. Quantification of device failure rate, despite being a critical consideration, cannot be described by our study design.

We did not measure cardiac output, stroke volume, and systemic vascular resistance. Therefore, the effects on changes in intrathoracic pressure on cardiac output are unknown. Changes in intrathoracic pressure may have adversely impacted cardiac output, which may in turn have affected the $EtCO_2$. However, given that the positive end-expiratory pressure was held constant in both groups, and the changes in lung tidal volumes were relatively small, the impact of intrathoracic pressure on cardiac output is likely to be small. Finally, our findings of a greater incidence of early postoperative delirium in the TN group need to be interpreted with caution, as confounders of postoperative delirium were not controlled, our study was not powered to investigate postoperative delirium, and mental state was only assessed by CAM, once pre-operatively and once postoperatively. Accordingly, our findings for delirium should be viewed as hypothesis generating. Nevertheless, if we were to consider that our effect size observed (i.e. risk difference of 0.3) could be due to chance and a smaller effect would be observed in a larger study, an appropriate powered randomised controlled trial for this outcome would be very feasible. If the proportion of patients with delirium in the intervention group is 10%, to achieve 90% power, the required sample size for each group would be ninety-two.

Conclusion

In summary, TMH was associated with a stable increase in rSO_2 from the baseline, while TN was associated with a decrease in rSO_2 from the baseline in both hemispheres. This effect was sustained and became more pronounced with the passage of time intra-operatively.

Author Contributions

Clarence Wong: This author contributed to data collection, data analysis, and manuscript write-up.

Leonid Churilov: This author contributed to data analysis and manuscript write-up.

Dean Cowie: This author contributed to patient recruitment, data collection, and preparation of manuscript.

Chong Tan: This author contributed to patient recruitment and preparation of manuscript.

Raymond Hu: This author contributed to patient recruitment and preparation of manuscript.

David Tremewen: This author contributed to patient recruitment and preparation of manuscript.

Brett Pearce: This author contributed to patient recruitment and preparation of manuscript.

Param Pillai: This author contributed to data collection and preparation of manuscript.

Dharshi Karalipillai: This author contributed to data collection and preparation of manuscript.

Rinaldo Bellomo: This author contributed to study design and preparation of manuscript.

Laurence Weinberg: This author designed the study, contributed to patient recruitment, data collection, data analysis, and preparation of manuscript.

References

1. Brosnan RJ, Steffey EP, LeCouteur RA, Imai A, Farver TB, Kortz GD. Effects of ventilation and isoflurane end-tidal concentration on intracranial and cerebral perfusion pressures in horses. *American journal of veterinary research.* 2003;64(1):21-25.
2. Faraci FM, Breese KR, Heistad DD. Cerebral vasodilation during hypercapnia. Role of glibenclamide-sensitive potassium channels and nitric oxide. *Stroke.* 1994;25(8):1679-1683.
3. Hino JK, Short BL, Rais-Bahrami K, Seale WR. Cerebral blood flow and metabolism during and after prolonged hypercapnia in newborn lambs. *Critical care medicine.* 2000;28(10):3505-3510.
4. Nakahata MDK, Kinoshita MDPDH, Hirano MDY, Kimoto MDY, Iranami MDH, Hatano MDPDY. Mild Hypercapnia Induces Vasodilation via Adenosine Triphosphate-sensitive K+Channels in Parenchymal Microvessels of the Rat Cerebral Cortex. *Anesthesiology.* 2003;99(6):1333-1339.
5. Kaku DA, Giffard RG, Choi DW. Neuroprotective effects of glutamate antagonists and extracellular acidity. *Science (New York, NY).* 1993;260(5113):1516-1518.
6. Vannucci RC, Brucklacher RM, Vannucci SJ. Effect of Carbon Dioxide on Cerebral Metabolism during Hypoxia-Ischemia in the Immature Rat. *Pediatr Res.* 1997;42(1):24-29.
7. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br J Anaesth.* 2009;103 Suppl 1:i3-13.
8. Elizabeth A, Frost M. Cerebral oximetry: emerging applications for an established technology. *Anesthesiol News.* 2012;38:10.
9. Steppan J, Hogue CW, Jr. Cerebral and tissue oximetry. *Best Pract Res Clin Anaesthesiol.* 2014;28(4):429-439.
10. Ahn A, Yang J, Inigo-Santiago L, Parnia S. A feasibility study of cerebral oximetry monitoring during the post-resuscitation period in comatose patients following cardiac arrest. *Resuscitation.* 2014;85(4):522-526.

11. Storm C, Leithner C, Krannich A, et al. Regional cerebral oxygen saturation after cardiac arrest in 60 patients--a prospective outcome study. *Resuscitation.* 2014;85(8):1037-1041.
12. Ito N, Nishiyama K, Callaway CW, et al. Noninvasive regional cerebral oxygen saturation for neurological prognostication of patients with out-of-hospital cardiac arrest: a prospective multicenter observational study. *Resuscitation.* 2014;85(6):778-784.
13. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesthesia and analgesia.* 2007;104(1):51-58.
14. Deschamps A, Hall R, Grocott H, et al. Cerebral Oximetry Monitoring to Maintain Normal Cerebral Oxygen Saturation during High-risk Cardiac Surgery: A Randomized Controlled Feasibility Trial. *Anesthesiology.* 2016;124(4):826-836.
15. Akca O, Liem E, Suleman MI, Doufas AG, Galandiuk S, Sessler DI. Effect of intra-operative end-tidal carbon dioxide partial pressure on tissue oxygenation. *Anaesthesia.* 2003;58(6):536-542.
16. Robinson TN, Eiseman B. Postoperative delirium in the elderly: diagnosis and management. *Clinical Interventions in Aging.* 2008;3(2):351-355.
17. Liu LL, Leung JM. Predicting adverse postoperative outcomes in patients aged 80 years or older. *Journal of the American Geriatrics Society.* 2000;48(4):405-412.
18. Inouye SK. Delirium in older persons. *The New England journal of medicine.* 2006;354(11):1157-1165.
19. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340.
20. Redford D, Paidy S, Kashif F. Absolute and trend accuracy of a new regional oximeter in healthy volunteers during controlled hypoxia. *Anesth Analg.* 2014;119(6):1315-1319.
21. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Annals of internal medicine.* 1990;113(12):941-948.

22. Sharon K, Inouye MD, MPH. Confusion Assessment Method: Training Manual and Coding Guide, Copyright 2003.
23. National Blood Authority. Blood Management Guidelines: Module 2 Perioperative. 2012; http://www.nba.gov.au/guidelines/module2/po-mod2.pdf2.
24. Vretzakis G, Georgopoulou S, Stamoulis K, et al. Cerebral oximetry in cardiac anesthesia. *Journal of thoracic disease.* 2014;6 Suppl 1:S60-69.
25. Lang TA, Altman DG. Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines. *International journal of nursing studies.* 2015;52(1):5-9.
26. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. *Critical care (London, England).* 2010;14(2):220.
27. Yokoyama I, Inoue Y, Kinoshita T, Itoh H, Kanno I, Iida H. Heart and brain circulation and CO2 in healthy men. *Acta physiologica (Oxford, England).* 2008;193(3):303-308.
28. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. *J Physiol.* 2011;589(Pt 12):3039-3048.
29. Giardino ND, Friedman SD, Dager SR. Anxiety, respiration, and cerebral blood flow: implications for functional brain imaging. *Compr Psychiatry.* 2007;48(2):103-112.
30. Vranken NPA, Weerwind PW, Sutedja NA, Severdija EE, Barenbrug PJC, Maessen JG. Cerebral Oximetry and Autoregulation during Cardiopulmonary Bypass: A Review. *The journal of extra-corporeal technology.* 2017;49(3):182-191.
31. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early cardiac arrest survivors: The impact of hypercapnia. *Resuscitation.* 2016;102:11-16.
32. Murphy GS, Szokol JW, Avram MJ, et al. Effect of ventilation on cerebral oxygenation in patients undergoing surgery in the beach chair position: a randomized controlled trial. *British journal of anaesthesia.* 2014;113(4):618-627.

33. Brian Johnny E, MD. Carbon Dioxide and the Cerebral Circulation *Anesthesiology: The Journal of the American Society of Anesthesiologists.* 1998;88(5):1365-1386.

34. Severdija EE, Vranken NP, Simons AP, et al. Hemodilution Combined With Hypercapnia Impairs Cerebral Autoregulation During Normothermic Cardiopulmonary Bypass. *Journal of cardiothoracic and vascular anesthesia.* 2015;29(5):1194-1199.

35. Rogers CA, Stoica S, Ellis L, et al. Randomized trial of near-infrared spectroscopy for personalized optimization of cerebral tissue oxygenation during cardiac surgery. *Br J Anaesth.* 2017;119(3):384-393.

36. Trafidlo T, Gaszynski T, Gaszynski W, Nowakowska-Domagala K. Intraoperative monitoring of cerebral NIRS oximetry leads to better postoperative cognitive performance: a pilot study. *International journal of surgery (London, England).* 2015;16(Pt A):23-30.

37. Casati A, Fanelli G, Pietropaoli P, et al. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth Analg.* 2005;101(3):740-747, table of contents.

38. Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger K-U. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. *Critical Care.* 2011;15(5):R218-R218.

39. Finsterer U, Luhr HG, Wirth AE. Effects of acute hypercapnia and hypocapnia on plasma and red cell potassium, blood lactate and base excess in man during anesthesia. *Acta anaesthesiologica Scandinavica.* 1978;22(4):353-366.

40. Adrogue HJ, Madias NE. Changes in plasma potassium concentration during acute acid-base disturbances. *The American journal of medicine.* 1981;71(3):456-467.

41. Natalini G, Seramondi V, Fassini P, et al. Acute respiratory acidosis does not increase plasma potassium in normokalaemic anaesthetized patients. A controlled randomized trial. *European Journal of Anaesthesiology.* 2006;18(6):394-400.

42. Akca O. Pain and Tissue Oxygenation. *Critical care medicine.* 2015;43:e462-463.
43. Hoiseth LO, Hisdal J, Hoff IE, Hagen OA, Landsverk SA, Kirkeboen KA. Tissue oxygen saturation and finger perfusion index in central hypovolemia: influence of pain. *Crit Care Med.* 2015;43(4):747-756.
44. MacLeod DB, Ikeda K, Vacchiano C, Lobbestael A, Wahr JA, Shaw AD. Development and validation of a cerebral oximeter capable of absolute accuracy. *Journal of cardiothoracic and vascular anesthesia.* 2012;26(6):1007-1014.
45. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. *Anesthesiology.* 2000;93(4):947-953.
46. Brady K, Joshi B, Zweifel C, et al. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke.* 2010;41(9):1951-1956.
47. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology.* 2012;116(4):834-840.
48. Akça O, Sessler DI, DeLong D, Keijner R, Ganzel B, Doufas AG. Tissue Oxygenation Response to Mild Hypercapnia during Cardiopulmonary Bypass with Constant Pump Output. *British journal of anaesthesia.* 2006;96(6):708-714.

Figures

Figure 1. CONSORT flow diagram
(Please refer to the attached diagram)

Figure 2. Percentage change in cerebral oximetry from baseline (%ΔrSO_2) over time
(Please refer to the attached diagram)

Figure Captions

Figure 1:

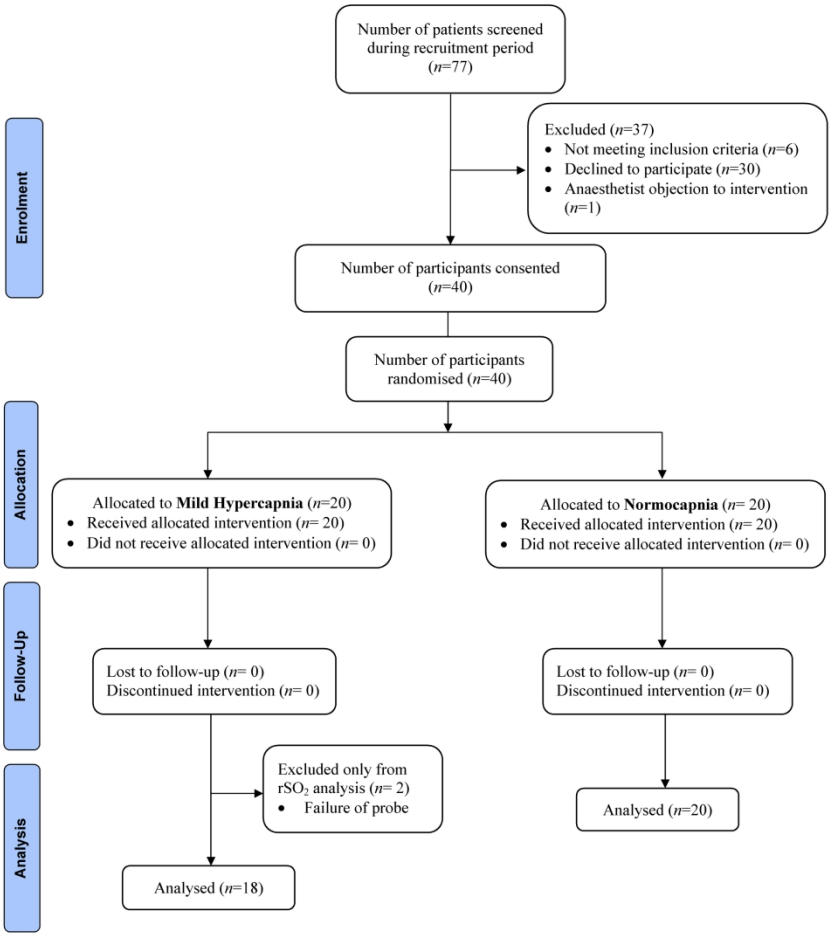
The progress of all participants through the trial displayed by the Consolidated Standards Of Reporting Trials (CONSORT) flow diagram.

Figure 2:

The solid lines represent the mean percentage change; while the shaded areas represent the standard deviation. The targeted mild hypercapnia (TMH) group is represented by the red line and the red area; while the targeted normocapnia (TN) group is represented by the blue line and the blue area.

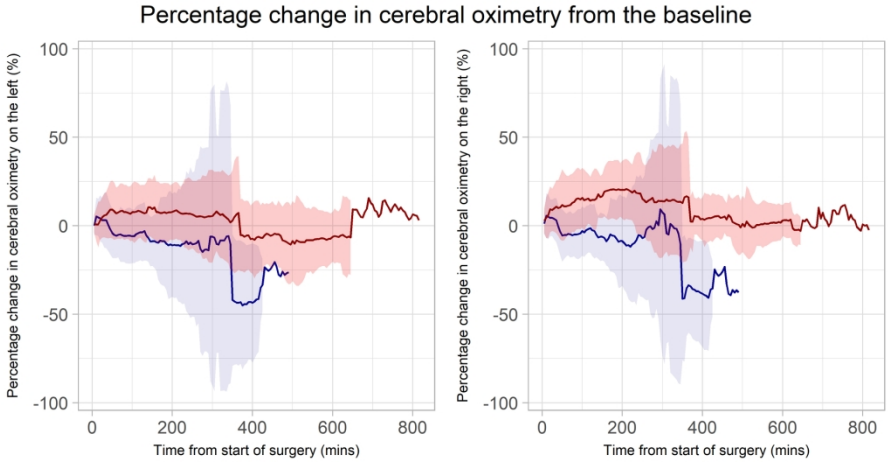
Left: percentage change of regional cerebral oxygen saturation from the baseline on the left hemisphere

Right: percentage change of regional cerebral oxygen saturation from the baseline on the right hemisphere



The progress of all participants through the trial displayed by the Consolidated Standards Of Reporting Trials (CONSORT) flow diagram.

203x287mm (300 x 300 DPI)



The solid lines represent the mean percentage change; while the shaded areas represent the standard deviation. The targeted mild hypercapnia (TMH) group is represented by the red line and the red area; while the targeted normocapnia (TN) group is represented by the blue line and the blue area.
Left: percentage change of regional cerebral oxygen saturation from the baseline on the left hemisphere
Right: percentage change of regional cerebral oxygen saturation from the baseline on the right hemisphere

177x93mm (300 x 300 DPI)

Supplementary File 1

```
#-----------------------------------------------------------------------------------------------------------
--
# TITLE: Create oximetry database from raw data files
# Author: Clarence Wong
# Last updated: 2/7/2017
# RStudio v. 1.0.136
#-----------------------------------------------------------------------------------------------------------
--

library(readr)
require(lubridate)
require(TTR)
require(xts)
require(zoo)
library(reshape2)

#-----------------------------------------------------------------------------------------------------------
--
# Read all data files and save as R object
#-----------------------------------------------------------------------------------------------------------
--

master<-0
for (i in 1:8)
{
  file <-
read.csv(paste("D:/SS/R_data/FINAL_oximetry_data/",as.character(i),".csv",sep=""))
  master <- rbind(master,file)
}
master$date_time <- paste(master$Date, master$Time..GMT.)
master$date_time <- mdy_hms(master$date_time)
converted_master <- master[,c(58,3:57)]

save(converted_master,file = "converted_master.RData")

database_times <- read_csv("D:/SS/R_data/database_times.csv")
date_vector <- database_times[,c(1,5,6,7,11,12)]

date_vector$start_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Monitoring Start`))
date_vector$end_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Monitoring End`))
```

```
date_vector$surg_start_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Start Time`))
date_vector$surg_end_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Finish Time`))

converted_date_vector <- date_vector[,c(1,7,8,9,10)]

save(converted_date_vector,file = "converted_date_vector.RData")

rm(master,date_vector,file)

#-----------------------------------------------------------------------------------------------------
--
# 1.  Convert data types and locate monitoring periods
# 2.  Identify oximettry values at various time points
# 3.  Compute percentage change from baseline
# 4.  Identify and locate problematic data
#-----------------------------------------------------------------------------------------------------
--

minutes_taken_as_baseline <- 2.5
minutes_interval <- 5

secs_taken_as_baseline <- minutes_taken_as_baseline*60
secs_interval <- minutes_interval*60

load("converted_master.RData")
load("converted_date_vector.RData")
print("data loaded. check data version")

oximetry_L <-
as.numeric(levels(converted_master$RSO2_A1)[converted_master$RSO2_A1])
oximetry_R <-
as.numeric(levels(converted_master$RSO2_A2)[converted_master$RSO2_A2])
PSI <- as.numeric(levels(converted_master$PSI)[converted_master$PSI])

# monitoring duration
duration_mins <-
difftime(converted_date_vector$end_date_time,converted_date_vector$start_date_time,uni
ts = "mins")
duration_secs <-
difftime(converted_date_vector$end_date_time,converted_date_vector$start_date_time,uni
ts = "secs")

locate_start = seq(-1,-1,length.out = dim(converted_date_vector)[1])
```

```
for (i in 1:dim(converted_date_vector)[1]){
if(length(which(converted_date_vector$start_date_time[i]==converted_master$date_time))
==1)
  {
    locate_start[i] <-
which(converted_date_vector$start_date_time[i]==converted_master$date_time)
  }
}

# create final_oximetry data frame
final_oximetry <- data.frame()
baseline_L_mu<-baseline_L_std<-baseline_L_N<-baseline_R_mu<-baseline_R_std<-
baseline_R_N<-rep(9999,dim(converted_date_vector)[1])
num_time_pts <- rep(1,40)

for(j in 1:dim(converted_date_vector)[1])
{
  # for each patient
  if(locate_start[j]==-1)
  {
    p_id <- j
    time_id<-minute_from_baseline<-percentage_total_monitoring_period<-L_delta<-
L_mu<-L_sig<-L_N<-R_delta<-R_mu<-R_sig<-R_N<-PSI_mu<-9999

  } else{

    locate_baseline <- locate_start[j]+secs_taken_as_baseline/2
    locate_times <- seq(0,0)
    num_measurements <- (as.numeric(duration_secs)[j]-
secs_taken_as_baseline)%/%secs_interval +1
    num_time_pts[j] <- num_measurements
    locate_times[1] <- locate_baseline
    locate_times[2] <- locate_times[1] + secs_interval/2
    locate_times[2:num_measurements]<-
seq(locate_times[2],locate_start[j]+as.numeric(duration_secs[j])/2,by=secs_interval/2)
    locate_times[num_measurements+1]<-locate_start[j]+as.numeric(duration_secs[j])/2

    baseline_L_mu[j] <- mean(oximetry_L[locate_start[j]:(locate_baseline-1)],na.rm =
TRUE)
    baseline_L_std[j] <- sd(oximetry_L[locate_start[j]:(locate_baseline-1)],na.rm = TRUE)
    baseline_L_N[j] <- length(oximetry_L[locate_start[j]:(locate_baseline-1)])-
sum(is.na(oximetry_L[locate_start[j]:(locate_baseline-1)]))
```

```
   baseline_R_mu[j] <- mean(oximetry_R[locate_start[j]:(locate_baseline-1)],na.rm =
TRUE)
   baseline_R_std[j] <- sd(oximetry_R[locate_start[j]:(locate_baseline-1)],na.rm = TRUE)
   baseline_R_N[j] <- length(oximetry_R[locate_start[j]:(locate_baseline-1)])-
sum(is.na(oximetry_R[locate_start[j]:(locate_baseline-1)]))

   L_delta <- L_mu <- L_sig <- L_N <- R_delta <- R_mu <- R_sig <- R_N <- PSI_mu <-
seq(0,0)

   for (k in 1:num_measurements)
   {
    L_mu[k] <- mean(oximetry_L[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    L_sig[k] <- sd(oximetry_L[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    L_N[k] <- length(oximetry_L[locate_times[k]:(locate_times[k+1]-1)])-
sum(is.na(oximetry_L[locate_times[k]:(locate_times[k+1]-1)]))

    R_mu[k] <- mean(oximetry_R[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    R_sig[k] <- sd(oximetry_R[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    R_N[k] <- length(oximetry_R[locate_times[k]:(locate_times[k+1]-1)])-
sum(is.na(oximetry_R[locate_times[k]:(locate_times[k+1]-1)]))

    PSI_mu[k] <- mean(PSI[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
   }

   L_delta <- (L_mu/baseline_L_mu[j] -1)*100
   R_delta <- (R_mu/baseline_R_mu[j] -1)*100

   time_id <- 1:num_measurements
   minute_from_baseline <- c(seq(minutes_interval,minutes_interval*(num_measurements-
1), by = minutes_interval),as.numeric(duration_mins[j]-minutes_taken_as_baseline))
   p_id <- rep(j,num_measurements)
   percentage_total_monitoring_period <-
((minute_from_baseline*60+secs_taken_as_baseline)/as.numeric(duration_secs[j]))*100

  }

  temp_df <-
data.frame(p_id,time_id,minute_from_baseline,percentage_total_monitoring_period,L_delt
a,L_mu,L_sig,L_N,R_delta,R_mu,R_sig,R_N,PSI_mu)
  final_oximetry <- rbind(final_oximetry,temp_df)
  rm(temp_df)

}

missing_L <- unique(final_oximetry$p_id[is.na(final_oximetry$L_delta)])
```

```
missing_R <- unique(final_oximetry$p_id[is.na(final_oximetry$R_delta)])
percentage_total_missing_L <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$L_delta)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$L_delta)])])
percentage_total_missing_R <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$R_delta)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$R_delta)])])
missing_data <- unique(final_oximetry$p_id[(final_oximetry$L_delta==9999)])
missing_data <- missing_data[!is.na(missing_data)]
missing_PSI <- unique(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])
percentage_total_missing_PSI <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])])

print("there are missing delta oximetry values in the following patients")
print(missing_L)
print(percentage_total_missing_L)

print(missing_R)
print(percentage_total_missing_R)

print(missing_data)

print("there are missing PSI values in the following patients")
print(missing_PSI)
print(percentage_total_missing_PSI)

other_data <-
data.frame(num_time_pts,baseline_L_mu,baseline_L_std,baseline_L_N,baseline_R_mu,
baseline_R_std,baseline_R_N)
other_data[is.na(other_data)]<-9999
save(other_data, file="other_data.RData")

final_oximetry[is.na(final_oximetry)]<-9999
save(final_oximetry,file = "final_oximetry.RData")


#-----------------------------------------------------------------------------------------------------------
--
# 1.  Convert baseline characteristic database from wide to long format
# 2.  Incorporating oximetry data in the database with time as a nested data in the hierarchy
# 3.  Create final database
#-----------------------------------------------------------------------------------------------------------
--
```

```
load("final_oximetry.RData")
load("other_data.RData")
print("check if final oximetry is latest")

baseline_results <- read.csv("D:/SS/R_data/FINAL_oximetry_data/all_baseline.csv",
sep=",", stringsAsFactors=FALSE)

baseline_results$baseline_L_mu <- other_data$baseline_L_mu
baseline_results$baseline_L_std <- other_data$baseline_L_std
baseline_results$baseline_L_N <- other_data$baseline_L_N
baseline_results$baseline_R_mu <- other_data$baseline_R_mu
baseline_results$baseline_R_std <- other_data$baseline_R_std
baseline_results$baseline_R_N <- other_data$baseline_R_N

baseline_results$P_id <- index(baseline_results)

baseline_results[baseline_results == "#N/A"]<-9999

#generate baseline_results with the same number of rows as final oximetry
baseline_results <- baseline_results[rep(seq_len((40)),num_time_pts),]


all_results <- cbind(baseline_results,final_oximetry)
if (sum(1*(all_results$P_id != all_results$p_id))==0)
{
  all_results <- all_results[,c(which(colnames(all_results)=="p_id"),1:109,112:122)]
}

save(all_results,file = "all_results.RData")

#UNCOMMENT TO WRITE CSV
#-------------------------------------------------
write.csv(all_results, file="all_results.csv")
```

Supplementary File 2

```
#-------------------------------------------------------------------------------------------------------
-------
# TITLE: Create baseline patient and surgical characteristics table, oximetry table, and
oximetry graphs
# Author: Clarence Wong
# Last updated: 2/7/2017
# RStudio v. 1.0.136
#-------------------------------------------------------------------------------------------------------
-------

library(readr)
require(lubridate)
require(TTR)
require(xts)
require(zoo)
require(tableone)
require(ggplot2)
library(grid)
require(gridExtra)
require(quantreg)

#-------------------------------------------------------------------------------------------------------
-------
# 1.  Create summary statistics for baseline characteristics
# 2.  Perform statistical analysis on secondary outcomes. e.g post-operative delirium
# 3.  Export tables in csv files
# Requires baseline characteristic and baseline oximetry data.
#-------------------------------------------------------------------------------------------------------
-------

baseline_db <- read.csv("D:/SS/R_data/baseline/all_baseline.csv", sep=",",
stringsAsFactors=TRUE)
load("other_data.RData")

other_data <- other_data[-c(1,2),]

baseline_db$baseline_L_mu <- other_data$baseline_L_mu
baseline_db$baseline_L_std <- other_data$baseline_L_std
baseline_db$baseline_L_N <- other_data$baseline_L_N
baseline_db$baseline_R_mu <- other_data$baseline_R_mu
baseline_db$baseline_R_std <- other_data$baseline_R_std
baseline_db$baseline_R_N <- other_data$baseline_R_N

baseline_db$P_id <- index(baseline_db)
```

```
baseline_db[baseline_db == "#N/A"]<-NA
baseline_db[baseline_db == 9999]<-NA
baseline_db$pCO2_2<-
as.numeric(levels(baseline_db$pCO2_2))[baseline_db$pCO2_2]
baseline_db$BMI<-as.numeric(levels(baseline_db$BMI))[baseline_db$BMI]
vars <-
c("Gender","Age","Weight","BMI","ASA","Diabetes","COPD","Maligancy","Other_C
omorbidities",

"Surgery_type","Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu")
factorVars <- c("ASA","Diabetes","COPD","Maligancy","Other_Comorbidities")
Tableone <- CreateTableOne(vars,"Group",baseline_db,factorVars)


baseline_db$LOS<-as.numeric(levels(baseline_db$LOS))[baseline_db$LOS]
baseline_db$pH_2<-as.numeric(levels(baseline_db$pH_2))[baseline_db$pH_2]
baseline_db$HCO3._2<-
as.numeric(levels(baseline_db$HCO3._2))[baseline_db$HCO3._2]
baseline_db$Base_excess_2<-
as.numeric(levels(baseline_db$Base_excess_2))[baseline_db$Base_excess_2]
baseline_db$Potassium_2<-
as.numeric(levels(baseline_db$Potassium_2))[baseline_db$Potassium_2]
baseline_db$Total_Hb_2<-
as.numeric(levels(baseline_db$Total_Hb_2))[baseline_db$Total_Hb_2]

baseline_db$pH<-apply(baseline_db[,c("pH_1","pH_2")],1,mean,na.rm=TRUE)
baseline_db$pCO2<-
apply(baseline_db[,c("pCO2_1","pCO2_2")],1,mean,na.rm=TRUE)
baseline_db$HCO3.<-
apply(baseline_db[,c("HCO3._1","HCO3._2")],1,mean,na.rm=TRUE)
baseline_db$Base_excess<-
apply(baseline_db[,c("Base_excess_1","Base_excess_2")],1,mean,na.rm=TRUE)
baseline_db$Potassium<-
apply(baseline_db[,c("Potassium_1","Potassium_2")],1,mean,na.rm=TRUE)
baseline_db$Total_Hb<-
apply(baseline_db[,c("Total_Hb_1","Total_Hb_2")],1,mean,na.rm=TRUE)

vars_2 <-
c("Surgery_type","Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu","L
OS",

"pH","pCO2","HCO3.","Base_excess","Potassium","Total_Hb","post_op_delirium")
factorVars_2 <- c("post_op_delirium")
Tabletwo <- CreateTableOne(vars_2,"Group",baseline_db,factorVars_2,argsExact =
"post_op_delirium")

print(Tabletwo,exact = "post_op_delirium",nonnormal =
c("Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu",
```

```
"LOS","pH","pCO2","HCO3.","Base_excess","Potassium","Total_Hb"))


write.csv(print(Tabletwo,exact = "post_op_delirium",nonnormal =
c("Duration_Surgery_Minutes","baseline_L_mu",

"baseline_R_mu","LOS","pH","pCO2","HCO3.",
                                                    "Base_excess","Potassium","Total_Hb")),
"Table_Two.csv")

#-----------------------------------------------------------------------------------------------------
-------
# 1.  Create summary statistics for percentage change of regional cerebral oxygen
saturation
# 2.  Create plots for regional cerebral oxygen saturation over time
# 3.  Export oximetry tables in csv files
# Requires baseline characteristic and baseline oximetry data.
#-----------------------------------------------------------------------------------------------------
-------

#-----------------------------------------------------------------------------------------------------
-------
# Normocapnic group

plot_db <- read.csv("D:/SS/R_data/oximetry/MASTER_results_deleted_missing.csv",
sep=",", stringsAsFactors=TRUE)

plot_db[plot_db == "#N/A"]<-NA
plot_db[plot_db == 9999]<-NA

normocapnia <- subset(plot_db, Group %in% 0)
hypercapnia <- subset(plot_db, Group %in% 1)

normo_plot <- ggplot(normocapnia, aes(x=minute_from_baseline, y=L_delta,
group=p_id)) + geom_line() +geom_point()+
  ggtitle("normocapnia: L delta")+ xlab("Time since start of operation (mins)")+
ylab("% change in oximetry from baseline")

hyper_plot <- ggplot(hypercapnia, aes(x=minute_from_baseline, y=L_delta,
group=p_id)) + geom_line() +geom_point()+
  ggtitle("hypercapnia: L delta")+ xlab("Time since start of operation (mins)")+ ylab("%
change in oximetry from baseline")

means <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x) sd(x, na.rm =
TRUE))
```

```
N <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x)
length(x[!is.na(x)]))

normo_df_L <- data.frame(means,stdevs)
times<- index(normo_df_L)*5
normo_df_L <- data.frame(means,stdevs,N, times)
total_normo_L <- ggplot(normo_df_L, aes(x=times, y=means)) +
geom_line(colour="blue4") +
  geom_ribbon(normo_df_L,mapping = aes(x=times,
ymax=means+stdevs,ymin=means-stdevs),fill="blue4",alpha=0.1)

means <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x) mean(x,
na.rm = TRUE))
stdevs <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x)
length(x[!is.na(x)]))

normo_df_R <- data.frame(means,stdevs)
times<- index(normo_df_R)*5
normo_df_R <- data.frame(means,stdevs,N, times)
total_normo_R <- ggplot(normo_df_R, aes(x=times, y=means)) +
geom_line(colour="blue4") +
  geom_ribbon(normo_df_R,mapping = aes(x=times,
ymax=means+stdevs,ymin=means-stdevs),fill="blue4",alpha=0.1)

#-----------------------------------------------------------------------------------------------
-------
# Hypercapnic group

means <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) length(x[!is.na(x)]))

hyper_df_L <- data.frame(means,stdevs)
times<- index(hyper_df_L)*5
hyper_df_L <- data.frame(means,stdevs,N, times)
total_hyper_L <- ggplot(hyper_df_L, aes(x=times, y=means))

means <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) length(x[!is.na(x)]))

hyper_df_R <- data.frame(means,stdevs)
```

```
times<- index(hyper_df_R)*5
hyper_df_R <- data.frame(means,stdevs,N, times)
total_hyper_R <- ggplot(hyper_df_R, aes(x=times, y=means))

total_L <- total_normo_L +
  geom_ribbon(hyper_df_L,mapping = aes(x=times, ymax=means+stdevs,ymin=means-
stdevs),fill="red2",alpha=0.2) +
  geom_line(hyper_df_L,mapping = aes(x=times, y=means),colour="red4") +
  theme_light() +
  xlab("Time since start of surgery (mins)")+ ylab("Average % change in cerebral
oximetry on the left") +
  theme(axis.title.y = element_text(size = rel(0.65), angle = 90)) +
  theme(axis.title.x = element_text(size = rel(0.65), angle = 00))

total_R <- total_normo_R +
  geom_ribbon(hyper_df_R,mapping = aes(x=times, ymax=means+stdevs,ymin=means-
stdevs),fill="red2",alpha=0.2) +
  geom_line(hyper_df_R,mapping = aes(x=times, y=means),colour="red4")+
  theme_light() +
  xlab("Time since start of surgery (mins)")+ ylab("Average % change in cerebral
oximetry on the right") +
  scale_color_manual(values=c("red4","blue4"))+
  theme(axis.title.y = element_text(size = rel(0.65), angle = 90)) +
  theme(axis.title.x = element_text(size = rel(0.65), angle = 00))

#tiff('oximetry_graph_high_res.tiff', units="in", width=7, height=3.6667, res=600,
compression = 'lzw')

grid.arrange(total_L, total_R, ncol = 2, top=textGrob("Percentage change in cerebral
oximetry from baseline",
                                        gp=gpar(fontsize=11,fontfamily="Times")),
          vp=viewport(width=0.9, height=0.9))

#insert ggplot code
#dev.off()

temp_hyper_L <- t(paste(round(hyper_df_L$mean,1)," (",
round(hyper_df_L$stdev,1),")"," {", hyper_df_L$N,"}", sep = ""))
temp_normo_L <- t(paste(round(normo_df_L$mean,1)," (",
round(normo_df_L$stdev,1),")"," {", normo_df_L$N,"}", sep = ""))

temp_hyper_R <- t(paste(round(hyper_df_R$mean,1)," (",
round(hyper_df_R$stdev,1),")"," {", hyper_df_R$N,"}", sep = ""))
temp_normo_R <- t(paste(round(normo_df_R$mean,1)," (",
round(normo_df_R$stdev,1),")"," {", normo_df_R$N,"}", sep = ""))

write.csv( temp_normo_L , "normo_df_L.csv")
write.csv( temp_normo_R , "normo_df_R.csv")
```

```
write.csv( temp_hyper_L , "hyper_df_L.csv")
write.csv( temp_hyper_R , "hyper_df_R.csv")
```

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6-7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6-7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	9
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12-13
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14,16,17
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	14
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	21
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	22-23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	21-22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19-21
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	4

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A randomised controlled trial to investigate the relationship between mild hypercapnia and cerebral oxygen saturation in patients undergoing major surgery

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029159.R3
Article Type:	Original research
Date Submitted by the Author:	27-Dec-2019
Complete List of Authors:	Wong, Clarence; Austin Hospital, Department of Anaesthesia Churilov, Leonid; The Florey Institute of Neuroscience and Mental Health; University of Melbourne Cowie, Dean; Austin Hospital, Department of Anaesthesia Tan, Chong; Austin Hospital, Department of Anaesthesia Hu, Raymond; Austin Hospital, Department of Anaesthesia Tremewen, David; Austin Hospital, Department of Anaesthesia Pearce, Brett; Austin Hospital, Department of Anaesthesia Pillai, Param; Austin Hospital, Department of Anaesthesia Karalipillai, Dharshi; Austin Hospital, Department of Anaesthesia Bellomo, Rinaldo; Austin Hospital, Department of Intensive Care; University of Melbourne Weinberg, Laurence; Austin Hospital, Department of Anaesthesia; University of Melbourne
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Evidence based practice, Health informatics
Keywords:	hypercapnia, oximetry, Spectroscopy, Near-Infrared, Respiration, Artificial, Delirium

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

A randomised controlled trial to investigate the relationship between mild hypercapnia and cerebral oxygen saturation in patients undergoing major surgery

Authors: Clarence Wong[1,2], Leonid Churilov[2,3], Dean Cowie[1], Chong Tan[1], Raymond Hu[1], David Tremewen[1], Brett Pearce[1], Param Pillai[1], Dharshi Karalipillai[1], Rinaldo Bellomo[1,2], Laurence Weinberg[1,2]

1. Department of Anaesthesia, Austin Hospital, Heidelberg, Victoria, Australia;

2. University of Melbourne, Parkville, Victoria, Australia;

3. The Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia

Correspondence

A/Prof Laurence Weinberg

Department of Anaesthesia, Austin Hospital

145 Studley Road, Heidelberg, Victoria 3084, Australia

Phone number: (61) 03 94965000

Email: laurence.weinberg@austin.org.au

Word Count

Abstract: 304

Introduction: 311

Methods: 2008

Results: 802

Discussion: 1674

Conclusion: 43

Body text: 4838

Abstract

Objectives: The effects of hypercapnia on regional cerebral oxygen saturation (rSO_2) during surgery are unclear. We conducted a randomised controlled trial to investigate the relationship between mild hypercapnia and rSO_2. We hypothesised that, compared with targeted normocapnia (TN), targeted mild hypercapnia (TMH) during major surgery would increase rSO_2.

Design: A prospective, randomised, controlled trial in adult participants undergoing elective major surgery.

Setting: A single tertiary centre in Heidelberg, Victoria, Australia.

Participants: 40 participants were randomised to either a TMH or TN group (20 to each).

Interventions: TMH (partial pressure of carbon dioxide in arterial blood, $PaCO_2$, 45-55 mmHg) or TN ($PaCO_2$ 35-40 mmHg) was delivered via controlled ventilation throughout surgery.

Primary and secondary outcome measures: The primary endpoint was the absolute difference between the two groups in percentage change in rSO_2 from baseline to completion of surgery. Secondary endpoints included intra-operative pH, bicarbonate concentration, base excess, serum potassium concentration, incidence of postoperative delirium, and length of stay (LOS) in hospital.

Results: The absolute difference between the two groups in percentage change in rSO_2 from the baseline to the completion of surgery was 19.0% higher in both hemispheres with TMH ($P<0.001$). On both sides, the percentage change in rSO_2 was greater in the TMH group than the TN group throughout the duration of surgery. The difference between the groups became more noticeable over time. Furthermore, postoperative delirium was higher in the TN group (risk difference 0.3, 95% CI [0.1 to 0.5], $P=0.02$). Length of stay was similar between groups (5 days vs. 5 days; $P=0.99$).

Conclusion: TMH was associated with a stable increase in rSO_2 from the baseline, while TN was associated with a decrease in rSO_2 in both hemispheres in patients undergoing major surgery. This resulted in a clear separation of percentage change in rSO_2 from the baseline between TMH and TN over time. Our findings provide the rationale for larger studies on TMH during surgery.

Clinical trial registration: The Australian New Zealand Clinical Trials Registry, unique identification number: ACTRN12616000320459

Keywords: Hypercapnia; Oximetry; Spectroscopy, Near-Infrared; Respiration, Artificial; Delirium

Article Summary

Strengths of this study

- High internal validity due to blinding and random allocation to groups
- Frequent sampling of oximetry data throughout monitoring period
- Non-invasive nature of near-infrared spectroscopy (NIRS) cerebral oximetry for regional cerebral oxygen saturation (rSO_2) measurements

Limitations of this study

- Study findings do not apply to emergency surgeries, intra-cranial surgeries, or surgeries requiring one lung ventilation.
- Interpretation of rSO_2 depends on an assumption that rSO_2 is the same in different regions of the brain.

Acknowledgement

Funding Statement

Masimo provided the oximetry sensors used for this trial. This study conception, design, trial management, data collection, data analysis, and the writing of the manuscript, have been executed completely independently of Masimo and any other external organisations. This work was supported by the Deparment of Anaesthesia Research Fund, Austin Hospital, Heidelberg, Victoria, Australia.

Declaration of interest

All authors declare no conflict of interest.

Presentation

Findings of this study were presented as a poster presentation at the PostGraduate Assembly in Anesthesiology held during 8-12th December 2018 at New York, United States of America.

Data sharing statement

De-identified participant data are available upon reasonable request.

Introduction

In patients undergoing major surgery, the effects of mild hypercapnia on regional cerebral oxygen saturation (rSO_2) have not been fully examined, and any beneficial or harmful effects of hypercapnia as a therapeutic ventilation strategy to improve cerebral oxygenation are unknown. In animal models, CO_2 is a well-known vasodilator, improving cerebral blood flow.[1-3] The neuroprotective mechanisms of mild hypercapnia, whilst not completely understood, have been postulated to be a result of an increase in cerebral blood flow, enhancement of oxygen delivery, improvements in cerebral glucose utilisation and oxidative metabolism,[4,5] and activation of adenosine triphosphate (ATP)-sensitive potassium channels to maintain normal neuronal activity in the setting of ischemia.[6]

The recent emergence of near-infrared spectroscopy (NIRS) cerebral oximetry has provided a practical method to measure rSO_2 continuously and non-invasively. This technology has gained substantial supportive evidence in resuscitation, critical care, and surgical applications.[7-9] Numerous studies have shown that NIRS can be applied clinically in the resuscitation and cardiac surgery settings, where cerebral desaturation events can be both effectively monitored and managed.[10-13] However, whilst absolute and relative saturation thresholds theoretically requiring prompt interventions have been proposed,[14] these thresholds have not been validated, and there is a lack of consensus on the indication and timing of interventions. In patients undergoing surgery, rSO_2 was reported to be higher with mild hypercapnia, however, the intra-operative temporal relationship between rSO_2 and mild hypercapnia remains unclear.[15]

Accordingly, we conducted a randomised controlled trial to test the hypothesis that targeted mild hypercapnia (TMH), defined as the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) between 45 and 55 mmHg, during elective major surgery would increase cerebral oxygen saturation compared to targeted normocapnia (TN), defined as $PaCO_2$ between 35 and 40 mmHg. As a secondary aim, we evaluated whether TMH would affect the development of postoperative delirium, a commonly reported complication that is linked to functional decline, institutionalisation, and higher mortality.[16-18]

Methods

Ethics approval and clinical trial registration

The study was approved by the Austin Health Research and Ethics Committee on 6th January 2016 (HREC/15/Austin/488), and all participants gave written informed consent. The study was prospectively registered on 10th March 2016 with the Australian New Zealand Clinical Trials Registry (ACTRN12616000320459). The study was reported in accordance with the CONSORT Guidelines for reporting randomised trials.[19]

Trial design, setting, and population

Between March 2016 and March 2017, we conducted the randomised controlled trial at the Austin Hospital, a university teaching, tertiary, metropolitan hospital at Heidelberg, Victoria. Following a pre-operative assessment at the anaesthesia pre-admissions clinic and the receipt of written informed consent, eligible patients undergoing elective major surgery were identified. Inclusion criteria included the following: adult patients (age over 18 years), surgery of greater than 2 hours' expected duration requiring at least one overnight admission, a clinical indication for continuous blood pressure monitoring via an invasive arterial line, and intermittent positive pressure ventilation via an endotracheal tube as part of standard anaesthesia care. Age criterion was modified from the previous criterion (age over 65 years) to age over 18 years in order to recruit patients who represent the intended study population. Exclusion criteria included patients undergoing cardiac surgery, procedures requiring one lung isolation, liver transplantation, intracranial surgery, GCS less than 15, known cognitive impairment, intellectual disability or a mental illness, moderate pulmonary hypertension (mean pulmonary arterial pressure greater than 40 mmHg), and American Society of Anesthesiology (ASA) status V.

Randomisation and blinding

An independent statistician generated a computerised sequence of 40 allocation codes, 20 for each group. A research nurse sealed the allocation codes into sequentially numbered opaque envelopes. The study participants, surgeons, and all peri-operative staff were blinded to treatment allocation. However, it was not possible to blind the attending anaesthetist who was responsible for the delivery of the intervention. Immediately after induction of anaesthesia,

patients were randomised to either targeted mild hypercapnia ($PaCO_2$ 45-55 mmHg) or targeted normocapnia ($PaCO_2$ 35-40 mmHg). The end-tidal carbon dioxide ($EtCO_2$) was titrated accordingly in order to achieve the desired intervention, but the anaesthetist did not have an rSO_2 goal to titrate to. Data collection for all the trial outcomes was collected by an independent researcher blinded to treatment allocation. The sequence was decoded after the data were analysed. The anaesthetist delivering the intervention did not participate in the assessment of postoperative delirium.

Outcomes and data collection

The primary endpoint was the absolute difference between the TMH and TN groups in percentage change in rSO_2 from baseline to completion of surgery. Secondary endpoints evaluated the effects of mild hypercapnia on the incidence of postoperative delirium, intra-operative pH, bicarbonate, base excess, serum potassium, and length of hospital stay (LOS).LOS was prespecified as secondary outcome in the original study protocol. However, it was not prespecified as a secondary outcome in the prospective Australian New Zealand Clinical Trials Registry (ANZCTR). Therefore, the trials registry was retrospectively updated to include LOS as a secondary outcome to align with the study protocol.

Measurement of rSO_2

Regional cerebral oxygen saturation was collected using the Masimo O_3™ regional oximetry component of the Root™ Patient Monitor platform (O_3™ Masimo, Irvine, CA). This regional oximetry device uses NIRS and reflectance oximetry to monitor rSO_2 in the brain, displaying both absolute and trend rSO_2 values. The absolute oximetry value is defined as the rSO_2 value measured by the oximetry probe calibrated by a fixed ratio of arterial to venous blood. In our study, only the absolute oximetry data were extracted and analysed. The accuracy of the Masimo O_3™ regional oximetry was investigated by *Redford et al*. previously, and the measurement error was reported to be approximately 4% when checked against reference blood samples taken from the radial artery and internal jugular bulb vein.[20] Regional cerebral oxygen saturation was measured in the two hemispheres separately, with a NIRS sensor attached to each side of patient's forehead. The baseline rSO_2 was recorded before commencing any premedication and before induction of anaesthesia. Subsequent rSO_2 measurements were recorded every two seconds until the last surgical suture was sited. Data were exported as comma separated values files after surgery and processed using manually

written R scripts on RStudio v.1.0.136 (**Supplementary File 1)**. The percentage change in rSO_2 ($\%\Delta rSO_2$) was computed by subtracting the baseline rSO_2 value from the measured rSO_2 value at all timepoints throughout surgery, multiplied by one hundred percent. Data from the left and right forehead were analysed separately.

Measurement of delirium

Delirium was assessed using a validated and widely utilised Confusion Assessment Method (CAM) rating scale, adapted from Inouye *et al.*, immediately on arrival to hospital, then within 18-24 hours after surgery.[21,22] Diagnosis of delirium requires the presence of both acute onset with fluctuating course and inattention, together with either disorganised thinking or altered level of consciousness. A single trained interviewer, blinded to randomisation and proficient and trained in CAM, conducted all the assessments pre-operatively when each patient arrived at the hospital and at 8am on the next day after surgery in the ward (within 18-24 hours postoperatively). The baseline cognitive function was not formally assessed with collateral history from family members or carers.

Measurement of $PaCO_2$ and intra-operative adherence to group allocation

Immediately after tracheal intubation with a cuffed endotracheal tube, minute ventilation was adjusted to achieve an $EtCO_2$ concentration of 45-55 mmHg in the TMH group or 35-40 mmHg in the TN group. Due to the presence of alveolar dead space, $EtCO_2$ can be lower than $PaCO_2$ by up to 5 mmHg. Therefore, an arterial blood gas (ABG) was obtained to check $PaCO_2$, and ventilation was further adjusted accordingly to achieve the desired $PaCO_2$ target ranges. The $PaCO_2$-$EtCO_2$ gradient was then maintained throughout surgery, with the assumption that the $PaCO_2$ would remain constant. Additional ABGs were sampled at the discretion of the anaesthetist if the gradient required re-evaluation, for example, requirements for an adjustment of the ventilation setting. Finally, at completion of surgery, an ABG was sampled to accurately document the $PaCO_2$ value and to assess whether $PaCO_2$ was being maintained within target values.

Arterial blood gas analysis

All arterial blood gas variables were collected by ABL80 FLEX Blood Gas Analyzer (Radiometer, Copenhagen, Denmark) with a fully automated micromode, eliminating the risk of user-induced bias or loss of accuracy with very small samples, and an interference-protected lactate analyser. ABG variables include partial pressure of oxygen (PaO_2), $PaCO_2$,

pH, bicarbonate concentration, base excess, lactate, haemoglobin concentration (Hb), and electrolytes such as sodium and potassium ion concentrations. The machine calculates the bicarbonate concentration using the Henderson-Hasselbalch equation and the standard base excess (SBE) using the Van Slyke equation by determining changes in bicarbonate, protein anion, and phosphate concentrations, with the reference points pH = 7.40, $PaCO_2$ = 40mmHg, and temperature = 37°C. Two or more ABG samples were measured intra-operatively, as described previously. The mean values of pH, bicarbonate concentration, base excess, and serum potassium concentration from the first and the last ABG samples were considered as some of the secondary outcomes for the study. Intra-operative pH, bicarbonate, and base excess are important variables that inform the acid–base status of a patient; in particular, bicarbonate and base excess are useful when determining the extent of metabolic contributions or compensation. Potassium concentration is a key physiological parameter that affects cardiac action potential conduction, and its relevance in the study is paramount, as hyperkalaemia from hypercapnic-induced acidosis is a potential complication of the intervention. Potential confounders to rSO_2 measurements, such as Hb and PaO_2, were recorded. Other variables, such as lactate and sodium concentration, were collected for routine clinical care, and they were not considered as part of the outcome measures.

Standardisation of care

All patients underwent a pre-operative multidisciplinary team assessment, including a haematology-led, multimodal peri-operative haemoglobin optimisation program based on the National Blood Authority of Australia's patient blood management initiatives to optimise pre-operative red cell mass, minimise peri-operative blood loss, and tolerate postoperative anaemia.[23] All participants were fasted two hours for clear fluids and six hours for solids, according to standard hospital fasting protocols. All participants received a general anaesthetic with propofol for induction, an inhalational agent for the maintenance of anaesthesia, with a 50% oxygen-to-air mixture to maintain oxygen saturations above 97%. Routine monitoring for all participants included continuous electrocardiogram (ECG), pulse oximetry, temperature, bispectral index (BIS) monitoring, and neuromuscular monitoring. Adequate depth of anaesthesia was ensured by targeting BIS readings between 40 and 60. Conduct of anaesthesia, including the use of additional invasive monitoring, intra-operative medications, intervention fluids, vasoactive medications, regional anaesthesia, and intraoperative opioids, were entirely at the discretion of the attending anaesthetist. In keeping

with hospital protocol, we transfused blood if the haemoglobin concentration was less than 75 g dL^{-1} or less than 80 g dL^{-1} in the presence of ongoing bleeding.

Sample size calculations

Based on our institution's pilot data and reported figures, normal rSO_2 values for awake patients could range from 60% to 80%,[24] which we assumed to be the case at the baseline (beginning of surgery). We assumed no change in rSO_2 in the control group and considered an absolute difference between the groups in percentage change in rSO_2 value from the baseline to the completion of surgery of 15% to be clinically important. Thus, the absolute changes in rSO_2 from the baseline to the end of surgery were hypothesised to be 0% in the control group and 12% (15% percentage change from the baseline of 80% rSO_2) in the intervention group. Assuming a two-tailed threshold for statistical significance of 0.05 and standard deviation of the absolute change of 10%, the total sample size of 40 patients (equally distributed between two groups) will yield the 0.9 power to observe a large treatment effect (Cohen's d=1.1 or higher).

Statistical analysis

The study was reported in accordance with the Statistical Analyses and Methods in the Published Literature (SAMPL) Guidelines.[25] The statistical analysis was performed using commercial statistical software STATA/IC v.13 with a P value of 0.05 to indicate statistical significance. Figures and tables were created by manually written R scripts on RStudio v. 1.0.136 (**Supplementary File 2)**. Fisher's exact test was used in the analysis of all categorical variables. For continuous variables, normality was determined by the Shapiro–Wilk test and further confirmed by a manual inspection of the skewness and kurtosis of the data. Parametric continuous data were compared by the Student's t-test, and non-parametric continuous data were compared by the Mann-Whitney U test. For normally distributed data, the results were presented as the mean (standard deviation); and for non-parametric data, the results were presented as the median [inter-quartile range] unless otherwise stated. A more detailed longitudinal analysis of time-by-treatment interaction was also conducted using a random effect generalised least squares regression model (due to the repeated measures nature of the data) with percentage change in rSO_2 at a given time point throughout the surgery as the output, the treatment group, the time (minutes from start of surgery), as well as the time-by-treatment interaction term as inputs. The duration of surgery varied between

different patients, and therefore, in order to compare $\%\Delta rSO_2$ at different time points across all the patients, the time was measured using the "minutes from the start of surgery" metric. For robustness analyses, similar models adjusted for age, baseline oximetry values, and pre-operative Hb levels were implemented, as well as models where time was measured not in minutes, but as a percentage of total surgery duration.

Patient and public involvement

Patients were involved in the study from the initial pre-admission consultation appointment where the rationale of the study, potential applications of the study outcomes, data privacy and management, and potential harmful effects were explained in detail. Patients were not directly involved in the development of the research question and outcome measures, and they were not involved in the design and conduct of the study. Potential burden of the intervention was not rated by the patients themselves; rather, potential harmful effects were monitored by the attending anaesthetist as part of routine clinical care. Study results and outcomes, once finalised, will be mailed out to study participants.

Results

Seventy-seven participants were screened for eligibility. Thirty-seven patients were excluded because they did not meet the inclusion criteria (*n*=6), they declined to participate (*n*=30), or the anaesthetist objected to the intervention (*n*=1). For logistical reasons, recruitment could only be performed when the interviewer conducting the CAM testing was available. The CONSORT diagram is presented in **Figure 1**. There were no violations or breaches of the study protocol; however, two participants in the hypercapnic group had a failure of bilateral probe attachment and lead connection problem that were unable to be rectified. These patients were subsequently excluded from the analyses of oxygenation, as no rSO_2 data were captured. They were included in the analysis of all other variables and endpoints. In the hypercapnic group, three participants had unilateral discontinuous oximetry readings due to intermittent signal dropout. In the normocapnic group, signal dropout occurred in two patients on the left side. The corresponding data were excluded.

The baseline participant and surgical characteristics are summarised in **Table 1**.

Table 1. Baseline patient characteristics and surgical characteristics

	TMH group (*n*=20)	**TN group (*n*=20)**
Patient characteristics		
Gender (Male : Female)	11:9	12:8
Age (years)	63.7 [32 to 81]	65.4 [31 to 81]
Age > 65 (years)	9 (45.0)	11 (55.0)
Weight (kg)	83.7 [56.8 to 110.6]	81.2 [67.9 to 94.5]
BMI (kg m^{-2})	33.6 [20.7 to 46.5]	32.8 [26.8 to 38.8]
ASA Status		
1	5 (25.0)	2 (10.0)
2	6 (30.0)	4 (20.0)
3	7 (35.0)	10 (50.0)
4	2 (10.0)	4 (20.0)
Diabetes	4 (22.2)	5 (25.0)

COPD	5 (27.8)	0 (0.0)	
Malignancy	11 (61.1)	7 (35.0)	
Other co-morbidities	11 (61.1)	16 (80.0)	
Surgical Characteristics			
Duration of surgery (mins)	219.0 [123.8 to 303.8]	144.0 [107.8 to 218.2]	(*P*=0.121)
Left baseline oximetry (%)	68.7 [63.9 to 72.2]	63.4 [57.3 to 69.6]	(*P*=0.233)
Right baseline oximetry (%)	67.9 [64.6 to 70.3]	64.0 [59.4 to 69.0]	(*P*=0.286)
Pulse oximetry (%)	98.5 [98.1 to 99.0]	98.5 [97.9 to 99.0]	(*P*=0.834)
LOS (days)	5 [2.0 to 12.0]	5 [1.8 to 11.5]	(*P*=0.988)
Type of surgery			
colorectal	2 (10.0)	1 (5.0)	
endocrine	2 (10.0)	2 (10.0)	
ear nose & throat	0 (0.0)	1 (5.0)	
hepatobiliary	6 (30.0)	9 (45.0)	
spinal surgery	1 (5.0)	1 (5.0)	
orthopedic	2 (10.0)	1 (5.0)	
thoracic	5 (25.0)	1 (5.0)	
urology	2 (10.0)	3 (15.0)	
vascular	0 (0.0)	1 (5.0)	

Data reported as number (%) or median [inter-quartile range], except for age, which is reported as mean [range]

ASA: American Society of Anesthesiologists

BMI: body mass index

COPD: chronic obstructive pulmonary disease

LOS: length of hospital stay

Other co-morbidities include any of the following, ischaemic heart disease, atrial fibrillation, hypertension, history of cerebral vascular disease, and chronic kidney impairment

Spinal surgery includes non-intracranial procedures

Thoracic surgery includes procedures not requiring one lung ventilation, e.g. mediastinoscopy with nodal dissection

TMH: targeted mild hypercapnia, TN: targeted normocapnia

Both groups were similar in terms of gender, age, weight, body mass index, ASA physical status, and type of surgery performed. In terms of co-morbidities, both groups were similar, except for the presence of chronic obstructive pulmonary disease. There was 100%

compliance to the designated $PaCO_2$ intra-operative targets. The median [inter-quartile range, IQR] $PaCO_2$ in the TMH group and TN groups were 51.5 mmHg [46.9 to 60.9] and 34.8 mmHg [32.8 to 38.1], respectively (P<0.001). With regards to surgical characteristics, the duration of surgery was longer in the TMN group, with a median [IQR] duration of 219 minutes [124 to 304] versus 144 minutes [108 to 218] in the TN group, although this was not significant at the 5% level (P=0.121). PaO_2 was similar between the two groups: 156.8 mmHg [146.3 to 217.2] in the TMH group and 142.5 mmHg [122.5 to 199.1] in the TN group (P=0.380). Oxygen saturation was similar: 98.5% in the TMH group [98.1 to 99.0] and 98.5% in the TN group [97.9 to 99.0] (P=0.834). Both groups also had similar mean arterial pressure (MAP) intra-operatively (P=0.307), similar total Hb (130.50 vs. 122.25 g L^{-1}; P=0.132), and similar total dose of intra-operative opioid received, 21.67 mg in the TMH group [13.75 to 32.50] and 16.67 mg in the TN group [10.00 to 22.50] (P=0.22). In terms of intra-operative positioning of patients, one patient from each group was positioned in steep reverse Trendelenburg with minimal tilt. All other patients were positioned in the supine position with a neutral head position.

Primary endpoint

On the left hemisphere, the median [IQR] baseline oximetry was 68.7% [63.9 to 72.2] in the TMH group vs. 63.4% [57.3 to 69.6] in the TN group (P=0.233). On the right hemisphere, the median [IQR] baseline oximetry was 67.9% [64.6 to 70.3] in the TMH group vs. 64.0% [59.4 to 69.9] in the TN group (P=0.286). On both sides, the $\%\Delta rSO_2$ was greater in the TMH group than the TN group throughout the duration of surgery (**Figure 2**). The mean (standard deviation, SD) percentage changes in rSO_2 from the baseline to the conclusion of the surgery in the TMH group were +8.56% (18.90%) on the left and +13.86% (18.17%) on the right; and in TN the group, they were -6.18% (17.24%) on the left and -5.48% (18.94%) on the right. The resulting treatment effects were 19% (95% CI [9.2 to 28.8]; P<0.001) on the left and 19% (95% CI [10.9 to 27.0]; P<0.001) on the right (**Table 2**).

Table 2. Percentage change in cerebral oximetry (%ΔrSO_2) from baseline

Time from start of surgery (mins)		15	30	45	60	75	90	105	120
Left	**TMH**	0.8 (12.9) {15}	5.8 (12.3) {15}	9.0 (15.9) {15}	7.0 (14.6) {15}	8.5 (15.4) {14}	7.3 (14.7) {13}	7.7 (17.4) {13}	8.1 (14.8) {13}
	TN	4.7 (10.5) {18}	3.2 (15.4) {18}	-1.9 (14.1) {17}	-5.6 (12.7) {17}	-5.3 (15.2) {17}	-5.5 (15.8) {17}	-6.0 (15.2) {17}	-3.6 (15.8) {14}
Right	**TMH**	6.0 (12.9) {17}	9.8 (13.2) {17}	10.4 (18.1) {17}	11.1 (17.4) {17}	13.0 (16.4) {16}	15.6 (17.3) {15}	14.4 (17.5) {14}	14.1 (13.6) {14}
	TN	5.2 (12.6) {20}	3.9 (11.7) {20}	-3.3 (13.2) {19}	-5.2 (12.1) {19}	-5.4 (12.3) {19}	-4.7 (14.1) {19}	-3.8 (13.7) {18}	-1.3 (13.9) {15}

Time from start of surgery (mins)		120	240	360	480	600	720	Mean % difference from start to completion of surgery	95% confidence interval	*P* value (treatment)
Left	**TMH**	8.1 (14.8) {13}	6.8 (20.6) {7}	6.4 (32.5) {4}	-8.6 (21.1) {3}	-6.1 (14.1) {3}	6.9 {1}	19.0	9.2 -28.8	<0.001
	TN	-3.6 (15.8) {14}	-10.4 (39.5) {5}	-43.4 (34.9) {2}	-27.8 {1}					
Right	**TMH**	14.1 (13.6) {14}	18.4 (23.5) {8}	16.8 (36.8) {4}	1.5 (14.9) {3}	3.0 (8.7) {3}	2.0 {1}	19.0	10.9- 27.0	<0.001
	TN	-1.3 (13.9) {15}	-5.3 (32.6) {5}	-35.4 (26.9) {2}	-37.8 {1}					

Data reported as mean (standard deviation) {sample size}, and presented every 15 minutes for the first 2 hours and every 2 hours afterwards

TMH: targeted mild hypercapnia, TN: targeted normocapnia

On the longitudinal time-by-treatment interaction analysis, the difference in $\%\Delta rSO_2$ on both left and right hemispheres between the two groups diverged with time, with the intervention group exhibiting a smaller percentage decrease over time compared to the control group (time-by-treatment interaction $P<0.001$ for both left and right hemispheres). We obtained very similar results on the robustness analyses when the above model was adjusted for age, baseline oximetry, and pre-operative Hb levels, as well as when the percentage of total duration of surgery, instead of minutes from the start of surgery, were included.

Secondary outcomes

Postoperative delirium was statistically significantly less common in the TMH group. Postoperative delirium was present in 0 out of 20 (0%) participants in the TMH group and 6 out of 20 (30%) participants in the TN group (risk difference 0.3, 95% CI [0.1 to 0.5], Fisher's exact $P=0.02$) (**Table 3).**

Table 3. Postoperative delirium and opioid doses

	TMH group (*n*=20)	**TN group (*n*=20)**	
Pre-medication			
Number of patients	0 (0.0)	2 (10.0)	
Mean midazolam dose (mg)	0	1.75	
Intra-operative opioid			
Total dose (mg)	21.67 [13.75 to 32.50]	16.67 [10.00 to 22.50]	(P=0.22)
Received i.v. morphine	2 (10.0)	1 (5.0)	
Received i.v. fentanyl	10 (50.0)	14 (70.0)	
Received i.v. oxycodone	9 (45.0)	7 (35.0)	
Received i.v. tramadol	4 (20.0)	0 (0.0)	
Received i.v. clonidine	0 (0.0)	2 (10.0)	
Intrathecal morphine			
Number of patients	5	2	
Mean dose (mcg)	220	350	

Epidural analgesia			
Number of patients	0	0	
Blood glucose level			
Glucose (mmol L-1)	7.1 [7.0 to 7.1]	6.6 [6.4 to 6.7]	(*P*=0.33)
Pre-operative CAM	0 [0.0 to 0.0]	0 [0.0 to 0.0]	
Postoperative CAM	0 [0.0 to 0.0]	1.5 [0.0 to 3.0]	
Presence of postoperative delirium	0 (0.0)	6 (30.0)	(*P*=0.02)

Data reported as median [inter-quartile range] or number (%)

CAM: Confusion Assessment Method

Note some patients received 2 or more different intra-operative opioids

Total dose of intra-operative opioid normalised to i.v. morphine equivalent

TMH: targeted mild hypercapnia, TN: targeted normocapnia

In terms of acid–base variables, median intra-operative pH was statistically significantly lower (7.31 vs. 7.46; *P*<0.001), and intra-operative bicarbonate was statistically significantly higher (25.00 vs. 24.00 mEq L^{-1}; *P*=0.020) in the TMH. No statistically significant differences in base excess (-1.00 vs. 1.00 mmol L^{-1}; *P*=0.069) and potassium (3.98 vs. 4.03 mEq L^{-1}; *P*=0.759) were observed intra-operatively. Length of hospital stay was also similar between the two groups (5 vs. 5 days; *P*=0.988). These results are summarised in **Table 4.**

Table 4. Arterial blood gas values and the corresponding $EtCO_2$

	TMH group (*n*=20)	**TN group (*n*=20)**	*P*-value
pH	7.31 [7.27 to 7.33]	7.46 [7.43 to 7.47]	<0.001
PaO_2 (mmHg)	156.8 [146.3 to 217.2]	142.5 [122.5 to 199.1]	0.380
$PaCO_2$ (mmHg)	51.50 [46.88 to 60.88]	34.75 [32.75 to 38.12]	<0.001
$EtCO_2$ (mmHg)	46.40 [39.80 to 50.20]	30.40 [28.50 to 32.00]	<0.001
Bicarbonate (mEq L^{-1})	25.00 [24.00 to 27.75]	24.00 [22.00 to 24.62]	0.020
Base excess (mmol L^{-1})	-1.00 [-2.50 to 0.25]	1.00 [-0.88 to 2.00]	0.069
Potassium (mEq L^{-1})	3.98 [3.73 to 4.38]	4.03 [3.58 to 4.31]	0.759
Total Hb (g L^{-1})	130.50 [118.12 to 140.62]	122.25 [106.88 to 131.25]	0.132

Data reported as median [inter-quartile range] or number (%)

$EtCO_2$: end tidal carbon dioxide

Hb: haemoglobin concentration

$PaCO_2$: partial pressure of carbon dioxide in arterial blood

PaO_2: partial pressure of oxygen in arterial blood

TMH: targeted mild hypercapnia, TN: targeted normocapnia

Discussion

We conducted a prospective, single centre, single blinded, randomised controlled trial evaluating the effects of TMH and TN on rSO_2 in patients undergoing major surgery. TMH led to a stable increase in both left and right NIRS-derived rSO_2 from the baseline values, while TN led to a decrease in rSO_2. This effect was sustained throughout surgery and became more pronounced with the passage of time. Furthermore, TMH was associated with a lower incidence of postoperative delirium within 24 hours after surgery.

Whilst the relationship between elevated $PaCO_2$ and cerebral blood flow (CBF) is well described,[26-29] the associations between hypercapnia and higher rSO_2 are poorly understood. Numerous factors, for instance, cardiac output, haemoglobin affinity for oxygen, cerebral autoregulation, and the ratio of cerebral arterial to venous blood volume, affect rSO_2 in the setting of hypercapnia, but changes in $PaCO_2$ and CBF, in turn, have a direct influence on these factors.[30,31] To complicate the subject further, the duration of effect of hypercapnia on rSO_2 is unknown. In our study, confounding variables, such as MAP, PaO_2, Hb, and intra-operative position, were similar between the TMH and TN groups. However, pH, which directly affects the haemoglobin affinity for oxygen via the Bohr Effect, was significantly different. Since we cannot measure the ratio of arterial to venous blood volume, it would be impetuous to comment on the mechanism behind the observed higher rSO_2 values in TMH. Clinically, similar observations have been reported previously. Eastwood et al. compared rSO_2 values at the end of alternating hypercapnic and normocapnic periods in post-cardiac arrest patients in a double cross-over study, and discovered that mild hypercapnia resulted in higher rSO_2.[32] When Akca *et al.* delivered mild hypercapnia intra-operatively to investigate tissue oxygenation and its relationship with wound infection risk after surgery, cerebral oxygen saturation was found to be higher in the mild hypercapnic group.[15] Similarly, rSO_2 remained higher in hypercapnic patients throughout shoulder surgery, and less cerebral desaturation events were observed by Murphy *et al*.[33] Our study is one of the few randomised controlled trials that investigated rSO_2 change over time. We found that the sustained difference in rSO_2 over time was a combined effect of a stable increase in rSO_2 from the baseline in the TMH group and a stable decrease in

rSO_2 from the baseline in the TN group. In the literature, the association between normocapnia and reduced CBF and lower levels of rSO_2 were reported briefly.[34] However, the exact mechanism and associations between normocapnia and variations in rSO_2 values are not entirely clear. Whilst theoretical absolute and relative saturation thresholds requiring prompt interventions have been proposed,[14] these thresholds have not been validated and there is a lack of consensus on the indication and timing of interventions. In our study, the reduction in rSO_2 from the baseline was small in the majority of patients in the TN group, and the attending anaesthetists had no rSO_2 target to titrate to. As a result, no interventions were performed intra-operatively in response to changes in rSO_2. Comparing the TMH and TN groups, the sustained difference in percentage change in rSO_2 over time is a novel finding.

Interestingly, the incidence of postoperative delirium after surgery was lower in the TMH group, while LOS remained similar between the groups. Patients who suffered from postoperative delirium were all in the TN group, but they were also older (median [IQR] age = 72 [59.5 to 77]) and had higher ASA scores (ASA scores of 3, 2, 1, 4 and 4). Their baseline medical co-morbidities and duration of surgery (median [IQR] duration of surgery = 171 minutes [83.5 to 254.5]) were similar to other study participants. There has been conflicting evidence in the literature regarding the relationship between rSO_2 and LOS on postoperative cognitive performance. Cognitive outcomes were similar in groups with or without NIRS-based rSO_2 optimisation in a recent randomised controlled trial.[14,35] On the other hand, Murkin *et al.* found that monitoring and reacting to cerebral desaturation during coronary artery bypass surgery was associated with clinical benefits.[13] Patients with shorter LOS (<10 days) had a higher mean rSO_2. Intra-operative NIRS rSO_2 monitoring led to a significant reduction in postoperative cognitive disturbance, confirmed by Trafidlo *et al.*[36] Casati *et al.* also reported that higher rSO_2 led to shorter LOS and improved Mini-Mental State Examination scores in elderly patients undergoing major abdominal surgery,[37] and Schoen *et al.* found that low pre-operative rSO_2 was associated with a higher incidence of postoperative delirium. Among patients who started at a normal rSO_2 level, those who developed delirium had a larger intra-operative drop in rSO_2.[38] Our findings were consistent with those of Schoen *et al.*; however, they need to be interpreted with

caution, as the ASA scores and age were slightly higher in the TN group, and our study was not designed to quantitatively investigate postoperative cognitive performance in hypercapnia.

Implications of our findings demonstrate that TMH can be delivered reliably during major surgery, and its effects on rSO_2 can be monitored with NIRS in most patients. Its delivery is reliably associated with increased levels of rSO_2, and the relatively higher rSO_2 is sustained over the duration of surgery, an observation that has not been reported in the literature. Furthermore, TMH may reduce the incidence of the development of immediate postoperative delirium. A clinical concern of mild hypercapnia is hypercapnic-induced acidosis and the subsequent development of hyperkalaemia. Whilst a linear correlation between arterial carbon dioxide and plasma pH is well reported,[39] the relationship between acute hypercapnia, respiratory acidosis, and plasma potassium is also poorly understood.[40] In the present study, we found no association between hypercapnia and serum potassium concentration, a finding also supported by others.[41] We did not observe any other deleterious or adverse effects from hypercapnic-induced acidosis such as cardiac arrhythmias in our study. Interestingly, whilst our study was not designed to measure differences in analgesia and partial pressure of oxygen in arterial blood, we observed a 10% higher median PaO_2 level in the TMH group and found that the median intra-operative analgesia requirements were also approximately 30% higher. Both arterial oxygen levels and pain have been reported to influence tissue oxygenation,[42] which was not directly measured in our study. The effect of pain on cerebral oxygenation is unclear and has not been borne out in clinical studies;[43] further studies exploring this association are needed. Finally, we have shown that NIRS-based cerebral oximetry is a non-invasive and practical method of measuring rSO_2, easily incorporated into the existing collection of routine monitoring variables, findings that are in agreement with other research groups.[20,44-46]

Our study has multiple strengths. Our findings have high internal validity because the study was a randomised controlled trial with concealed allocation and blinded assessment, minimising selection and ascertainment bias. The rSO_2 data were exported

directly to RStudio, and ABG data were analysed by the ABL Blood Gas Analyzer, rendering sampling error from data entry unlikely, thereby increasing the robustness of our findings. Sampling of continuous oximetry data resulted in a stream of oximetry data throughout the monitoring periods, maximising the details of our assessment. Although the duration of surgery was different for individual patients, oximetry data were not normalised to another time scale, enabling a fair comparison of data across the study groups. NIRS-derived rSO_2 has been criticised for potential extra-cranial contamination that would confound true rSO_2.[47] However, there is sufficient evidence to support the accuracy of NIRS-derived rSO_2,[20,44] particularly in the case of hypercapnia, where extra-cranial signal interference has been shown to be insignificant, justifying its reliability.[48] Moreover, as the technology was the same in both groups, any inaccuracy should not have been a source of bias.

Our study also has a number of limitations. The attending anaesthetists were not blinded due to the nature of the intervention. Nevertheless, bias was mitigated by the fact that measurements were taken directly from the cerebral oximetry machine, and the assessment of delirium was conducted by an independent researcher blinded to the intervention. The external validity of our findings was restricted by the small sample size from one single centre. The sample size calculation was based on the assumption that there were no changes in rSO_2 values from the baseline in the TN group. The observed negative change can therefore impact the calculation. The strong nature of interaction between treatment and time for rSO_2 outcome should be treated with caution due to the potential minor departures of the data from the linear trend. Our findings were not applicable to patients undergoing emergency surgery, intracranial surgery, or surgery requiring one lung ventilation. The cerebral oximetry probes were only attached to the forehead, measuring rSO_2 within the frontal cortex region, which carries the assumption that rSO_2 was homogenous across every area of the brain. Quantification of device failure rate, despite being a critical consideration, cannot be described by our study design.

We did not measure cardiac output, stroke volume, and systemic vascular resistance. Therefore, the effects on changes in intrathoracic pressure on cardiac output are unknown. Changes in intrathoracic pressure may have adversely impacted cardiac output, which may in turn have affected the $EtCO_2$. However, given that the positive end-expiratory pressure was held constant in both groups, and the changes in lung tidal volumes were relatively small, the impact of intrathoracic pressure on cardiac output is likely to be small. Finally, our findings of a greater incidence of early postoperative delirium in the TN group need to be interpreted with caution, as confounders of postoperative delirium were not controlled, our study was not powered to investigate postoperative delirium, and mental state was only assessed by CAM, once pre-operatively and once postoperatively. Accordingly, our findings for delirium should be viewed as hypothesis generating. Nevertheless, if we were to consider that our effect size observed (i.e. risk difference of 0.3) could be due to chance and a smaller effect would be observed in a larger study, an appropriate powered randomised controlled trial for this outcome would be very feasible. If the proportion of patients with delirium in the intervention group is 10%, to achieve 90% power, the required sample size for each group would be ninety-two.

Conclusion

In summary, TMH was associated with a stable increase in rSO_2 from the baseline, while TN was associated with a decrease in rSO_2 from the baseline in both hemispheres. This effect was sustained and became more pronounced with the passage of time intra-operatively.

Author Contributions

Clarence Wong: This author contributed to data collection, data analysis, and manuscript write-up.

Leonid Churilov: This author contributed to data analysis and manuscript write-up.

Dean Cowie: This author contributed to patient recruitment, data collection, and preparation of manuscript.

Chong Tan: This author contributed to patient recruitment and preparation of manuscript.

Raymond Hu: This author contributed to patient recruitment and preparation of manuscript.

David Tremewen: This author contributed to patient recruitment and preparation of manuscript.

Brett Pearce: This author contributed to patient recruitment and preparation of manuscript.

Param Pillai: This author contributed to data collection and preparation of manuscript.

Dharshi Karalipillai: This author contributed to data collection and preparation of manuscript.

Rinaldo Bellomo: This author contributed to study design and preparation of manuscript.

Laurence Weinberg: This author designed the study, contributed to patient recruitment, data collection, data analysis, and preparation of manuscript.

References

1. Brosnan RJ, Steffey EP, LeCouteur RA, Imai A, Farver TB, Kortz GD. Effects of ventilation and isoflurane end-tidal concentration on intracranial and cerebral perfusion pressures in horses. *American journal of veterinary research.* 2003;64(1):21-25.
2. Faraci FM, Breese KR, Heistad DD. Cerebral vasodilation during hypercapnia. Role of glibenclamide-sensitive potassium channels and nitric oxide. *Stroke.* 1994;25(8):1679-1683.
3. Hino JK, Short BL, Rais-Bahrami K, Seale WR. Cerebral blood flow and metabolism during and after prolonged hypercapnia in newborn lambs. *Critical care medicine.* 2000;28(10):3505-3510.
4. Nakahata MDK, Kinoshita MDPDH, Hirano MDY, Kimoto MDY, Iranami MDH, Hatano MDPDY. Mild Hypercapnia Induces Vasodilation via Adenosine Triphosphate-sensitive K+Channels in Parenchymal Microvessels of the Rat Cerebral Cortex. *Anesthesiology.* 2003;99(6):1333-1339.
5. Kaku DA, Giffard RG, Choi DW. Neuroprotective effects of glutamate antagonists and extracellular acidity. *Science (New York, NY).* 1993;260(5113):1516-1518.
6. Vannucci RC, Brucklacher RM, Vannucci SJ. Effect of Carbon Dioxide on Cerebral Metabolism during Hypoxia-Ischemia in the Immature Rat. *Pediatr Res.* 1997;42(1):24-29.
7. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br J Anaesth.* 2009;103 Suppl 1:i3-13.
8. Elizabeth A, Frost M. Cerebral oximetry: emerging applications for an established technology. *Anesthesiol News.* 2012;38:10.
9. Steppan J, Hogue CW, Jr. Cerebral and tissue oximetry. *Best Pract Res Clin Anaesthesiol.* 2014;28(4):429-439.
10. Ahn A, Yang J, Inigo-Santiago L, Parnia S. A feasibility study of cerebral oximetry monitoring during the post-resuscitation period in comatose patients following cardiac arrest. *Resuscitation.* 2014;85(4):522-526.

11. Storm C, Leithner C, Krannich A, et al. Regional cerebral oxygen saturation after cardiac arrest in 60 patients--a prospective outcome study. *Resuscitation.* 2014;85(8):1037-1041.
12. Ito N, Nishiyama K, Callaway CW, et al. Noninvasive regional cerebral oxygen saturation for neurological prognostication of patients with out-of-hospital cardiac arrest: a prospective multicenter observational study. *Resuscitation.* 2014;85(6):778-784.
13. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesthesia and analgesia.* 2007;104(1):51-58.
14. Deschamps A, Hall R, Grocott H, et al. Cerebral Oximetry Monitoring to Maintain Normal Cerebral Oxygen Saturation during High-risk Cardiac Surgery: A Randomized Controlled Feasibility Trial. *Anesthesiology.* 2016;124(4):826-836.
15. Akca O, Liem E, Suleman MI, Doufas AG, Galandiuk S, Sessler DI. Effect of intra-operative end-tidal carbon dioxide partial pressure on tissue oxygenation. *Anaesthesia.* 2003;58(6):536-542.
16. Robinson TN, Eiseman B. Postoperative delirium in the elderly: diagnosis and management. *Clinical Interventions in Aging.* 2008;3(2):351-355.
17. Liu LL, Leung JM. Predicting adverse postoperative outcomes in patients aged 80 years or older. *Journal of the American Geriatrics Society.* 2000;48(4):405-412.
18. Inouye SK. Delirium in older persons. *The New England journal of medicine.* 2006;354(11):1157-1165.
19. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340.
20. Redford D, Paidy S, Kashif F. Absolute and trend accuracy of a new regional oximeter in healthy volunteers during controlled hypoxia. *Anesth Analg.* 2014;119(6):1315-1319.
21. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Annals of internal medicine.* 1990;113(12):941-948.

22. Sharon K, Inouye MD, MPH. Confusion Assessment Method: Training Manual and Coding Guide, Copyright 2003.
23. National Blood Authority. Blood Management Guidelines: Module 2 Perioperative. 2012; http://www.nba.gov.au/guidelines/module2/po-mod2.pdf2.
24. Vretzakis G, Georgopoulou S, Stamoulis K, et al. Cerebral oximetry in cardiac anesthesia. *Journal of thoracic disease.* 2014;6 Suppl 1:S60-69.
25. Lang TA, Altman DG. Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines. *International journal of nursing studies.* 2015;52(1):5-9.
26. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. *Critical care (London, England).* 2010;14(2):220.
27. Yokoyama I, Inoue Y, Kinoshita T, Itoh H, Kanno I, Iida H. Heart and brain circulation and CO2 in healthy men. *Acta physiologica (Oxford, England).* 2008;193(3):303-308.
28. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. *J Physiol.* 2011;589(Pt 12):3039-3048.
29. Giardino ND, Friedman SD, Dager SR. Anxiety, respiration, and cerebral blood flow: implications for functional brain imaging. *Compr Psychiatry.* 2007;48(2):103-112.
30. Vranken NPA, Weerwind PW, Sutedja NA, Severdija EE, Barenbrug PJC, Maessen JG. Cerebral Oximetry and Autoregulation during Cardiopulmonary Bypass: A Review. *The journal of extra-corporeal technology.* 2017;49(3):182-191.
31. Severdija EE, Vranken NP, Simons AP, et al. Hemodilution Combined With Hypercapnia Impairs Cerebral Autoregulation During Normothermic Cardiopulmonary Bypass. *Journal of cardiothoracic and vascular anesthesia.* 2015;29(5):1194-1199.
32. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early cardiac arrest survivors: The impact of hypercapnia. *Resuscitation.* 2016;102:11-16.

33. Murphy GS, Szokol JW, Avram MJ, et al. Effect of ventilation on cerebral oxygenation in patients undergoing surgery in the beach chair position: a randomized controlled trial. *British journal of anaesthesia.* 2014;113(4):618-627.

34. Brian Johnny E, MD. Carbon Dioxide and the Cerebral Circulation *Anesthesiology: The Journal of the American Society of Anesthesiologists.* 1998;88(5):1365-1386.

35. Rogers CA, Stoica S, Ellis L, et al. Randomized trial of near-infrared spectroscopy for personalized optimization of cerebral tissue oxygenation during cardiac surgery. *British journal of anaesthesia.* 2017;119(3):384-393.

36. Trafidlo T, Gaszynski T, Gaszynski W, Nowakowska-Domagala K. Intraoperative monitoring of cerebral NIRS oximetry leads to better postoperative cognitive performance: a pilot study. *International journal of surgery (London, England).* 2015;16(Pt A):23-30.

37. Casati A, Fanelli G, Pietropaoli P, et al. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth Analg.* 2005;101(3):740-747, table of contents.

38. Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger K-U. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. *Critical Care.* 2011;15(5):R218-R218.

39. Finsterer U, Luhr HG, Wirth AE. Effects of acute hypercapnia and hypocapnia on plasma and red cell potassium, blood lactate and base excess in man during anesthesia. *Acta anaesthesiologica Scandinavica.* 1978;22(4):353-366.

40. Adrogue HJ, Madias NE. Changes in plasma potassium concentration during acute acid-base disturbances. *The American journal of medicine.* 1981;71(3):456-467.

41. Natalini G, Seramondi V, Fassini P, et al. Acute respiratory acidosis does not increase plasma potassium in normokalaemic anaesthetized patients. A controlled randomized trial. *European Journal of Anaesthesiology.* 2006;18(6):394-400.

42. Akca O. Pain and Tissue Oxygenation. *Critical care medicine.* 2015;43:e462-463.
43. Hoiseth LO, Hisdal J, Hoff IE, Hagen OA, Landsverk SA, Kirkeboen KA. Tissue oxygen saturation and finger perfusion index in central hypovolemia: influence of pain. *Crit Care Med.* 2015;43(4):747-756.
44. MacLeod DB, Ikeda K, Vacchiano C, Lobbestael A, Wahr JA, Shaw AD. Development and validation of a cerebral oximeter capable of absolute accuracy. *Journal of cardiothoracic and vascular anesthesia.* 2012;26(6):1007-1014.
45. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. *Anesthesiology.* 2000;93(4):947-953.
46. Brady K, Joshi B, Zweifel C, et al. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke.* 2010;41(9):1951-1956.
47. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology.* 2012;116(4):834-840.
48. Akça O, Sessler DI, DeLong D, Keijner R, Ganzel B, Doufas AG. Tissue Oxygenation Response to Mild Hypercapnia during Cardiopulmonary Bypass with Constant Pump Output. *British journal of anaesthesia.* 2006;96(6):708-714.

Figures

Figure 1. CONSORT flow diagram
(Please refer to the attached diagram)

Figure 2. Percentage change in cerebral oximetry from baseline (%ΔrSO_2) over time
(Please refer to the attached diagram)

Figure Captions

Figure 1:

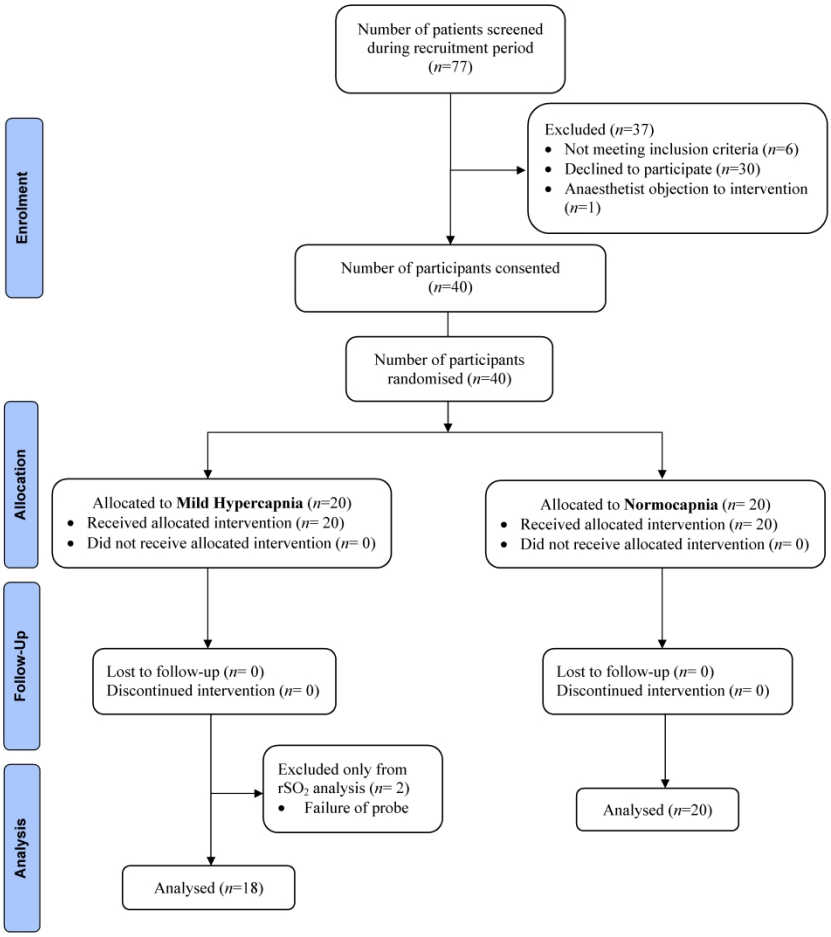
The progress of all participants through the trial displayed by the Consolidated Standards Of Reporting Trials (CONSORT) flow diagram.

Figure 2:

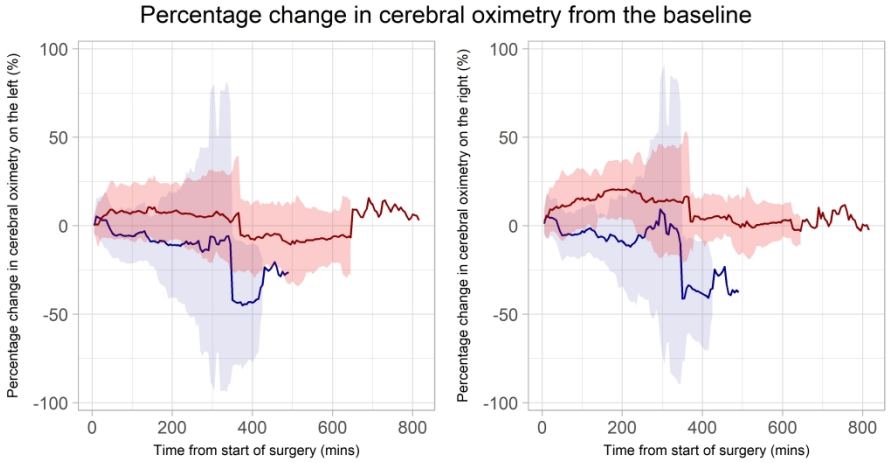
The solid lines represent the mean percentage change; while the shaded areas represent the standard deviation. The targeted mild hypercapnia (TMH) group is represented by the red line and the red area; while the targeted normocapnia (TN) group is represented by the blue line and the blue area.

Left: percentage change of regional cerebral oxygen saturation from the baseline on the left hemisphere

Right: percentage change of regional cerebral oxygen saturation from the baseline on the right hemisphere



The progress of all participants through the trial displayed by the Consolidated Standards Of Reporting Trials (CONSORT) flow diagram.



The solid lines represent the mean percentage change; while the shaded areas represent the standard deviation. The targeted mild hypercapnia (TMH) group is represented by the red line and the red area; while the targeted normocapnia (TN) group is represented by the blue line and the blue area.
Left: percentage change of regional cerebral oxygen saturation from the baseline on the left hemisphere
Right: percentage change of regional cerebral oxygen saturation from the baseline on the right hemisphere

177x93mm (600 x 600 DPI)

Supplementary File 1

```
#-----------------------------------------------------------------------------------------------------------
--
# TITLE: Create oximetry database from raw data files
# Author: Clarence Wong
# Last updated: 2/7/2017
# RStudio v. 1.0.136
#-----------------------------------------------------------------------------------------------------------
--

library(readr)
require(lubridate)
require(TTR)
require(xts)
require(zoo)
library(reshape2)

#-----------------------------------------------------------------------------------------------------------
--
# Read all data files and save as R object
#-----------------------------------------------------------------------------------------------------------
--

master<-0
for (i in 1:8)
{
  file <-
read.csv(paste("D:/SS/R_data/FINAL_oximetry_data/",as.character(i),".csv",sep=""))
  master <- rbind(master,file)
}
master$date_time <- paste(master$Date, master$Time..GMT.)
master$date_time <- mdy_hms(master$date_time)
converted_master <- master[,c(58,3:57)]

save(converted_master,file = "converted_master.RData")

database_times <- read_csv("D:/SS/R_data/database_times.csv")
date_vector <- database_times[,c(1,5,6,7,11,12)]

date_vector$start_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Monitoring Start`))
date_vector$end_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Monitoring End`))
```

```
date_vector$surg_start_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Start Time`))
date_vector$surg_end_date_time <- mdy_hms(paste(date_vector$`Date of
surgery`,date_vector$`Finish Time`))

converted_date_vector <- date_vector[,c(1,7,8,9,10)]

save(converted_date_vector,file = "converted_date_vector.RData")

rm(master,date_vector,file)

#-----------------------------------------------------------------------------------------------------
--
# 1.  Convert data types and locate monitoring periods
# 2.  Identify oximettry values at various time points
# 3.  Compute percentage change from baseline
# 4.  Identify and locate problematic data
#-----------------------------------------------------------------------------------------------------
--

minutes_taken_as_baseline <- 2.5
minutes_interval <- 5

secs_taken_as_baseline <- minutes_taken_as_baseline*60
secs_interval <- minutes_interval*60

load("converted_master.RData")
load("converted_date_vector.RData")
print("data loaded. check data version")

oximetry_L <-
as.numeric(levels(converted_master$RSO2_A1)[converted_master$RSO2_A1])
oximetry_R <-
as.numeric(levels(converted_master$RSO2_A2)[converted_master$RSO2_A2])
PSI <- as.numeric(levels(converted_master$PSI)[converted_master$PSI])

# monitoring duration
duration_mins <-
difftime(converted_date_vector$end_date_time,converted_date_vector$start_date_time,uni
ts = "mins")
duration_secs <-
difftime(converted_date_vector$end_date_time,converted_date_vector$start_date_time,uni
ts = "secs")

locate_start = seq(-1,-1,length.out = dim(converted_date_vector)[1])
```

```
for (i in 1:dim(converted_date_vector)[1]){
if(length(which(converted_date_vector$start_date_time[i]==converted_master$date_time))
==1)
  {
    locate_start[i] <-
which(converted_date_vector$start_date_time[i]==converted_master$date_time)
  }
}

# create final_oximetry data frame
final_oximetry <- data.frame()
baseline_L_mu<-baseline_L_std<-baseline_L_N<-baseline_R_mu<-baseline_R_std<-
baseline_R_N<-rep(9999,dim(converted_date_vector)[1])
num_time_pts <- rep(1,40)

for(j in 1:dim(converted_date_vector)[1])
{
  # for each patient
  if(locate_start[j]==-1)
  {
    p_id <- j
    time_id<-minute_from_baseline<-percentage_total_monitoring_period<-L_delta<-
L_mu<-L_sig<-L_N<-R_delta<-R_mu<-R_sig<-R_N<-PSI_mu<-9999

  } else{

    locate_baseline <- locate_start[j]+secs_taken_as_baseline/2
    locate_times <- seq(0,0)
    num_measurements <- (as.numeric(duration_secs)[j]-
secs_taken_as_baseline)%/%secs_interval +1
    num_time_pts[j] <- num_measurements
    locate_times[1] <- locate_baseline
    locate_times[2] <- locate_times[1] + secs_interval/2
    locate_times[2:num_measurements]<-
seq(locate_times[2],locate_start[j]+as.numeric(duration_secs[j])/2,by=secs_interval/2)
    locate_times[num_measurements+1]<-locate_start[j]+as.numeric(duration_secs[j])/2

    baseline_L_mu[j] <- mean(oximetry_L[locate_start[j]:(locate_baseline-1)],na.rm =
TRUE)
    baseline_L_std[j] <- sd(oximetry_L[locate_start[j]:(locate_baseline-1)],na.rm = TRUE)
    baseline_L_N[j] <- length(oximetry_L[locate_start[j]:(locate_baseline-1)])-
sum(is.na(oximetry_L[locate_start[j]:(locate_baseline-1)]))
```

```
   baseline_R_mu[j] <- mean(oximetry_R[locate_start[j]:(locate_baseline-1)],na.rm =
TRUE)
   baseline_R_std[j] <- sd(oximetry_R[locate_start[j]:(locate_baseline-1)],na.rm = TRUE)
   baseline_R_N[j] <- length(oximetry_R[locate_start[j]:(locate_baseline-1)])-
sum(is.na(oximetry_R[locate_start[j]:(locate_baseline-1)]))

   L_delta <- L_mu <- L_sig <- L_N <- R_delta <- R_mu <- R_sig <- R_N <- PSI_mu <-
seq(0,0)

   for (k in 1:num_measurements)
   {
    L_mu[k] <- mean(oximetry_L[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    L_sig[k] <- sd(oximetry_L[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    L_N[k] <- length(oximetry_L[locate_times[k]:(locate_times[k+1]-1)])-
sum(is.na(oximetry_L[locate_times[k]:(locate_times[k+1]-1)]))

    R_mu[k] <- mean(oximetry_R[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    R_sig[k] <- sd(oximetry_R[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
    R_N[k] <- length(oximetry_R[locate_times[k]:(locate_times[k+1]-1)])-
sum(is.na(oximetry_R[locate_times[k]:(locate_times[k+1]-1)]))

    PSI_mu[k] <- mean(PSI[locate_times[k]:(locate_times[k+1]-1)],na.rm = TRUE)
   }

   L_delta <- (L_mu/baseline_L_mu[j] -1)*100
   R_delta <- (R_mu/baseline_R_mu[j] -1)*100

   time_id <- 1:num_measurements
   minute_from_baseline <- c(seq(minutes_interval,minutes_interval*(num_measurements-
1), by = minutes_interval),as.numeric(duration_mins[j]-minutes_taken_as_baseline))
   p_id <- rep(j,num_measurements)
   percentage_total_monitoring_period <-
((minute_from_baseline*60+secs_taken_as_baseline)/as.numeric(duration_secs[j]))*100

  }

  temp_df <-
data.frame(p_id,time_id,minute_from_baseline,percentage_total_monitoring_period,L_delt
a,L_mu,L_sig,L_N,R_delta,R_mu,R_sig,R_N,PSI_mu)
  final_oximetry <- rbind(final_oximetry,temp_df)
  rm(temp_df)

}

missing_L <- unique(final_oximetry$p_id[is.na(final_oximetry$L_delta)])
```

```
missing_R <- unique(final_oximetry$p_id[is.na(final_oximetry$R_delta)])
percentage_total_missing_L <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$L_delta)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$L_delta)])])
percentage_total_missing_R <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$R_delta)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$R_delta)])])
missing_data <- unique(final_oximetry$p_id[(final_oximetry$L_delta==9999)])
missing_data <- missing_data[!is.na(missing_data)]
missing_PSI <- unique(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])
percentage_total_missing_PSI <-
100*(rle(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])$lengths) /
(num_time_pts[unique(final_oximetry$p_id[is.na(final_oximetry$PSI_mu)])])

print("there are missing delta oximetry values in the following patients")
print(missing_L)
print(percentage_total_missing_L)

print(missing_R)
print(percentage_total_missing_R)

print(missing_data)

print("there are missing PSI values in the following patients")
print(missing_PSI)
print(percentage_total_missing_PSI)

other_data <-
data.frame(num_time_pts,baseline_L_mu,baseline_L_std,baseline_L_N,baseline_R_mu,
baseline_R_std,baseline_R_N)
other_data[is.na(other_data)]<-9999
save(other_data, file="other_data.RData")

final_oximetry[is.na(final_oximetry)]<-9999
save(final_oximetry,file = "final_oximetry.RData")


#-----------------------------------------------------------------------------------------------------------
--
# 1.  Convert baseline characteristic database from wide to long format
# 2.  Incorporating oximetry data in the database with time as a nested data in the hierarchy
# 3.  Create final database
#-----------------------------------------------------------------------------------------------------------
--
```

```
load("final_oximetry.RData")
load("other_data.RData")
print("check if final oximetry is latest")

baseline_results <- read.csv("D:/SS/R_data/FINAL_oximetry_data/all_baseline.csv",
sep=",", stringsAsFactors=FALSE)

baseline_results$baseline_L_mu <- other_data$baseline_L_mu
baseline_results$baseline_L_std <- other_data$baseline_L_std
baseline_results$baseline_L_N <- other_data$baseline_L_N
baseline_results$baseline_R_mu <- other_data$baseline_R_mu
baseline_results$baseline_R_std <- other_data$baseline_R_std
baseline_results$baseline_R_N <- other_data$baseline_R_N

baseline_results$P_id <- index(baseline_results)

baseline_results[baseline_results == "#N/A"]<-9999

#generate baseline_results with the same number of rows as final oximetry
baseline_results <- baseline_results[rep(seq_len((40)),num_time_pts),]


all_results <- cbind(baseline_results,final_oximetry)
if (sum(1*(all_results$P_id != all_results$p_id))==0)
{
  all_results <- all_results[,c(which(colnames(all_results)=="p_id"),1:109,112:122)]
}

save(all_results,file = "all_results.RData")

#UNCOMMENT TO WRITE CSV
#-------------------------------------------------
write.csv(all_results, file="all_results.csv")
```

Supplementary File 2

```
#-------------------------------------------------------------------------------------------------------
-------
# TITLE: Create baseline patient and surgical characteristics table, oximetry table, and
oximetry graphs
# Author: Clarence Wong
# Last updated: 2/7/2017
# RStudio v. 1.0.136
#-------------------------------------------------------------------------------------------------------
-------

library(readr)
require(lubridate)
require(TTR)
require(xts)
require(zoo)
require(tableone)
require(ggplot2)
library(grid)
require(gridExtra)
require(quantreg)

#-------------------------------------------------------------------------------------------------------
-------
# 1.  Create summary statistics for baseline characteristics
# 2.  Perform statistical analysis on secondary outcomes. e.g post-operative delirium
# 3.  Export tables in csv files
# Requires baseline characteristic and baseline oximetry data.
#-------------------------------------------------------------------------------------------------------
-------

baseline_db <- read.csv("D:/SS/R_data/baseline/all_baseline.csv", sep=",",
stringsAsFactors=TRUE)
load("other_data.RData")

other_data <- other_data[-c(1,2),]

baseline_db$baseline_L_mu <- other_data$baseline_L_mu
baseline_db$baseline_L_std <- other_data$baseline_L_std
baseline_db$baseline_L_N <- other_data$baseline_L_N
baseline_db$baseline_R_mu <- other_data$baseline_R_mu
baseline_db$baseline_R_std <- other_data$baseline_R_std
baseline_db$baseline_R_N <- other_data$baseline_R_N

baseline_db$P_id <- index(baseline_db)
```

```
baseline_db[baseline_db == "#N/A"]<-NA
baseline_db[baseline_db == 9999]<-NA
baseline_db$pCO2_2<-
as.numeric(levels(baseline_db$pCO2_2))[baseline_db$pCO2_2]
baseline_db$BMI<-as.numeric(levels(baseline_db$BMI))[baseline_db$BMI]
vars <-
c("Gender","Age","Weight","BMI","ASA","Diabetes","COPD","Maligancy","Other_C
omorbidities",

"Surgery_type","Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu")
factorVars <- c("ASA","Diabetes","COPD","Maligancy","Other_Comorbidities")
Tableone <- CreateTableOne(vars,"Group",baseline_db,factorVars)


baseline_db$LOS<-as.numeric(levels(baseline_db$LOS))[baseline_db$LOS]
baseline_db$pH_2<-as.numeric(levels(baseline_db$pH_2))[baseline_db$pH_2]
baseline_db$HCO3._2<-
as.numeric(levels(baseline_db$HCO3._2))[baseline_db$HCO3._2]
baseline_db$Base_excess_2<-
as.numeric(levels(baseline_db$Base_excess_2))[baseline_db$Base_excess_2]
baseline_db$Potassium_2<-
as.numeric(levels(baseline_db$Potassium_2))[baseline_db$Potassium_2]
baseline_db$Total_Hb_2<-
as.numeric(levels(baseline_db$Total_Hb_2))[baseline_db$Total_Hb_2]

baseline_db$pH<-apply(baseline_db[,c("pH_1","pH_2")],1,mean,na.rm=TRUE)
baseline_db$pCO2<-
apply(baseline_db[,c("pCO2_1","pCO2_2")],1,mean,na.rm=TRUE)
baseline_db$HCO3.<-
apply(baseline_db[,c("HCO3._1","HCO3._2")],1,mean,na.rm=TRUE)
baseline_db$Base_excess<-
apply(baseline_db[,c("Base_excess_1","Base_excess_2")],1,mean,na.rm=TRUE)
baseline_db$Potassium<-
apply(baseline_db[,c("Potassium_1","Potassium_2")],1,mean,na.rm=TRUE)
baseline_db$Total_Hb<-
apply(baseline_db[,c("Total_Hb_1","Total_Hb_2")],1,mean,na.rm=TRUE)

vars_2 <-
c("Surgery_type","Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu","L
OS",

"pH","pCO2","HCO3.","Base_excess","Potassium","Total_Hb","post_op_delirium")
factorVars_2 <- c("post_op_delirium")
Tabletwo <- CreateTableOne(vars_2,"Group",baseline_db,factorVars_2,argsExact =
"post_op_delirium")

print(Tabletwo,exact = "post_op_delirium",nonnormal =
c("Duration_Surgery_Minutes","baseline_L_mu","baseline_R_mu",
```

```
"LOS","pH","pCO2","HCO3.","Base_excess","Potassium","Total_Hb"))


write.csv(print(Tabletwo,exact = "post_op_delirium",nonnormal =
c("Duration_Surgery_Minutes","baseline_L_mu",

"baseline_R_mu","LOS","pH","pCO2","HCO3.",
                                                    "Base_excess","Potassium","Total_Hb")),
"Table_Two.csv")

#-----------------------------------------------------------------------------------------------------
-------
# 1.  Create summary statistics for percentage change of regional cerebral oxygen
saturation
# 2.  Create plots for regional cerebral oxygen saturation over time
# 3.  Export oximetry tables in csv files
# Requires baseline characteristic and baseline oximetry data.
#-----------------------------------------------------------------------------------------------------
-------

#-----------------------------------------------------------------------------------------------------
-------
# Normocapnic group

plot_db <- read.csv("D:/SS/R_data/oximetry/MASTER_results_deleted_missing.csv",
sep=",", stringsAsFactors=TRUE)

plot_db[plot_db == "#N/A"]<-NA
plot_db[plot_db == 9999]<-NA

normocapnia <- subset(plot_db, Group %in% 0)
hypercapnia <- subset(plot_db, Group %in% 1)

normo_plot <- ggplot(normocapnia, aes(x=minute_from_baseline, y=L_delta,
group=p_id)) + geom_line() +geom_point()+
  ggtitle("normocapnia: L delta")+ xlab("Time since start of operation (mins)")+
ylab("% change in oximetry from baseline")

hyper_plot <- ggplot(hypercapnia, aes(x=minute_from_baseline, y=L_delta,
group=p_id)) + geom_line() +geom_point()+
  ggtitle("hypercapnia: L delta")+ xlab("Time since start of operation (mins)")+ ylab("%
change in oximetry from baseline")

means <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x) sd(x, na.rm =
TRUE))
```

```
N <- tapply(normocapnia$L_delta,normocapnia$time_id,function(x)
length(x[!is.na(x)]))

normo_df_L <- data.frame(means,stdevs)
times<- index(normo_df_L)*5
normo_df_L <- data.frame(means,stdevs,N, times)
total_normo_L <- ggplot(normo_df_L, aes(x=times, y=means)) +
geom_line(colour="blue4") +
  geom_ribbon(normo_df_L,mapping = aes(x=times,
ymax=means+stdevs,ymin=means-stdevs),fill="blue4",alpha=0.1)

means <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x) mean(x,
na.rm = TRUE))
stdevs <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(normocapnia$R_delta,normocapnia$time_id,function(x)
length(x[!is.na(x)]))

normo_df_R <- data.frame(means,stdevs)
times<- index(normo_df_R)*5
normo_df_R <- data.frame(means,stdevs,N, times)
total_normo_R <- ggplot(normo_df_R, aes(x=times, y=means)) +
geom_line(colour="blue4") +
  geom_ribbon(normo_df_R,mapping = aes(x=times,
ymax=means+stdevs,ymin=means-stdevs),fill="blue4",alpha=0.1)

#-----------------------------------------------------------------------------------------------
-------
# Hypercapnic group

means <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(hypercapnia$L_delta,hypercapnia$time_id,function(x) length(x[!is.na(x)]))

hyper_df_L <- data.frame(means,stdevs)
times<- index(hyper_df_L)*5
hyper_df_L <- data.frame(means,stdevs,N, times)
total_hyper_L <- ggplot(hyper_df_L, aes(x=times, y=means))

means <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) mean(x, na.rm
= TRUE))
stdevs <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) sd(x, na.rm =
TRUE))
N <- tapply(hypercapnia$R_delta,hypercapnia$time_id,function(x) length(x[!is.na(x)]))

hyper_df_R <- data.frame(means,stdevs)
```

```
times<- index(hyper_df_R)*5
hyper_df_R <- data.frame(means,stdevs,N, times)
total_hyper_R <- ggplot(hyper_df_R, aes(x=times, y=means))

total_L <- total_normo_L +
  geom_ribbon(hyper_df_L,mapping = aes(x=times, ymax=means+stdevs,ymin=means-
stdevs),fill="red2",alpha=0.2) +
  geom_line(hyper_df_L,mapping = aes(x=times, y=means),colour="red4") +
  theme_light() +
  xlab("Time since start of surgery (mins)")+ ylab("Average % change in cerebral
oximetry on the left") +
  theme(axis.title.y = element_text(size = rel(0.65), angle = 90)) +
  theme(axis.title.x = element_text(size = rel(0.65), angle = 00))

total_R <- total_normo_R +
  geom_ribbon(hyper_df_R,mapping = aes(x=times, ymax=means+stdevs,ymin=means-
stdevs),fill="red2",alpha=0.2) +
  geom_line(hyper_df_R,mapping = aes(x=times, y=means),colour="red4")+
  theme_light() +
  xlab("Time since start of surgery (mins)")+ ylab("Average % change in cerebral
oximetry on the right") +
  scale_color_manual(values=c("red4","blue4"))+
  theme(axis.title.y = element_text(size = rel(0.65), angle = 90)) +
  theme(axis.title.x = element_text(size = rel(0.65), angle = 00))

#tiff('oximetry_graph_high_res.tiff', units="in", width=7, height=3.6667, res=600,
compression = 'lzw')

grid.arrange(total_L, total_R, ncol = 2, top=textGrob("Percentage change in cerebral
oximetry from baseline",
                                        gp=gpar(fontsize=11,fontfamily="Times")),
          vp=viewport(width=0.9, height=0.9))

#insert ggplot code
#dev.off()

temp_hyper_L <- t(paste(round(hyper_df_L$mean,1)," (",
round(hyper_df_L$stdev,1),")"," {", hyper_df_L$N,"}", sep = ""))
temp_normo_L <- t(paste(round(normo_df_L$mean,1)," (",
round(normo_df_L$stdev,1),")"," {", normo_df_L$N,"}", sep = ""))

temp_hyper_R <- t(paste(round(hyper_df_R$mean,1)," (",
round(hyper_df_R$stdev,1),")"," {", hyper_df_R$N,"}", sep = ""))
temp_normo_R <- t(paste(round(normo_df_R$mean,1)," (",
round(normo_df_R$stdev,1),")"," {", normo_df_R$N,"}", sep = ""))

write.csv( temp_normo_L , "normo_df_L.csv")
write.csv( temp_normo_R , "normo_df_R.csv")
```

```
write.csv( temp_hyper_L , "hyper_df_L.csv")
write.csv( temp_hyper_R , "hyper_df_R.csv")
```

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6-7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6-7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	9
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12-13
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14,16,17
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	14
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	21
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	22-23
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	21-22
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19-21
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	4

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.