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SOUTH AFRICAN
EXCERPTS EDITION

Volume 12 Number 3 2012

- Status of national guidelines in dictating individual clinical practice and defining negligence
- High STOP-Bang score indicates a high probability of obstructive sleep apnoea
- Impact of phenylephrine administration on cerebral tissue oxygen saturation and blood volume is modulated by carbon dioxide in anaesthetized patients

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References: 1. Dhillon S. Tramadol/paracetamol fixed-dose combination. *Clin Drug Investig* 2010;30(10):711-738. **2.** Jurnista® package insert. October 2011. **3.** Gupta S, Sathyan G. Providing constant analgesia with OROS® hydromorphone. *Journal of Pain and Symptom Management* 2007;33(25):S19-S24. **4.** Hale M, Tudor IC, Khanna S *et al.* Efficacy and tolerability of once-daily OROS® hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: results of a 6-week, randomized, open-label, non-inferiority analysis. *Clinical Therapeutic* 2007;29(5):874-888. **5.** Turgeon J, Gröning R, Sathyan G, *et al.* The pharmacokinetics of a long-acting OROS hydromorphone formulation. *Expert Opinion Drug Delivery* 2010;7(1):137-144. **6.** Drover DR, Angst MS, Valle M, *et al.* Input characteristics and bioavailability after administration of immediate and a new extended-release formulation of hydromorphone in healthy volunteers. *Anesthesiology* 2002; 97(4):827-836. **7.** Durogesic® package insert. April 2011. **8.** Kornick CA, Santiago-Palma J, Moryl N, *et al.* Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. *Drug Safety* 2003;26(13):951-973.

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Reni Rouncivell
Tel: (012) 661 3294 / Fax: 086 561 5122
Cell: 082 441 6904
reni@medspec.co.za

Advertising
Lelani Adendorff
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Guest Comment

Prof Mike James, the editor of this Journal has requested that I write the editorial while he is undergoing his medical therapy. I am joined by the entire readership of the Journal and all the members of the South African Society of Anaesthesiologists in wishing him well and we trust that he will make a speedy recovery.

We are all aware of the emergency situation where rapid sequence intubation is mandatory. We are equally aware that even with the best intention that we may encounter a situation where intubation becomes impossible. All anaesthesiologists are familiar with succinylcholine and all are aware of its advantages and disadvantages. Many studies have been performed to try and obtain the same ideal intubating conditions as those obtained when using succinylcholine. Using other agents including vecuronium and rocuronium, we were not able to obtain complete paralysis in the same time as that obtained using succinylcholine. Furthermore, should intubation not have been possible then we had the problem of a paralysed patient with no airway control. The consequences of such a set of circumstances could prove fatal.

We in South Africa do not yet have sugammadex available. The question that is being asked is whether reversal of non-depolarising neuromuscular blocking agents can be rapidly reversed by sugammadex during a rapid sequence induction when intubation proves difficult. This exact question has been examined by Sorensen et al. It would appear that time to reestablishment of spontaneous ventilation is longer when succinylcholine is used than when the rocuronium-sugammadex combination was used. We should note that no mention is made of intubation conditions when the rocuronium was used but we know that they will not be as good as the neuromuscular blockade obtained when using succinylcholine.

Another topic of great interest is the period of starvation for infants prior to induction of anaesthesia. It is fairly well accepted that clear fluid can be given to children up to two hours prior to anaesthetic induction for elective surgery. Exactly how much fluid remains a subject of debate. We also know that sugared clear fluid is being used both as a pacifying agent and to prevent hypoglycaemic episodes. The questions arise as to how much fluid may we give and when should this fluid be given. A Schmitz et al have attempted to determine the effects of different volumes of sugared fluid on gastric emptying and residual volumes in children. The study allowed for fluid to be administered one hour prior to induction. We should note that the gastric emptying rate was similar for the different ingested volumes. Equally notable is the fact that residual gastric volumes were significantly less when 3 mg/kg of fluid was given when compared with 7mg/kg. This is a small study and the subjects were children of school-going age as cooperation of the children was required for the MRI studies. The results are not necessarily extrapolatable to neonates and small infants.

Finally we should take note of the editorial by Fearnley, Bell, and Bodenham. They, using case reports, highlight the potential problems of our dependence on guidelines for practice. Many of these guidelines are not applicable to medical practitioners around the world as they are "created" for specific health care systems and specific countries. These guidelines do not consider specific clinical situations that we may encounter in our everyday practice of anaesthesia in South Africa. Our patients demand that we do what is best for them and not necessarily what some foreign guideline demands. Failure to comply with some of these guidelines would not be deemed as negligent practice in South Africa.

Dr. Milton Raff
BSc (WITS), MBChB (Pret), FFA (SA)

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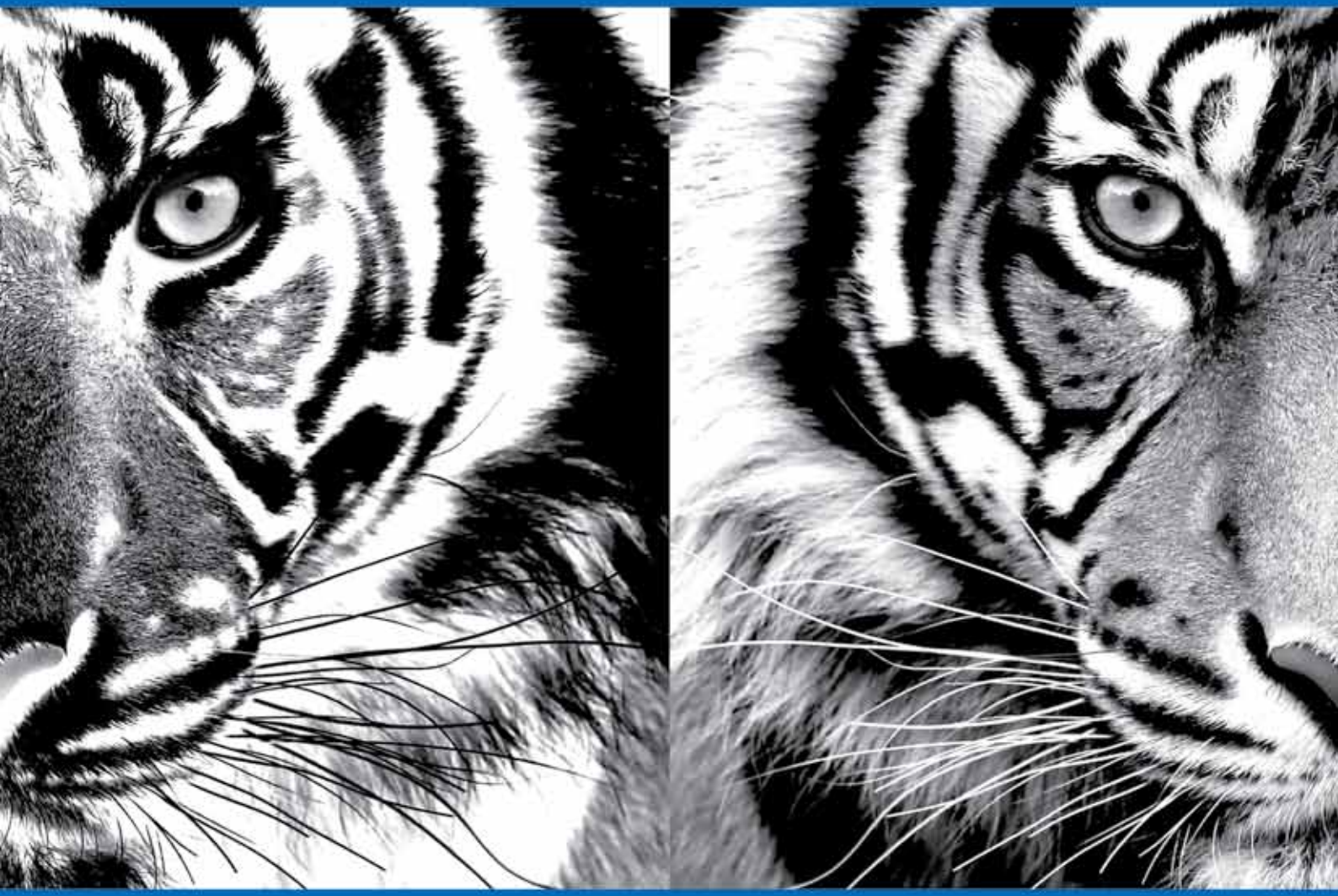

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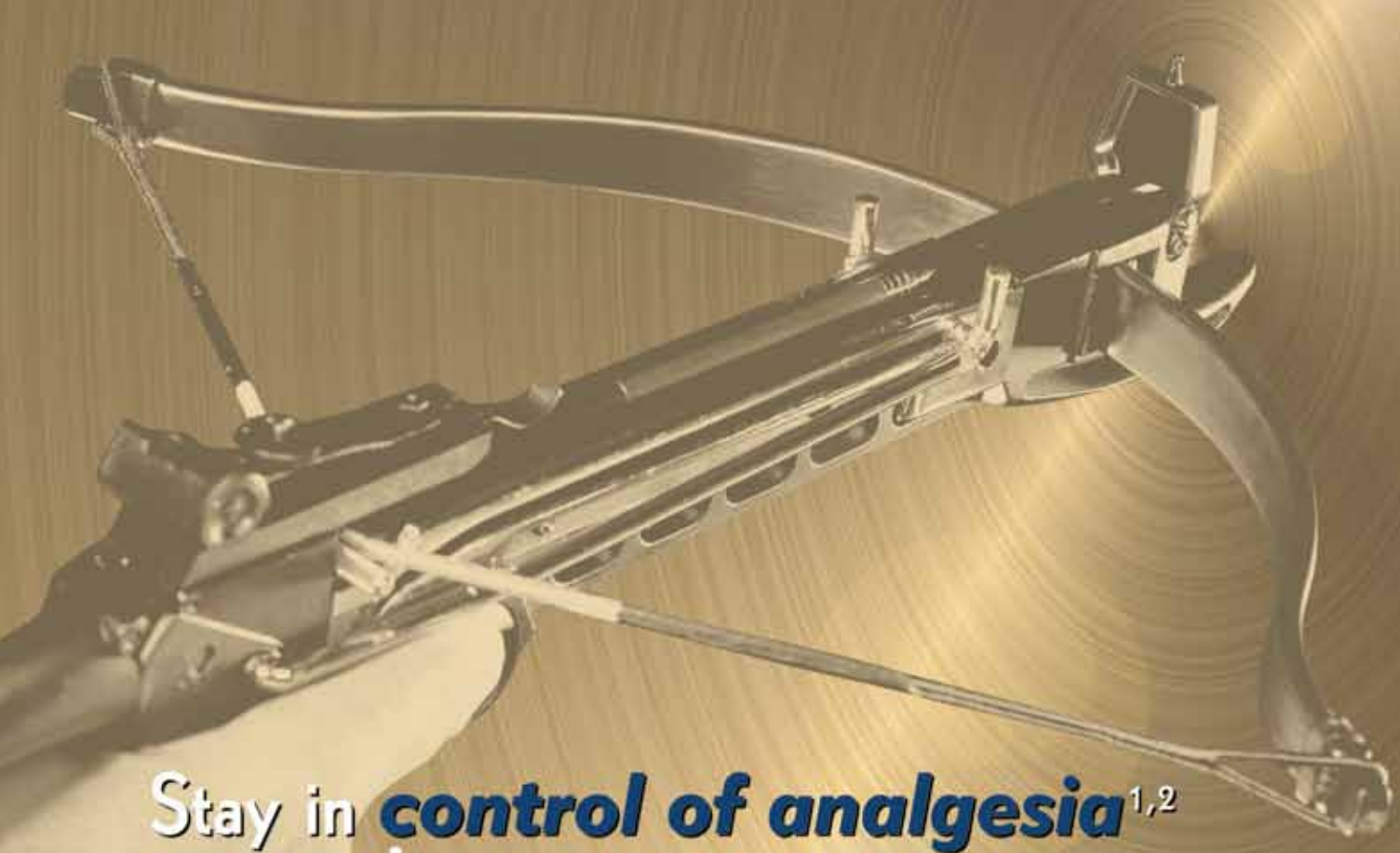

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EDITORIAL

Status of national guidelines in dictating individual clinical practice and defining negligence

R. A. Fearnley[1], M. D. D. Bell[2] and A. R. Bodenham[2]*

[1] Department of Anaesthesia, Kings College Hospital, London, UK
[2] Department of Anaesthesia, The General Infirmary, Leeds LS1 3EX, UK

* E-mail: andy.bodenham@leedsth.nhs.uk

With a major emphasis on patient safety, clinical practice is increasingly undertaken in a setting of guidelines from a range of advisory and regulatory bodies. Concerns remain about the survival of clinical discretion in the face of such directives, with uncertainty as to their validity and authority, and reservations as to potential adverse consequences. The role of such guidelines in defining negligence is also unclear, and it is this element which provides the trigger for this commentary.

To illustrate this conflict between clinical practice and guidelines, we report the case of a complication of central venous catheterization using a landmark-based technique. This incident occurred 2 yr after the publication of NICE guidance recommending the routine use of ultrasound for this procedure.[1] This rare complication of vascular access resulted in a civil claim, raising important questions on the status of national guidelines in defining medical negligence.

In 2004, a 42-yr-old female was listed for breast reconstruction surgery. At preoperative anaesthetic assessment, the patient was informed of an indication for central venous access and the risk of pneumothorax was both discussed and documented. After induction of general anaesthesia, catheterization of the right internal jugular vein was attempted using a landmark approach, by a consultant anaesthetist who documented that the internal carotid artery was hit on the first pass of the 18 G introducer needle. No additional instrumentation was performed and direct pressure was applied over the insertion site for 10 min. Surgery and anaesthesia continued uneventfully and no immediate postoperative complications were noted. The patient made an unremarkable early recovery and was discharged home a week later.

Six weeks after surgery, the patient attended for routine follow-up and complained of tinnitus in her right ear and a persistent headache. She later developed a sensation of blood rushing in both ears and a neurology review some 5 months after surgery revealed a loud bruit and palpable thrill at the base of her neck. Cerebral angiography demonstrated a fistula between the vertebral artery and internal jugular vein, involving the cervico-vertebral venous plexus. A small left occipital infarct was seen on brain computed tomography, which was considered likely to be related to the fistula, even though it was on the contralateral side.

An interventional radiology opinion was sought and the patient underwent successful vertebral artery stent occlusion of the fistula under local anaesthesia.[2] The patient was left with a small visual field defect but all other symptoms resolved. Months later, a claim for damages was issued and expert medical opinions were commissioned both for the Claimant and defending hospital. None of the authors of this publication was involved with the original clinical procedure, although one (A.R.B.) assisted with the hospital's internal investigation.

Legal claims: breaching the medical duty of care, establishing harm, and establishing causation

Establishing medical negligence and successful litigation requires that three key criteria should be satisfied.

The Claimant must first be owed a duty of care, established whenever a patient undergoes treatment, and rarely contested. Secondly, a breach of that duty of care by a failure to provide a required standard of medical care must be established. Thirdly, as a direct result of that breach, the Claimant must have suffered physical or psychological harm, or other tangible losses.

Principal arguments for the Claimant

Causation

The Claimant pointed out that there was a clear temporal relationship between the development of the symptoms and needle placement in an artery in the neck. There were no other plausible causes for the arterio-venous fistula, which is a rare but recognized complication of such procedures.[3] It was argued that had ultrasound guidance been used, then on the balance of probabilities, the arterial puncture and its sequelae would have been avoided.

Breach of duty

The Claimant stated that the attending anaesthetist should have utilized ultrasound guidance to ensure first-pass needle insertion into the jugular vein, while avoiding damage to vulnerable adjacent structures. Such practice should, it was argued, have followed the UK (2002) NICE national guidance recommending the routine use of ultrasound guidance for internal jugular catheterization. As the procedure in question took place some 2 yr after release of this guideline, the Claimant argued that such techniques should have been in routine use in a major teaching centre by this time. There were delays in recognizing the diagnosis at surgical follow-up, but this was not pursued by the Claimant's legal team. The issue of the patient not being consented to the possible risk of vascular injury during attempted central venous cannulation was also not specifically raised by the Claimant.

Arguments by the defending hospital

Causation

This was not disputed by the defending hospital.

Breach of duty

The Defence contested breach of duty. It argued that while NICE guidelines had indeed been published 2 yr before the incident, and implementation of such guidance is supposed to be in place within 3 months of publication, the clinical reality was much more complex. The anaesthetist's chosen approach was a recognized technique, the one he was most familiar with and therefore the technique that would be expected to minimize the risk of harm to the patient. His practice was also in keeping with a significant number of anaesthetists at the time of the event[4] and thus, it was argued, did not constitute a breach of duty.

Consent

It was argued that the rarity of this particular complication meant that it could not have been reasonably anticipated and it was correspondingly reasonable not to list it during the consent process.

An invitation to pass judgement

At this juncture, we invite the reader to consider the legal arguments made above and come to a conclusion as to which opinion they would adopt if invited as an expert witness or whom they would find in favour of were they to be passing judgement. As an additional point of interest, the authors also invite the reader to consider whether their position would differ if the incident had occurred in 2011 rather than 2004.

Legal aspects of the Defence: the Bolam principle and beyond

The Defence of this case is grounded primarily upon the enduring Bolam principle whereby the doctor is not liable for his diagnosis, treatment, or refusal to give information to the patient, if he follows a responsible body of medical opinion.[5] The actions of the anaesthetist were correspondingly defended on the grounds that his practice was in keeping with that of a large number of UK anaesthetists at the time of the incident, and this had not hitherto been legally or otherwise defined as 'irresponsible'. Practical reasons for a widespread failure to implement and follow NICE guidance at the time of the event were also voiced by the defence team.

Modification of the Bolam principle by the case of *Bolitho* is however an important consideration as opinion within that judgement demonstrates; 'it is not enough for a defendant to call a number of doctors to say that what he had done or not done was in accord with accepted clinical practice ... The court must be vigilant to see whether the reasons given for putting a patient at risk are valid ... or whether they stem from a residual adherence to out of date ideas'.[6] Given that percutaneous central venous cannulation may be associated with mechanical complications in up to 5–19% of the patients and accurate needle tip guidance with real-time two-dimensional ultrasound should theoretically make the complication seen in this case entirely avoidable, legal deliberations would focus on whether a failure to use ultrasound places patients at unnecessary risk. To quote Justice Reynolds in the case of *Albrighton v Royal Alfred Hospital*; 'It is not the law that if all or most of the medical practitioners in Sydney habitually fail to take an available precaution to avoid foreseeable risk of injury to the patients that none can be found guilty of negligence'.[7] Such deliberations would of course be made more convoluted were attempts to follow an ultrasound-guided technique to result in injury if concerns existed about the adequacy of training in this technique.[8] Rather than simplistically applying the Bolam principle therefore, it is likely that the Courts will seek to interpret and appraise the authority and

applicability of newly issued guidelines in the context of current practice as described by expert witnesses, an additional variable expanded upon below. Should discrepancies exist between what was done and what could or should have been done, practitioners can anticipate that the Court would predictably align itself with a clinical approach that minimizes the risk of patient harm.

Additional points of reference for assessing medical competence, performance, and conduct

While the Bolam principle remains a benchmark for the Courts, it is important to acknowledge that as clinical practice within anaesthesia changes over time, the threshold for 'acceptable clinical practice' will continue to evolve. Given such evolution, establishing 'acceptable practice' in all but the most extreme cases may be challenging, lengthy, and destructive for both Claimant and Defendant. Additional points of reference for the more equivocal cases may be sought from the various regulatory and professional bodies established to promote patient safety and maintain professional standards within anaesthesia and critical care. Despite the responsibilities of the Royal College of Anaesthetists, the Association of Anaesthetists of Great Britain and Ireland, the National Institute for Health and Clinical Excellence, the National Patient Safety Agency, or any of the innumerable societies associated with specialist areas of anaesthesia, the professional standards set out by such bodies through the publication of guidelines are in the main not comprehensive, unambiguous, or prescriptive. Even the application of the fundamental principles underlying *good medical practice* and expected of any doctor registered with the General Medical Council demands only that the standard of care and practice should be 'good' rather than of the 'highest' standard.[9] It is seen therefore that reference to such professional standards may not unequivocally establish whether the care provided by a practitioner was merely suboptimal or whether it had fallen below a reasonable or acceptable standard. It is because of this equivocation that the processing of a negligence claim is predominantly opinion-based and thus, predictably adversarial, protracted, and expensive. In relation to that opinion, it has to be acknowledged that a partisan approach by expert witnesses can contribute to those negative sequelae, and despite recent publicity as to the emerging accountability expected of experts,[10] it is predictable that without more stringent scrutiny of this aspect of professional activity, the spectrum of 'conduct, competence, and performance' in this field will compromise both the pursuit of justice and endorsement of improved standards of care. We raise the question as to whether the absence of truly prescriptive guidance from professional bodies concerning some key areas of practice, such as the use of ultrasound guidance for central venous cannulation, is an acceptable situation or whether this perpetuates the scenario described above and represents a systemic failure to maximize patient safety according to the current levels of evidence.

Implementing guidelines: time, training, funding, and other obstacles

The defending Trust in this particular case highlighted a number of practical obstructions to the timely implementation of the NICE Guidance. The assertion that novel therapies or guidelines cannot be implemented immediately was first given legal significance in the case of *Crawford v Board of Governors of Charing Cross Hospital* where the presiding Lord Justice Denning stated: 'it would be quite wrong to suggest that the medical man is negligent because he does not at once put into operation the suggestion that some contributor or other might make in a medical journal'.[11] The case before Lord Justice Denning was by no means identical to the case that we are considering but the concept of new ideas, evidence, or guidance requiring a period of time for dissemination and integration into clinical practice is an important one. In the UK, the NHS has been directed by the Secretary of State to provide funding and resources to facilitate the implementation of guidance issued by NICE, through its Technology Appraisal Programme. The recommendation is that this should occur within 3 months of the publication of such guidance. Extensions to this may be granted by the Secretary of State on advice from NICE but to date this has only occurred in relation to about 10% of the technology appraisals issued.[12] The reality is that funding to allow acquisition of new equipment and staff training must be obtained through savings elsewhere. The need for structured training and assessment of personnel involved in the use of new technology is clearly an additional obstacle to rapid implementation. This final point is deserving of slightly closer attention and is clearly more applicable to some forms of technology than others. The learning curve and operator dependence in the use of pulse oximetry or end-tidal CO_2 monitoring is much less than that associated with the use of ultrasound for vascular access procedures or the performance of nerve blockade. While logically much greater time and expense would be required to achieve competency in the latter, acknowledgement of the huge differences in training required to deploy different forms of technology and subsequent allowances of increased time for institutions to get 'up to speed' seems to be lacking. But how much delay is acceptable? It is difficult to be authoritative as the concept of significantly delayed implementation of guidance is not new within the NHS. Three years after the death of a young girl in the Accident and Emergency Department of a London Hospital in 2000 from a hypoxic gas mixture, a survey identified 25 Trusts that were still using anaesthetic machines that were non-compliant with the relevant Patient Safety Alert.[13] Ultimately, a degree of risk analysis is clearly required, but any absolute failure to implement high-impact guidance concerning clinical practice that may result in significant morbidity or mortality should be viewed as indefensible

from an individual and institutional perspective. The Corporate Manslaughter and Corporate Homicide Act 2007 will obviously not be directly relevant to most complications but the intrinsic intention to identify 'the persons who play significant roles in the making of decisions about how the whole or a substantial part of its activities are to be managed or organised' clearly exposes the responsibilities of departmental heads in matters such as these.[14]

Counter arguments to prescriptive guidelines: limiting clinical discretion and intrinsic fallibility

Concerns relating to the pressure exerted by guidelines on clinicians' ability to maintain professional judgement are still articulated.[15] Critics argue that unquestioning compliance with such guidelines is detrimental and that universal application to every patient ignores the many individual variables affecting specific patients. Furthermore, significant conflicting influences may additionally be derived from patient choice and socio-economic and workforce constraints.[16] Even the most authoritative guidelines may also be subject to change in the face of new evidence which is now becoming available at an unprecedented rate. Proponents of clinical guidelines believe that they are primarily a means of eliminating variations in clinical practice in the interests of unifying and improving the quality, efficiency, and safety of patient care. Such ideals are central to the modern NHS and clinical guidelines may or may not represent tools to facilitate the realization of such objectives allowing measurement of performance according to rates of implementation. Given the increasingly dominant role such guidelines play in the way healthcare is administered in this and other countries, one would assume that all such guidelines would be equally robust in their conception and design. However, not all guidelines issued by national organizations and speciality societies appear grounded in the rigorous methodology that would justify the authority they profess to hold, be this in terms of their influence on clinical practice, or their use in establishing legal standards.[17]

Ten years on from NICE Technology Appraisal 49: robust or fallible guidance?

The original analysis that formed the basis for NICE Guidance 49 suggested that ultrasound guidance would avoid 90 arterial punctures (typically the carotid) for every 1000 patients treated. Recent studies have added further support to these recommendations but the transition to routine ultrasound guidance for central venous cannulation has been slow and incomplete.[18 19] Despite this, in the case of the use of ultrasound during central venous catheter insertion by the jugular route, the evidence base is now so compelling that the authors would question whether in the event of complications of arterial cannulation during central venous access without using ultrasound, the issue is less a matter of financial compensation and more one of disregard for patient safety which merits the attention of the GMC, or criminal charges if the outcome of the complication is death.

The legal outcome in this particular case

After extensive correspondence between the opposing legal teams and a face-to-face meeting between commissioned medical experts, the case was withdrawn by the Claimant's solicitors, after substantial legal costs had been incurred by both the Claimant and the defending Hospital Trust.

Despite the unparalleled proliferation of national guidelines, health-care professionals are now expected to take all guidance issued by organizations such as NICE into account during their clinical practice. This is a significant challenge to anaesthetists and especially to those who may be called upon to provide care in specialist areas of anaesthesia that no longer constitutes part of their routine clinical work.

It is clear that there are a number of reasons why direct translation of published guidelines into legal standards of care has not extended beyond representing just one piece of evidence destined to be combined with others when determining medical liability. While there currently remains reliance upon expert medical testimony when establishing acceptable practice, future medico-legal cases may rely increasingly on guidelines issued by national organizations to determine benchmarks for acceptable clinical practice, further weakening the Bolam principle.[20] A recent article in the educational supplement of this journal supports this theory.[21] While there is no absolute legal obligation to follow guidance issued by organizations such as NICE, clinicians must be confident that they can justify deviation from these guidelines as being in the patient's best interest and that such deviation represents an acceptable standard of care. The intention to deviate from such guidelines should also be highlighted for the patient and become an explicit component of consent. In the context of central venous access, assuming ultrasound devices and a clinician adequately trained in its use are readily available, there are few situations where patient risk is not likely to be reduced by using this technology and this should become the minimum acceptable standard of care from a clinical and legal perspective. The NICE guidance should correspondingly receive unequivocal endorsement by the relevant professional bodies at this 10 yr interval after dissemination.

Declaration of interest

A.R.B. was an expert advisor to NICE when their technology appraisal was produced in 2002.

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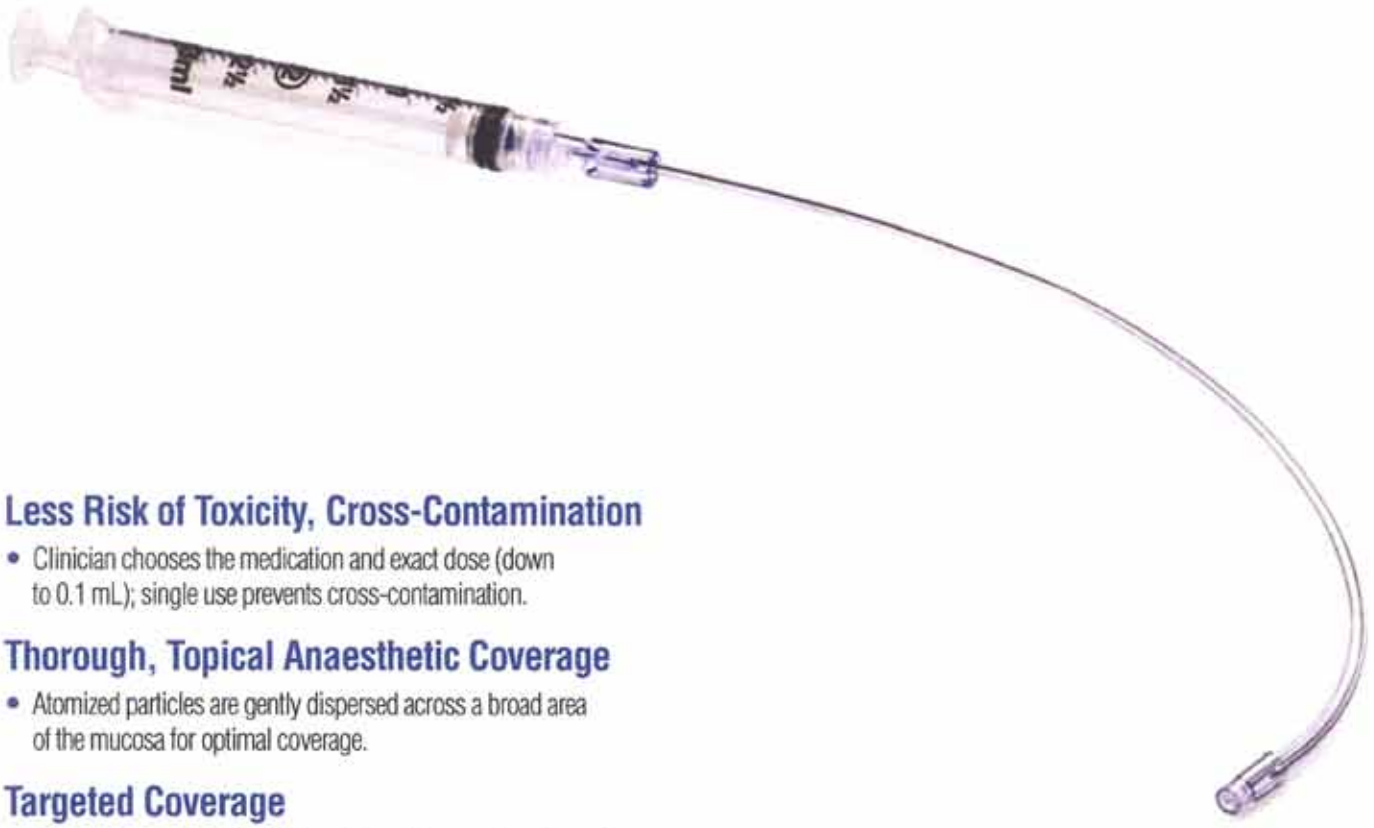

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BJA

High STOP-Bang score indicates a high probability of obstructive sleep apnoea

F. Chung[1]*, R. Subramanyam[1], P. Liao[1], E. Sasaki[1], C. Shapiro[2] and Y. Sun[1]

[1] Department of Anaesthesia and [2] Department of Psychiatry, Toronto Western Hospital, University Health Network, University of Toronto, 399 Bathurst Street, Toronto, ON, Canada M5T 2S8

*Corresponding author. E-mail: frances.chung@uhn.ca

Editor's key points

- The authors investigated the value of STOP-Bang score in predicting obstructive sleep apnoea (OSA) in surgical patients.
- Results from 746 patients were analysed.
- The odds ratio of moderate-to-severe OSA increased with the increase in the score.
- Importantly, the study shows the usefulness of STOP-Bang score in predicting OSA.

Background. The STOP-Bang questionnaire is used to screen patients for obstructive sleep apnoea (OSA). We evaluated the association between STOP-Bang scores and the probability of OSA.

Methods. After Institutional Review Board approval, patients who visited the preoperative clinics for a scheduled inpatient surgery were approached for informed consent. Patients answered STOP questionnaire and underwent either laboratory or portable polysomnography (PSG). PSG recordings were scored manually. The BMI, age, neck circumference, and gender (Bang) were documented. Over 4 yr, 6369 patients were approached and 1312 (20.6%) consented. Of them, 930 completed PSG, and 746 patients with complete data on PSG and STOP-Bang questionnaire were included for data analysis.

Results. The median age of 746 patients was 60 yr, 49% males, BMI 30 kg m^{-2}, and neck circumference 39 cm. OSA was present in 68.4% with 29.9% mild, 20.5% moderate, and 18.0% severe OSA. For a STOP-Bang score of 5, the odds ratio (OR) for moderate/severe and severe OSA was 4.8 and 10.4, respectively. For STOP-Bang 6, the OR for moderate/severe and severe OSA was 6.3 and 11.6, respectively. For STOP-Bang 7 and 8, the OR for moderate/severe and severe OSA was 6.9 and 14.9, respectively. The predicted probabilities for moderate/severe OSA increased from 0.36 to 0.60 as the STOP-Bang score increased from 3 to 7 and 8.

Conclusions. In the surgical population, a STOP-Bang score of 5–8 identified patients with high probability of moderate/severe OSA. The STOP-Bang score can help the healthcare team to stratify patients for unrecognized OSA, practice perioperative precautions, or triage patients for diagnosis and treatment.

Keywords: mass screening; obstructive/ep (epidemiology); polysomnography; prospective studies; questionnaires; sleep apnoea; snoring/di (diagnosis); snoring/ep (epidemiology)

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Obstructive sleep apnoea (OSA) is a common medical condition affecting 2–26% of the general population[1] and can occur in all age groups.[2] Studies have shown that even asymptomatic OSA is independently associated with an increased morbidity and mortality.[3 4] Patients with OSA were found to have an increase in postoperative complications.[5–9] It is, therefore, imperative to have an early diagnosis of OSA. However, it is estimated that 82% of men and 92% of women with moderate-to-severe sleep apnoea have not been diagnosed.[10] The use of preoperative screening instruments will help to identify the patients with undiagnosed OSA.[11–13]

The STOP-Bang questionnaire is a scoring model consisting of eight easily administered questions starting with the acronym STOP-Bang (Appendix) and is scored based on Yes/No answers (score: 1/0). Thus, the scores range from a value of 0 to 8. A score of $\geq$3 has shown a high sensitivity for detecting OSA: 93% and 100% for moderate and severe OSA, respectively.[11]

Owing to its high sensitivity at a score of $\geq$3, the STOP-Bang questionnaire is considered very helpful to rule out patients having moderate and severe OSA.[11] However, the specificity at the same cut-off is low: 47% and 37% for moderate and severe OSA, respectively, resulting in fairly high false-positive rates. The objective of this study is to evaluate the predictive probabilities for OSA at different scores on the STOP-Bang questionnaire. We hypothesize that a high STOP-Bang score indicates a high probability of moderate/severe OSA.

Methods

The study was conducted in the preoperative clinics of Toronto Western Hospital and Mount Sinai Hospital, Toronto, Ontario, Canada. Institutional Review Board approvals were obtained from both institutions (MSH: 06-0143-E and 07-0183-E; UHN: 06-0135-AE and 07-0515-AE). Patients aged 18 yr or older, who were ASA I–IV, and were undergoing elective procedures in general surgery, gynaecology, orthopaedics, urology, plastic surgery, ophthalmology, or spinal surgery were included in the screening process and approached for consent by the research assistants for the preoperative polysomnograpy (PSG). Patients who were unwilling or unable to give informed consent or patients who were expected to have abnormal EEG findings (e.g. brain tumour, epilepsy surgery, patients with deep brain stimulator) were excluded.

All the patients were asked to complete the STOP questionnaire.[11] Information concerning BMI, age, neck circumference, and gender (Bang) were collected by a research assistant. In the initial 2 yr period of the study, the patients were invited to undergo a laboratory PSG. During the subsequent 2 yr of the study, the patients underwent a portable PSG study at home. The results of the PSG were used to evaluate the various scores of the STOP-Bang questionnaire.

The portable PSG was performed with a level 2 portable sleep device (Embletta X100) which is shown to be a reliable alternative for standard PSG in surgical patients.[14] The PSG recordings were performed at the patients' home. The recording montage consisted of two EEG channels (C3 and C4), electrooculogram (left or right), and chin muscle EMGs. Thoracic and abdominal respiratory effort bands, body position sensors, and pulse oximeter were also used.

The device was attached to patients by a well-trained PSG technician at their home and the overnight recordings were unattended. The patients were advised on how to remove the device which was picked up the next morning from the patients' home by the same sleep technician. A certified PSG technologist who was blinded to the study information analysed the PSG. The manual scoring was performed using Somnologia Studio 5.0 as the scoring platform. Manual scoring was performed according to the Manual of the American Academy of Sleep Medicine.[15]

The laboratory PSG was performed overnight and patients went to bed at their usual bedtime. A standard EEG montage consisting of EEG, electrooculogram, submental EMG, and ECG obtained with surface electrodes were used to collect the sleep architectural data. A pulse oximeter measured the oxygen saturation. Additional recordings included the respiratory effort by thoraco-abdominal excursion, respiratory inductive plethysmography, and oronasal airflow.

A certified polysomnographic technologist scored the polysomnographic recordings under the supervision of a sleep physician who assessed and approved the reports. The technologist was blinded to the results of the STOP-Bang questionnaire and other clinical information about the patients. The sleep stages and apnoea–hypopnea index (AHI) were scored according to the American Academy of Sleep Medicine Task Force recommendations.[16]

The diagnosis of OSA was based on an AHI >5 with fragmented sleep and daytime sleepiness. The severity of OSA with both laboratory and portable PSG was classified based on the AHI values: >5–15 as mild OSA, >15–30 as moderate OSA, and >30 as severe OSA.[15 16]

Statistical analysis

Statistical analyses were performed using SAS version 9.2. The patient characteristic data are presented with descriptive statistics; median and inter-quartile range were used for non-normally distributed continuous data, and frequency and percentage were used for categorical data. Predicted probabilities for each score at cut-off points of all OSA (AHI>5), moderate/severe OSA (AHI>15), and severe OSA (AHI>30) were calculated using logistic regression, and plotted. The probability and its 95% confidence interval (95% CI) were calculated for each score. The STOP-Bang scores of 7 and 8 were combined due to the small number of patients with either score. A similar strategy was followed with scores 0, 1, and 2.

To assess the performance of the STOP-Bang questionnaire, multiple 2×2 contingency tables were used to calculate sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) for each score. The response was dichotomized using all OSA (AHI>5), moderate/severe OSA (AHI>15), and severe OSA (AHI>30) as the cut-offs. The area under the receiver operating curves was calculated using logistic regression to assess the diagnostic ability of the STOP-Bang questionnaire.

Multinomial logistic regression was used to compare the severity of the AHI with the STOP-Bang questionnaire score. For the dependent variable, an AHI ≤5 was classified as non-OSA and was used as the reference. For the independent variable, patients who scored 0, 1, or 2 were grouped as the reference. Odds ratios (ORs) and 95% confidence intervals of each STOP-Bang score group (3, 4, 5, 6, 7, and 8) at different AHI cut-offs were calculated.

Results

A total of 6369 patients were approached for consent and screened for OSA by the STOP-Bang questionnaire. Of the 2870 patients screened and invited for laboratory PSG, 414 (14.4%) patients gave consent. Of the 3499 patients screened and invited for portable PSG, 898 (25.7%) patients gave consent. Laboratory PSG was completed by 219 patients, and 711 patients completed portable PSG. Of the 930 patients who completed the PSG, 212 patients with a laboratory PSG and 534 patients with a portable PSG answered all of the items in the STOP questionnaire and had complete documentation of BMI, age, gender, and neck circumference. These 746 patients were used for the analysis (Fig. 1).

The summary of age, gender, BMI, and neck circumference of the different patient groups is shown in Table 1. The patient characteristics were similar between the 930

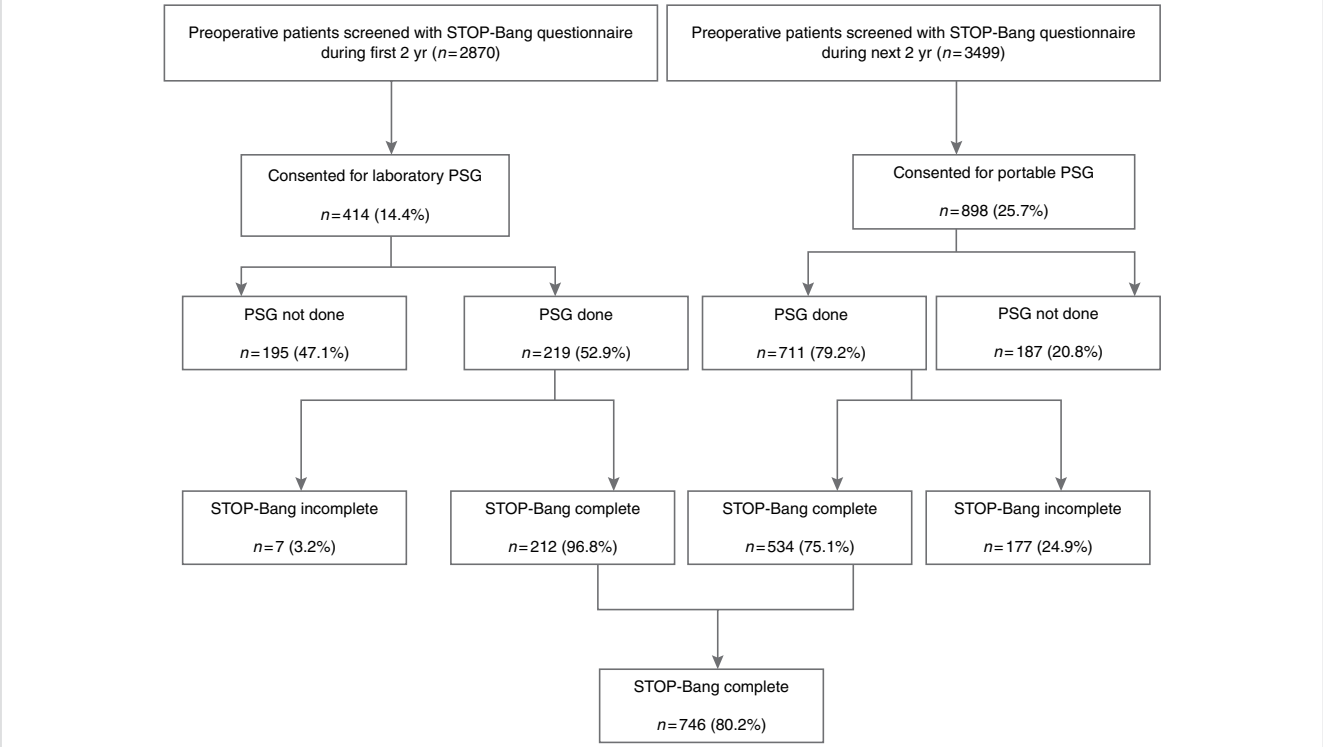

Fig 1 Screening flow chart of patients. PSG, polysomnography.

Table 1 Patient characteristics. Data shown as median (inter-quartile range) or number with percentage in parenthesis. *$n=1634$. †STOP-Bang incomplete due to missing data

	PSG not done	PSG done		
		Total	STOP-Bang complete	STOP-Bang incomplete
n	5439	930	746	184
Gender [male/female]	2504/2935 (46/54)	445/485 (48/52)	365/381 (49/51)	80/104 (44/56)
Age (yr)	58 (47–69)	60 (52–69)	60 (51–68)	61 (54–69)
Neck circumference (cm)	38 (35–40)*	39 (36–42)	39 (36–42)	—†
BMI (kg m^{-2})	27 (24–31)	30 (26–34)	30 (26–35)	30 (26–34)

patients who underwent a PSG and the 5439 patients who did not undergo a PSG due to the reasons of no consent or no show. The 184 patients, who underwent a PSG but did not complete all the elements of the STOP-Bang questionnaire, were excluded from the analysis set. Patient characteristics other than the neck circumference were similar between the 184 patients excluded from the analysis set and the 746 patients used for the analysis.

Of the 746 patients used for analysis, there were 510 (68.4%), 287 (38.5%), and 134 (18.0%) patients who had OSA (AHI>5), moderate/severe OSA (AHI>15), and severe OSA (AHI>30), respectively. The distribution of each of the STOP-Bang scores is detailed in Figure 2. Most patients had a STOP-Bang score of 3 (22.9%) and 4 (22.3%).

The area under the receiver operating curves was 0.65 (95% CI: 0.61–0.70), 0.67 (95% CI: 0.63–0.70), and 0.71 (95% CI: 0.66–0.75) for all OSA, moderate/severe OSA, and severe OSA, respectively. Although the areas under the receiver operating curves do not show perfect discrimination, the confidence intervals do not include 0.5, confirming the diagnostic ability of the STOP-Bang questionnaire. The STOP-Bang questionnaire had the best discrimination with severe OSA.

For a STOP-Bang score of 5, the OR for moderate/severe was 4.8 (95% CI: 2.8–8.0) and for severe OSA was 10.4 (95% CI: 4.5–24.3). For a STOP-Bang score of 6, the OR for moderate/severe was 6.3 (95% CI: 3.4–11.7) and for severe OSA was 11.6 (95% CI: 4.6–28.7). For a STOP-Bang score of 7 and 8, the OR for moderate/severe was 6.9 (95% CI: 3.3–14.3) and for severe OSA was 14.9 (95% CI: 5.6–39.6) (Table 2).

The sensitivity, specificity, PPVs, and NPVs for all OSA, moderate/severe OSA, and severe OSA are summarized in Table 3. As the STOP-Bang score increased from 3 to 8, the sensitivity

decreased from 68.4% to 0.4% for moderate/severe OSA patients, and 94.8% to 0% for severe OSA patients. When the STOP-Bang score was 5, the specificity for moderate/severe OSA was 56.1% and for severe OSA was 74.2%.

The predicted probabilities of having OSA, moderate/severe OSA, or severe OSA are shown in Table 4. The probabilities of having OSA were greater as the STOP-Bang score increased. This trend was the same across the groups of all OSA, moderate/severe OSA, and severe OSA (Fig. 3). As the STOP-Bang score increased from 0–2 to 7 and 8, the probability of having OSA, moderate/severe OSA, and severe OSA increased from 46% (95% CI: 39–53%) to 86% (95% CI: 72–93%), 18% (95% CI: 13–24%) to 60% (95% CI: 44–73%), and 4% (95% CI: 2–8%) to 38% (95% CI: 29–53%), respectively (Table 4).

Discussion

The results of the study showed that with an increase in the STOP-Bang score, there was a corresponding increase in the predicted probability, OR, and specificity for having OSA, moderate/severe, and severe OSA. This was accompanied by a progressive decrease in sensitivity. For a STOP-Bang score of 5, the OR for moderate/severe and severe OSA was 4.8 and 10.4, respectively. For STOP-Bang 7 and 8, the OR for moderate/severe and severe OSA was 6.9 and 14.9, respectively. The STOP-Bang questionnaire was initially introduced as a scoring model for the preoperative patients.[11] The results from this study further validated the value of STOP-Bang questionnaire as a screening tool in surgical patients. The association between the STOP-Bang score and the probability of OSA would provide the perioperative care team a useful tool to stratify patients for unrecognized OSA and triage patients for diagnosis and treatment.

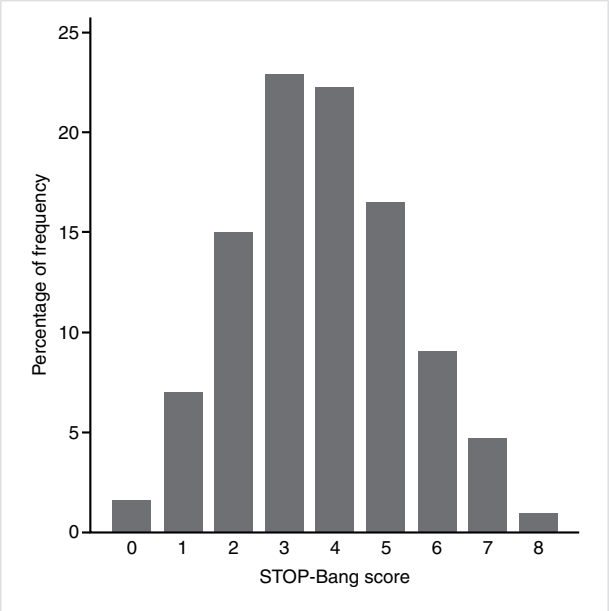

Fig 2 Distribution of patients according to their STOP-Bang score.

It is estimated that nearly 80% of men and 93% of women with moderate-to-severe sleep apnoea are undiagnosed,[17] which poses a variety of problems for anaesthesiologists. OSA patients are known to have a higher incidence of difficult intubation,[18] postoperative complications,[19 20] increased intensive care unit admissions,[7] and greater duration of hospital stay.[21] Memtsoudis and colleagues[9] found that OSA was associated with a significantly higher incidence of pulmonary complications. However, no association between postoperative complication and OSA severity was found in obese patients undergoing bariatric surgery.[22] This may be due to the fact that most patients with OSA (93%) received perioperative positive airway pressure therapy, and all patients were closely monitored after operation with pulse oximetry on either regular nursing floors or in intensive or intermediate care units.[22] Recently, a Canadian publication[23] and the American Society of Anesthesiologists guidelines[24] both stressed the importance of preoperative diagnosis and perioperative management of OSA patients to avoid postoperative complications.

To identify patients at high risk of OSA is the first step for the perioperative care of OSA patients and prevention of adverse events. Although no test or parameter has been widely accepted as a tool to identify the OSA patients who are particularly at risk for severe postoperative pulmonary adverse events, a recent study does show that patients classified as STOP-Bang high risk had an increased incidence of postoperative complications.[25]

The STOP-Bang questionnaire is concise and easy to use. It consisted of eight questions with a yes or no answer

Table 2 ORs (95% CIs) of different STOP-Bang scores for OSA at different AHI cut-offs. AHI, apnoea–hypopnoea index; OSA, obstructive sleep apnoea; Mod/Sev OSA, moderate/severe OSA

STOP-Bang score	ORs for OSA at different AHI cut-offs		
	All OSA (AHI>5)	Mod/Sev OSA (AHI>15)	Severe OSA (AHI>30)
Score 3 *vs* Score 0–2	3.01 (1.92–4.70)	2.59 (1.58–4.27)	3.56 (1.48–8.58)
Score 4 *vs* Score 0–2	3.15 (2.01–4.96)	3.33 (2.03–5.46)	5.33 (2.27–12.50)
Score 5 *vs* Score 0–2	3.98 (2.38–6.66)	4.75 (2.81–8.03)	10.39 (4.45–24.26)
Score 6 *vs* Score 0–2	4.52 (2.34–8.74)	6.29 (3.39–11.66)	11.55 (4.64–28.71)
Score 7 and 8 *vs* Score 0–2	7.04 (2.82–17.55)	6.88 (3.32–14.25)	14.86 (5.58–39.56)

Table 3 Predictive parameters of different STOP-Bang score cut-offs. *Percentage out of the 746 patients (*n*, number of patients in the AHI group who scored the STOP-Bang score indicated or higher). AHI, apnoea–hypopnoea index; PPV, positive predictive value; NPV, negative predictive value

STOP-Bang score cut-off	*n* (%)*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All OSA (AHI>5)					
1	504 (67.6)	98.8	2.5	68.7	50.0
2	488 (65.4)	95.7	17.8	71.6	65.6
3	429 (57.5)	84.1	40.3	75.3	54.0
4	306 (41.1)	60.0	60.6	76.7	41.2
5	185 (24.8)	36.3	79.7	79.4	36.7
6	90 (12.1)	17.7	91.5	81.8	34.0
7	36 (4.8)	7.1	97.5	85.7	32.7
8	4 (0.5)	0.8	98.7	57.1	31.5
Moderate/severe OSA (AHI>15)					
1	285 (38.2)	97.8	0.7	16.7	61.2
2	283 (37.9)	86.9	1.4	6.3	58.5
3	256 (34.3)	68.4	10.8	17.6	55.1
4	195 (26.1)	44.4	32.1	26.5	51.1
5	126 (16.9)	23.3	56.1	31.4	45.9
6	64 (8.6)	10.0	77.7	35.1	41.8
7	25 (3.4)	3.7	91.3	37.2	40.5
8	1 (0.1)	0.4	98.7	14.3	61.3
Severe OSA (AHI>30)					
1	134 (18.0)	100.0	2.0	18.3	100.0
2	134 (18.0)	100.0	10.5	19.7	100.0
3	127 (17.0)	94.8	27.6	22.3	96.0
4	105 (14.1)	78.4	52.0	26.3	91.6
5	75 (10.1)	56.0	74.2	32.2	88.5
6	38 (5.1)	28.4	88.2	34.6	84.9
7	16 (2.1)	11.9	95.8	38.1	83.2
8	0 (0)	0	98.9	0	81.9

Table 4 Predicted probabilities per score for all OSA, moderate/severe OSA, and severe OSA. CI, confidence interval; AHI, apnoea–hypopnoea index; *n*, number; Mod/Sev OSA, moderate/severe OSA

Score	All OSA (AHI>5)		Mod/Sev OSA (AHI>15)		Severe OSA (AHI>30)	
	n	Probability (95% CI)	*n*	Probability (95% CI)	*n*	Probability (95% CI)
0–2	81	0.46 (0.39–0.53)	31	0.18 (0.13–0.24)	7	0.04 (0.02–0.08)
3	123	0.72 (0.65–0.78)	61	0.36 (0.29–0.43)	22	0.13 (0.09–0.19)
4	121	0.73 (0.66–0.79)	69	0.42 (0.34–0.49)	30	0.18 (0.13–0.25)
5	95	0.77 (0.69–0.84)	62	0.50 (0.42–0.59)	37	0.30 (0.23–0.39)
6	54	0.79 (0.68–0.87)	39	0.57 (0.45–0.69)	22	0.32 (0.22–0.44)
7 and 8	36	0.86 (0.72–0.93)	25	0.60 (0.44–0.73)	16	0.38 (0.29–0.53)

and has been used as a preoperative screening tool for OSA.[12 26–28]

Recently, the STOP-Bang questionnaire has been validated in two studies of patients referred to the sleep clinic.[29–30] Farney's study showed that the STOP-Bang questionnaire can be used to estimate the probabilities of no, mild, moderate, and severe OSA. The greater the cumulative score of risk factors as reflected by the STOP-Bang model, the greater the probability of severe OSA.[29] With any score >4, the probability of having severe OSA increases continuously. With a score of 8, the probability of severe OSA was 81.9%.[29] Although our results also showed a similar association between the probabilities of having severe OSA and the score on STOP-Bang, we did not see such a high probability of severe OSA with a higher STOP-Bang score. This may be due to the difference in the study population. Our patients were preoperative patients. The patients in Farney's study were the patients referred to sleep clinic population which have a high prevalence of severe OSA.

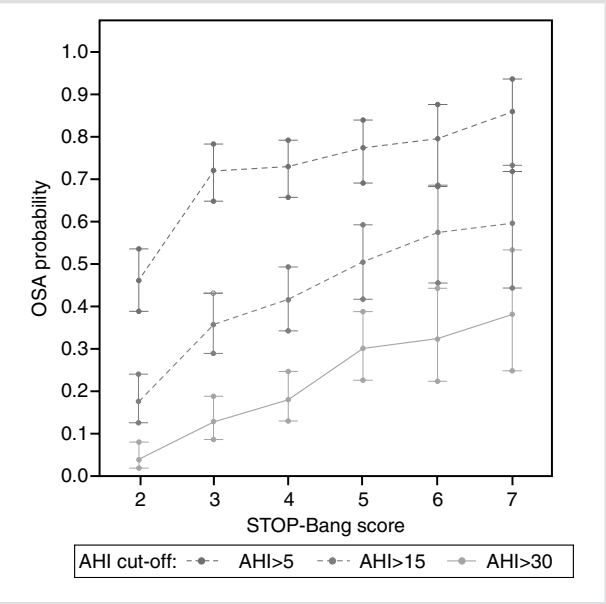

Fig 3 Plot of predicted probabilities for AHI cut-offs of >5, >15, and >30 with the corresponding STOP-Bang score. The vertical bars indicate the 95% confidence intervals. STOP-Bang scores of 0, 1, and 2 are grouped together and are shown as score 2. Scores 7 and 8 are grouped together and is shown as score 7. As the STOP-Bang scores increased, the predicted probabilities were greater. AHI, apnoea–hypopnoea index.

Since a STOP-Bang score of ≥3 demonstrated a very high sensitivity and NPV for moderate/severe OSA, this cut-off may be good for a surgical population with high OSA prevalence such as bariatric surgical patients. We would be confident in excluding the possibility of moderate/severe or severe OSA in patients with a STOP-Bang score of 0–2. On the other hand, the patients with a STOP-Bang score of 5–8 have a high specificity to detect moderate and severe OSA. These scores may be useful in the general patient population which has a low OSA prevalence to reduce false-positive rate. It enables identification of those patients most in need of urgent evaluation and to exclude patients from possible harm due to unrecognized sleep apnoea.[29] However, further research is needed so that the STOP-Bang can be validated in the different clinical populations.

It is a challenge to establish a practical perioperative care pathway for OSA patients. It is not known whether patients with a STOP-Bang score of 5–8 with co-morbidities having major surgery would benefit from sleep medicine referral, expedited polysomnography (PSG), and continuous positive airway pressure (CPAP) treatment. There have been no studies in the literature to prove that preoperative PSG is of benefit to the surgical patients with suspected OSA. Overnight-attended PSG is an old standard in the diagnosis of OSA, but it is expensive and cumbersome. Often, there is a timeline for patients undergoing surgery. Portable home-based monitoring devices or single channel recording such as nocturnal oximetry might be used as an alternative for the diagnosis of OSA in patients with high probability of moderate-to-severe OSA.[31] Thus, a combination of STOP-BANG questionnaire to identify patients at risk of OSA and nocturnal oximetry may allow for a more rapid diagnosis of OSA. Alternatively, in the patients classified as high risk of OSA by the STOP-Bang questionnaire, especially those with a STOP-Bang score of ≥5, practicing perioperative precautions (preparation for possible difficult intubation, using short-acting anaesthesia agents, adequate neuromuscular blocking agent reversal, and use of CPAP after operation) and postoperative monitoring is helpful to prevent adverse outcomes.[23 24 32] If patients get earlier treatment for their OSA because of screening in preoperative clinics, there may be long-term health benefits for the patients, besides reducing risk for OSA-related perioperative adverse event. More collaboration between anaesthesiologists, surgeons, and sleep physicians is needed.

There are a few limitations with our study. The study could be criticized because PSG was performed with both the standard PSG in the laboratory and the portable PSG at home. Embletta X-100 is a level 2 diagnostic device for SDB. When installed by a well-trained technician and scored by a certified PSG technologist, parameters measuring sleep-disordered breathing and sleep architecture from Embletta X-100 were comparable with in-laboratory standard PSG.[15] Although home monitoring is validated[15 33] and all PSG recordings were scored by certified PSG technologists, some inconsistency in the two approaches may exist. Secondly, the study population is surgical patients referred to preoperative clinics. These results may not be applicable to other patient populations. Further validation in the different population, especially the general population, needs to be done. Also, there may be a selection bias involved in the patient recruiting process, the subjects having some OSA-related symptoms might be more motivated to give consent to this study. Finally, like all other screening studies for sleep apnoea, central apnoeas were also not evaluated separately in the report.

In conclusion, the predicted probabilities were greater as the STOP-Bang score increased, showing that patients had a greater probability of having OSA when they scored higher on the STOP-Bang questionnaire. A STOP-Bang score of <3 will allow the healthcare team to rule out patients who do not have OSA. A STOP-Bang score of 5–8 will allow the team to identify patients with increased probability of moderate/severe OSA. The STOP-Bang score can help the healthcare team to stratify patients for unrecognized OSA, practice perioperative precautions, or triage patients for diagnosis and treatment.

Authors' roles

F.C. is the principal investigator. F.C. helped design the study, conduct the study, and write the manuscript and had the overall responsibility for the study. R.S. helped design the study, and write the manuscript. P.L. helped design the study, conduct the study, and write the manuscript. E.S. analysed the data and helped write the manuscript. C.S. helped

design the study and supervised sleep studies. Y.S. was responsible for the scoring of PSG.

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Declaration of interest

None declared.

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Appendix

STOP-Bang questionnaire[11]

1. Snoring: Do you snore loudly (loud enough to be heard through closed doors)?	
Yes	No
2. Tired: Do you often feel tired, fatigued, or sleepy during daytime?	
Yes	No
3. Observed: Has anyone observed you stop breathing during your sleep?	
Yes	No
4. Blood pressure: Do you have or are you being treated for high blood pressure?	
Yes	No
5. BMI: BMI more than 35 kg m^{-2}?	
Yes	No
6. Age: Age over 50 yr old?	
Yes	No
7. Neck circumference: Neck circumference >40 cm?	
Yes	No
8. Gender: Male?	
Yes	No

High risk of OSA: Yes to ≥ 3 questions.
Low risk of OSA: Yes to <3 questions.
Questionnaire reproduced from Chung *et al.*[11] with permission from Wolters Kluwer Health.

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BJA

Impact of phenylephrine administration on cerebral tissue oxygen saturation and blood volume is modulated by carbon dioxide in anaesthetized patients†

L. Meng[1,6]*, A. W. Gelb[2], B. S. Alexander[3], A. E. Cerussi[4], B. J. Tromberg[4], Z. Yu[5] and W. W. Mantulin[4]

[1] Department of Anesthesiology and Perioperative Care, University of California Irvine Medical Center, Orange, CA 92868, USA
[2] Department of Anesthesia and Perioperative Care, UCSF School of Medicine, 521 Parnassus Ave., San Francisco, CA 94143, USA
[3] School of Medicine, University of California, 1001 Health Sciences Road, Irvine, CA 92697, USA
[4] Beckman Laser Institute, University of California, 1002 Health Sciences Road, Irvine, CA 92612, USA
[5] Department of Statistics, University of California, 2214 Bren Hall, Irvine, CA 92697, USA
[6] Present address: Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710, USA

* Corresponding author. E-mail: meng.lingzhong@gmail.com

Editor's key points

- Phenylephrine is known to reduce cerebral oxygenation.
- Fourteen patients received phenylephrine during normocapnia, hypocapnia, and hypercapnia.
- Hypocapnia intensified, and hypercapnia blunted, the phenylephrine-induced reduction in cerebral oxygenation.
- The study presents important data regarding interaction between CO_2 and phenylephrine and the effects on cerebral oxygenation.

Background. Multiple studies have shown that cerebral tissue oxygen saturation (Sct_{O_2}) is decreased after phenylephrine treatment. We hypothesized that the negative impact of phenylephrine administration on Sct_{O_2} is affected by arterial blood carbon dioxide partial pressure (Pa_{CO_2}) because CO_2 is a powerful modulator of cerebrovascular tone.

Methods. In 14 anaesthetized healthy patients, i.v. phenylephrine bolus was administered to increase the mean arterial pressure ~20–30% during hypocapnia, normocapnia, and hypercapnia. Sct_{O_2} and cerebral blood volume (CBV) were measured using frequency domain near-infrared spectroscopy, a quantitative technology. Data collection occurred before and after each treatment.

Results. Phenylephrine caused a significant decrease in Sct_{O_2} during hypocapnia [$\Delta Sct_{O_2} = -3.4$ (1.5)%, $P<0.001$], normocapnia [$\Delta Sct_{O_2} = -2.4$ (1.5)%, $P<0.001$], and hypercapnia [$\Delta Sct_{O_2} = -1.4$ (1.5)%, $P<0.01$]. Decreases in Sct_{O_2} were significantly different between hypocapnia, normocapnia, and hypercapnia ($P<0.001$). Phenylephrine also caused a significant decrease in CBV during hypocapnia ($P<0.01$), but not during normocapnia or hypercapnia.

Conclusion. The negative impact of phenylephrine treatment on Sct_{O_2} and CBV is intensified during hypocapnia while blunted during hypercapnia.

Keywords: carbon dioxide; cerebral blood volume; cerebral tissue oxygen saturation; modulation; phenylephrine

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Phenylephrine is one of the most commonly used vasopressors including in patients with acute neurological injury. There are a number of reports that cerebral tissue oxygen saturation (Sct_{O_2}) measured using near-infrared spectroscopy (NIRS) is decreased, even though arterial pressure is increased, after phenylephrine bolus and infusion administration in anaesthetized and awake humans.[1–4] Because cerebrovascular tone is powerfully modulated by carbon dioxide (CO_2), we hypothesized that the magnitude of the phenylephrine-induced decrease in Sct_{O_2} is influenced by arterial blood CO_2 partial pressure (Pa_{CO_2}). During hypercapnia, one may see a reduction in the decrease in Sct_{O_2} due to hypercapnia-mediated cerebral vasodilation, and during hypocapnia, the opposite effect may occur. Manipulation of Pa_{CO_2} is common in the operating theatre and intensive care unit. Within this context, a full understanding of how Sct_{O_2} is affected by phenylephrine administration at different Pa_{CO_2} levels will facilitate clinical decision making. This will be especially true in patients who are at an increased risk of cerebral ischaemia and hypoxia. In this study, it was our aim to determine whether the phenylephrine-induced decrease in Sct_{O_2}, measured using frequency domain (FD)-NIRS, is different at distinct Pa_{CO_2} levels in healthy anaesthetized surgical patients.

†Parts of the data were presented at International Anesthesia Research Society 2011 Annual Meeting, Vancouver, Canada, and American Society of Anesthesiologists 2011 Annual Meeting, Chicago, IL, USA.

Methods

After Institutional Research Board approval, ASA I–II patients undergoing elective non-neurosurgical procedures at University of California Irvine Medical Center were recruited for this study (Table 1). Both verbal and written informed consents were obtained. Exclusion criteria were: age ≤18 yr old, cerebrovascular disease, symptomatic cardiac disease, symptomatic pulmonary disease, poorly controlled hypertension (systolic arterial pressure ≥140 mm Hg), and poorly controlled diabetes mellitus (blood glucose ≥160 mg dl^{-1}) or diabetes mellitus requiring insulin treatment. All patients received nothing by mouth 8 h before surgery.

Measurements

Sct_{O_2} and total haemoglobin concentration (THC, the sum of oxy- and deoxy-haemoglobin concentrations) were measured by the Oxiplex TS cerebral oximeter (ISS Inc., Champaign, IL, USA), a non-invasive, portable, and quantitative FD-NIRS device.[5] It emits and detects near-infrared light at two different wavelengths (690 and 830 nm). The light is amplitude modulated (i.e. turned on and off) at 110 MHz. The spacing between the source and detector fibres on the optical probe (1.96, 2.46, 2.92, and 3.45 cm) is sufficient for light to access the surface of the brain.[6] The measured optical properties characterize cerebral tissue and are not appreciably influenced by extra-cerebral layers.[6 7] Cerebral blood volume (CBV) is calculated via the following equation:[8 9]

$$\mathrm{CBV} = \left(\frac{\mathrm{THC} \times \mathrm{MW_{Hb}} \times 10^{-5}}{\mathrm{HGB} \times D_{\mathrm{bt}} \times \mathrm{CLVHR}}\right)$$

CBV is in ml 100 g^{-1}, THC is in μmol, MW_{Hb} is the molecular weight of haemoglobin (64 458 g mol^{-1}), HGB is systemic blood haemoglobin concentration (g dl^{-1}), D_{bt} is brain tissue density (1.0335 g ml^{-1}), and CLVHR=0.69 is the cerebral to large vessel haematocrit ratio.

Cardiac output (CO) was monitored using oesophageal Doppler (CardioQ, Deltex Medical, Chichester, West Sussex, UK). The CO values used for analysis were based on the average of every 10 successive stroke volumes. The mean arterial pressure (MAP) was monitored at the external ear canal level via an arterial pressure transducing system (Vigileo-FloTrac, Edwards Lifesciences, Irvine, CA, USA). End-tidal CO_2 (E'_{CO_2}) was determined by the gas analyzer built into the anaesthesia machine (Aisys, GE Healthcare, Madison, WI, USA). Pa_{CO_2} was analysed using a handheld blood analyzer (iSTAT, Abbott Laboratories, Abbott Park, IL, USA). Arterial blood oxygen saturation was determined by finger pulse oximeter (Sp_{O_2}) (LNOP Adt, Masimo Corp., Irvine, CA, USA). The depth of anaesthesia was monitored via the bispectral index (BIS) monitor (S/5™ M-BIS, GE Healthcare).

Protocol

After induction of anaesthesia with fentanyl (1.5–2 μg kg^{-1}) and propofol (2–3 mg kg^{-1}), all patients were intubated tracheally and maintained with total i.v. anaesthesia using propofol 75–150 μg kg^{-1} min^{-1} and remifentanil 0.2–0.5 μg kg^{-1} min^{-1} to target a BIS between 30 and 40. Muscle relaxation was maintained with cisatracurium. A radial intra-arterial catheter, a BIS monitor, an oesophageal Doppler probe, and two FD-NIRS probes (left and right forehead) were placed in addition to the other routine monitors. Pressure-regulated volume-controlled mechanical ventilation was used with the inspired oxygen fraction ($F_{I_{O_2}}$) fixed at 50%, inspiratory to expiratory (*I:E*) time ratio fixed at 1:2, and positive end-expiratory pressure fixed at zero. The formal study was conducted during a stable intraoperative period.

Three different E'_{CO_2} levels were achieved via minute ventilation adjustments (Fig. 1). Normocapnia, defined as an E'_{CO_2} 5.1–5.3 kPa and confirmed with Pa_{CO_2}, was first achieved with a tidal volume (TV) of ~6–10 ml kg^{-1} and a respiratory

Table 1 Patient characteristic and surgery data

Patient #	Age (yr)	Sex	Height (cm)	Weight (kg)	ASA	Co-morbidity	Major home medications	Surgery
1	49	M	178	73	I	None	None	Tibia fracture repair
2	55	F	155	58	II	Leiomyosarcoma	Gabapentin	Right femur radical resection
3	60	M	185	95	II	Controlled hypertension	Metoprolol	Robotic laparoscopic prostatectomy
4	41	M	173	73	I	None	None	Laparoscopic cholecystectomy
5	55	M	185	85	II	Kidney mass	None	Robotic laparoscopic nephrectomy
6	55	M	188	95	II	Prostate cancer	None	Robotic laparoscopic prostatectomy
7	27	F	160	61	I	Cervical cancer	None	Robotic laparoscopic hysterectomy
8	23	M	165	63	I	Retroperitoneal tumour	None	Retroperitoneal tumour resection
9	68	M	180	84	II	Controlled hypertension	Diovan	Abdominal hernia repair
10	37	F	165	103	II	Controlled diabetes	Lisinopril, glipizide	Hepatectomy
11	35	M	173	71	I	Humerus tumour	None	Humerus hardware removal
12	56	M	180	84	II	Controlled hypertension	Metoprolol	Robotic laparoscopic prostatectomy
13	22	M	183	83	I	Urethral stricture	None	Urethral stricture repair
14	31	M	183	95	I	None	None	Tibia fracture repair

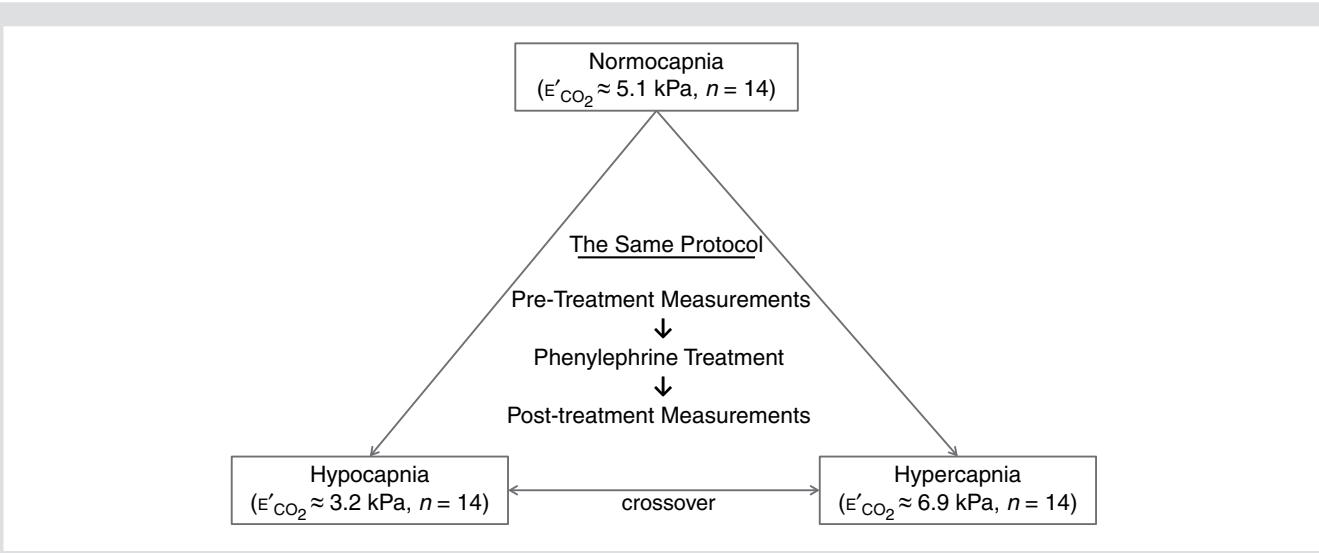

Fig 1 Study protocol. E'_{CO_2}, end-tidal carbon dioxide.

rate (RR) of ~8–10 bpm. Once the condition had remained stable for at least 5 min, an i.v. phenylephrine bolus was administered to increase MAP by ~20–30%. Physiological measurements were recorded immediately before and again after phenylephrine administration when the increase in MAP reached the highest level. The mean values of three successive recordings for each parameter were used for analysis. After the completion of the normocapnia study, both hypocapnia via an increase in TV and RR of ~40–50% and hypercapnia via a decrease in TV and RR of ~40–50% were achieved. Hypocapnia was defined as E'_{CO_2} 3.1–3.3 kPa (confirmed with Pa_{CO_2}) and hypercapnia as E'_{CO_2} 6.7–6.9 kPa (confirmed with Pa_{CO_2}). The same protocol used in the normocapnia study was used during both hypocapnia and hypercapnia studies. For any given patient, the same dose of phenylephrine was used at all CO_2 levels. However, the dose of phenylephrine varied (100, 150, or 200 μg) between patients due to inter-individual differences in body weight, response to vasopressor treatment, and extent of anaesthesia-related hypotension. The intervals between phenylephrine boluses were greater than 15 min.

Statistical analysis

Data are presented as mean (SD). Power analysis showed that a sample size of $n=10$ would be required (α level 0.05 and statistical power >80%) in order to detect an expected reduction in NIRS-determined Sct_{O_2} of 3 (3)%. Both one-way analysis of variance (ANOVA) with repeated measurements and the Friedman rank sum test were used to analyse the differences in pre-treatment measurements [E'_{CO_2}, Sct_{O_2}, CBV, MAP, CO, heart rate (HR), Sp_{O_2}, and BIS], post-treatment measurements (Pa_{CO_2}), and phenylephrine-induced changes ($\Delta E'_{CO_2}$, ΔSct_{O_2}, ΔCBV, ΔMAP, ΔCO, ΔHR, ΔSp_{O_2}, and ΔBIS) between hypocapnia, normocapnia, and hypercapnia. Both paired Student's *t*-test and Wilcoxon's signed-rank test were used to analyse the differences between pre- and post-treatment measurements (E'_{CO_2}, Sct_{O_2}, CBV, MAP, CO, HR, Sp_{O_2}, and BIS) at each CO_2 level. *P*-values reported are agreeable with both parametric and non-parametric analyses. *P*-values reported for Pearson's correlations were calculated by Student's *t*-test using linear regression analysis. *P*-value <0.05 was regarded as significant.

Results

Out of 16 patients studied, complete data were obtained in 14 patients [11 males, three females, age 44 (15) yr old, height 175 (10) cm, and weight 80 (14) kg] (Table 1). Two patients were not included in analysis due to incomplete Pa_{CO_2} data secondary to either blood gas analyzer malfunctioning or blood sample mishandling.

Hypocapnia, normocapnia, and hypercapnia were successfully achieved via minute ventilation adjustments as demonstrated by E'_{CO_2} ($P<0.0001$) and confirmed by Pa_{CO_2} ($P<0.0001$; Table 2). The pre-treatment measurements of Sct_{O_2} were significantly different between hypocapnia, normocapnia, and hypercapnia ($P<0.0001$). The pre-treatment measurements of MAP were also significantly different between different CO_2 levels ($P<0.001$). However, the pre-treatment measurements of CBV, CO, HR, Sp_{O_2}, and BIS all showed no significant difference between different CO_2 levels ($P>0.05$).

Phenylephrine treatment induced significant increases in MAP during hypocapnia ($P<0.001$), normocapnia ($P<0.001$), and hypercapnia ($P<0.01$; Table 2). Sct_{O_2} was significantly decreased after phenylephrine treatment during hypocapnia ($P<0.001$), normocapnia ($P<0.001$), and hypercapnia ($P<0.01$). CBV was also significantly decreased during hypocapnia ($P<0.01$), but not during normocapnia and hypercapnia ($P>0.05$). Both CO ($P<0.001$) and HR ($P<0.01$) were also significantly decreased after phenylephrine treatment at all

Table 2 Measurements before (pre) and after (post) phenylephrine bolus treatments during hypocapnia, normocapnia, and hypercapnia. Data are presented as means (SD). Sct_{O_2}, cerebral tissue oxygen saturation; CBV, cerebral blood volume; THC, total haemoglobin concentration; OxyHb, cerebral tissue oxy-haemoglobin concentration; DeoxyHb, cerebral tissue deoxy-haemoglobin concentration; E'_{CO_2}, end-tidal carbon dioxide; Pa_{CO_2}, arterial blood carbon dioxide partial pressure; MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; Sp_{O_2}, oxygen saturation per pulse oxymetry; BIS, bispectral index; Δ=post–pre. *$P<0.001$, †$P<0.01$, and ‡$P<0.05$ (post *vs* pre)

	Hypocapnia			Normocapnia			Hypercapnia		
	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ
Sct_{O_2} (%)	70.6 (5.5)	67.1 (5.5)*	−3.4 (1.5)	73.2 (5.2)	70.7 (4.9)*	−2.4 (1.5)	75.7 (4.7)	74.3 (5.0)†	−1.4 (1.5)
CBV (ml 100 g^{-1})	3.0 (0.5)	2.9 (0.5)†	−0.05 (0.05)	3.0 (0.6)	3.0 (0.6)	−0.001 (0.05)	3.1 (0.6)	3.1 (0.5)	−0.0002 (0.04)
THC (μmol)	40.7 (9.7)	40.1 (9.4)†	−0.7 (0.6)	41.0 (9.7)	41.0 (9.4)	−0.02 (0.7)	43.0 (10.3)	43.0 (10.5)	0.01 (0.7)
OxyHb (μmol)	29 (8.2)	27.2 (7.6)*	−1.8 (1.0)	30.3 (8.2)	29.3 (7.7)†	−1.1 (1.0)	32.8 (8.9)	32.2 (8.8)‡	−0.6 (0.9)
DeoxyHb (μmol)	11.7 (2.5)	12.8 (2.5)*	1.2 (0.6)	10.7 (2.2)	11.8 (2.4)*	1 (0.7)	10.2 (2.1)	10.8 (2.2)†	0.6 (0.6)
E'_{CO_2} (mm Hg)	3.2 (0.3)	3.2 (0.3)	−0.01 (0.1)	5.1 (0.3)	5.2 (0.4)	0.05 (0.3)	6.8 (0.7)	7.1 (0.7)†	0.3 (0.1)
Pa_{CO_2} (mm Hg)	N/A	3.9 (0.5)	N/A	N/A	5.9 (0.5)	N/A	N/A	8.0 (0.7)	N/A
pH	N/A	7.5 (0.07)	N/A	N/A	7.4 (0.05)	N/A	N/A	7.3 (0.03)	N/A
MAP (mm Hg)	76 (15)	99 (12)*	23 (9)	73 (15)	100 (15)*	27 (13)	66 (11)	93 (9)†	27 (8)
CO (litre min^{-1})	4.8 (1.5)	3.2 (1.1)*	−1.5 (0.8)	4.8 (1.4)	3.2 (1.1)*	−1.6 (0.8)	5.2 (1.5)	3.7 (1.4)*	−1.5 (0.8)
HR (beats min^{-1})	63 (14)	50 (13)*	−13 (5)	59 (13)	47 (10)*	−12 (7)	59 (13)	52 (13)†	−7 (6)
Sp_{O_2} (%)	100 (0.6)	100 (0.6)	0 (0.4)	100 (0.8)	100 (0.7)	0.07 (0.3)	99 (1)	99 (1)	0.3 (1)
BIS	37 (9)	35 (9)	−2 (4)	35 (7)	35 (9)	0.8 (7)	36 (8)	37 (11)	0.4 (6)

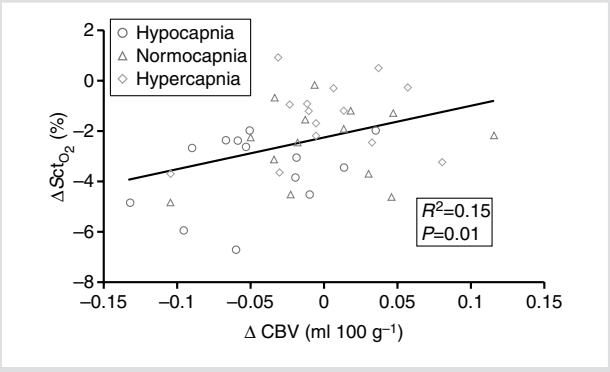

Fig 2 Pearson's correlation between changes in cerebral tissue oxygen saturation (ΔSct_{O_2}) and changes in CBV (ΔCBV).

CO_2 levels. Interestingly, E'_{CO_2} was significantly increased after phenylephrine administration during hypercapnia ($P<0.01$) even though the magnitude was small [2 (1) mm Hg], but not during hypocapnia and normocapnia ($P>0.05$). Changes in both Sp_{O_2} and BIS were not significant at any CO_2 levels ($P>0.05$).

Correlation between changes in Sct_{O_2} and changes in CBV was significant ($R^2=0.15$, $P<0.05$) (Fig. 2, pooled data).

Phenylephrine-induced changes in both Sct_{O_2} and CBV were significantly different between hypocapnia, normocapnia, and hypercapnia ($P<0.01$ and <0.05, respectively; Fig. 3 and Table 2). In contrast, changes in other physiological variables, including MAP, CO, HR, Sp_{O_2}, and BIS, showed no significant difference between different CO_2 levels ($P>0.05$).

Discussion

This is the first study to evaluate whether the negative impact of phenylephrine bolus treatment on Sct_{O_2} is modulated by CO_2. The results demonstrate that hypocapnia intensifies, while hypercapnia blunts, the phenylephrine-induced decrease in Sct_{O_2} in propofol–remifentanil-anaesthetized healthy patients. In addition, phenylephrine also causes a significant decrease in CBV during hypocapnia, but not during normocapnia and hypercapnia.

The Sct_{O_2}-decreasing effect of phenylephrine bolus and infusion administrations has been shown in both anaesthetized and awake humans.[1–4] Phenylephrine, a pure α_1-agonist, is one of the most commonly used vasopressors in the perioperative setting. A similar drug, norepinephrine, has also been shown to cause a decrease in Sct_{O_2} after its infusion administration.[10] How increased arterial pressure, and thus increased perfusion pressure, leads to a decrease in Sct_{O_2} needs careful consideration. Sct_{O_2} measures an admixture of arterial and venous blood per unit of cerebral tissue seen by light.[11 12] NIRS measurements show changes when the cerebral arterial to venous blood volume ratio (*A*:*V* ratio) changes. A hypothetical mechanism for how *A*:*V* ratio is affected by phenylephrine treatment is presented in Figure 4. We propose that the flow velocity in cerebral arterial bed (mainly arterioles) is increased by a phenylephrine-induced increase in perfusion pressure. At the same time, cerebral blood flow (CBF)-regulating vessels (mainly arterioles) constrict due to stretch or increased transmural pressure-mediated vasoconstriction. In accordance with autoregulation, CBF (velocity multiplied by cross-sectional area) is maintained because the increase in velocity is offset by the decrease in cross-sectional area. Cerebral

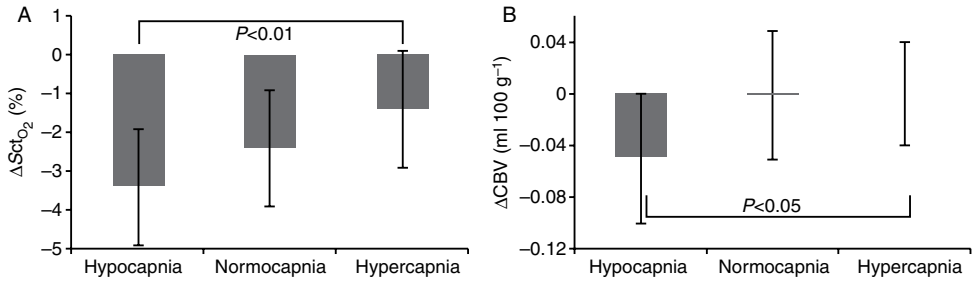

Fig 3 (A) Cerebral tissue oxygen saturation (Sct_{O_2}) and (B) CBV changes (Δ) during hypocapnia, normocapnia, and hypercapnia.

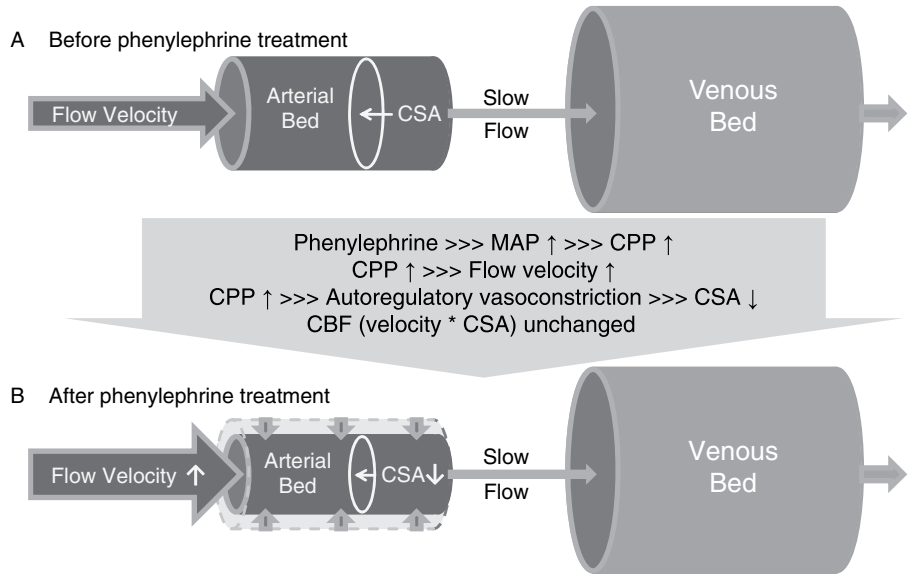

Fig 4 Hypothetical explanation of how phenylephrine treatment induces cerebral autoregulatory vasoconstriction. CSA, cross-sectional area; MAP, mean arterial pressure; CPP, cerebral perfusion pressure; CBF, cerebral blood flow.

vasoconstriction is an indirect autoregulation-mediated consequence, because phenylephrine does not cross the blood–brain barrier and it cannot constrict cerebral vessels directly.[13] A decreased arterial blood contribution secondary to cerebral arteriolar constriction may be partially accountable for the observed decrease in Sct_{O_2}. The findings that flow velocity measured by transcranial Doppler (TCD) is increased while cerebral oxygenation measured by NIRS is decreased after phenylephrine administration are consistent with the above proposed mechanism.[4] However, caution is needed here because it has been shown that the TCD-measured flow velocity is either slightly decreased or maintained during norepinephrine infusion, another vasopressor with some comparable features to phenylephrine.[10 14] Ito and colleagues' study using positron emission tomography demonstrated that changes in CBV during hypocapnia and hypercapnia are caused by changes in arterial blood volume without changing venous and capillary blood volume.[15] This observation, even though it was based on Pa_{CO_2} manipulation and not vasopressor administration, supports our speculation that a decreased *A*:*V* ratio may have occurred during cerebral vasoconstriction. The significant correlation between changes in CBV and Sct_{O_2} in this study also suggests a possible cause–effect relationship between changes in cerebral *A*:*V* ratio and changes in Sct_{O_2} measured by NIRS. The above hypothetical explanation based on autoregulatory vasoconstriction is also supported by the CO_2's modulating effect demonstrated by this study. Specifically, the worsening decrease in Sct_{O_2} during hypocapnia may merely reflect a more robust autoregulatory mechanism because it has been shown that an impaired autoregulation can be restored by hypocapnia.[16] Nonetheless, the mechanism of how phenylephrine induces cerebral vasoconstriction is complicated. The recent finding that sympathetic nerve activity (SNA) from the superior cervical ganglion is increased after pharmacologically (including phenylephrine) induced

rapid and large increase in arterial pressure suggests a role of SNA in cerebral circulation regulation.[17 18] Increased SNA to the brain leads to cerebral vasoconstriction and prevents abrupt cerebral over-perfusion and haemorrhage.[17 18] The biophysical change induced by this SNA mechanism is similar to the above proposed autoregulatory mechanism.

The results of this study agree with our previous findings in that both CO and Sct_{O_2} are consistently decreased after phenylephrine treatment.[1] These concordant changes imply that the decrease in CO is likely to account for the decrease in Sct_{O_2}. This is further supported by the observation that CBF estimated using transcranial Doppler is decreased when CO, but not MAP, is decreased via lower body negative pressure.[19] However, if the decrease in CO were solely responsible for the decrease in Sct_{O_2}, we would have observed similar decreases in Sct_{O_2} at different CO_2 levels, because this study shows that the decreases in CO at different CO_2 levels are comparable. Conversely, we have observed significantly different decreases in Sct_{O_2} at different CO_2 levels. This implies that while the decrease in CO may be responsible for the decrease in Sct_{O_2}, the other mechanisms such as the decreased *A*:*V* ratio proposed above may also play a significant role.

The difference between FD-NIRS, the technology adopted by this study, and continuous wave (CW)-NIRS, the technology currently adopted by clinical practice has been described. In brief, FD-NIRS is regarded as a quantitative approach because it has the ability to differentiate between photon absorption and scattering while CW-NIRS is only regarded as a trend monitor due to its inability to differentiate between the two optical properties. Nonetheless, both technologies are similar in that they are not appreciably affected by the extracerebral tissue layers, if the spacing between optodes is optimized.[6 7 20 21] For example, selective clamping of the external carotid artery in a patient with a defective Circle of Willis shows that FD-NIRS measurements are not affected during external carotid artery occlusion (Fig. 5A). Conversely, in the same patient, clamping of the internal carotid artery shows that pronounced changes in NIRS measurements occur (Fig. 5B). Clearly, the quantitative FD-NIRS result is both spatially and temporally responsive to changes in cerebral perfusion and oxygenation.

Even though phenylephrine causes a consistent decrease in Sct_{O_2}, the magnitude of the decrease is very small (~1.5–3.5% absolute change depending on CO_2 level) and seems unlikely to be clinically significant. Al-Rawi and colleagues found that a relative 13% decrease from baseline, which is approximately twice as great as that seen here, correlates with cerebral ischaemia in patients undergoing carotid artery procedures.[22] Importantly, the decrease in Sct_{O_2} may reflect, at least partially, a decreased arterial blood contribution to NIRS measurements due to cerebral vasoconstriction. Therefore, the phenylephrine-induced decrease in Sct_{O_2} may not represent real or significant cerebral ischaemia and hypoxia if it is partially attributed to a

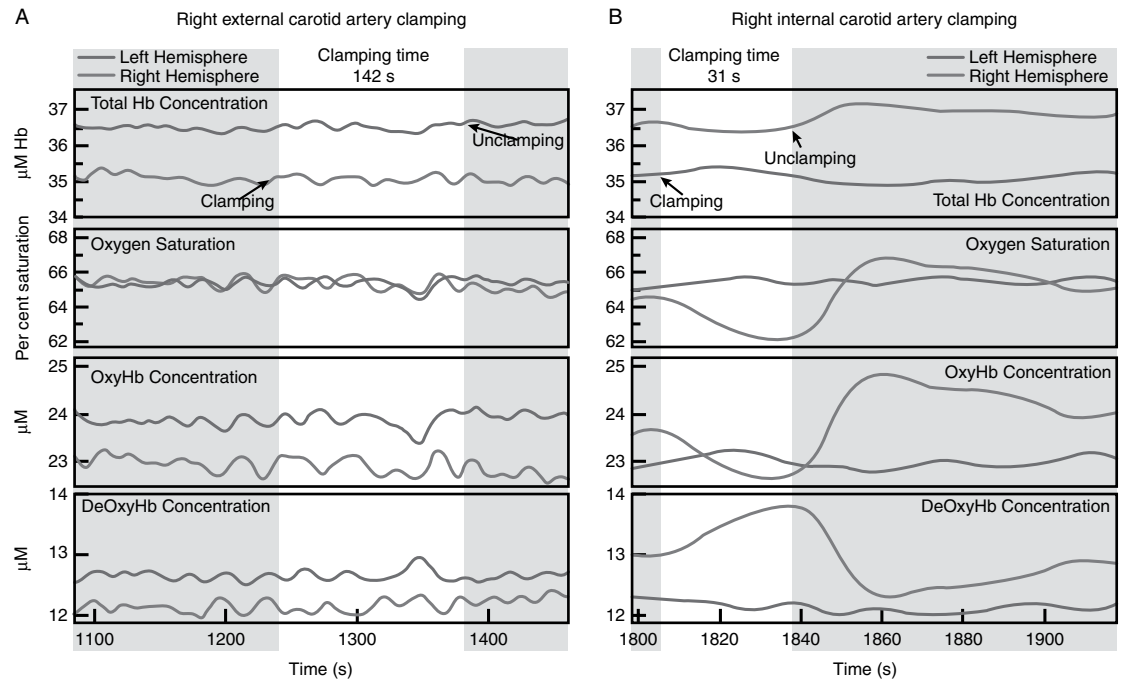

Fig 5 FD-NIRS measurements of THC (top panel), cerebral tissue oxygen saturation (second panel), oxy-haemoglobin concentration (third panel), and deoxy-haemoglobin concentration (bottom panel) during right external carotid artery clamping (A) and right internal carotid artery clamping (B) in a patient with defective collateral circulation through the Circle of Willis. Note that the time scales (s) are different between (A) and (B). (Courtesy of Fady T. Charbel, MD, FACS.)

functional pressure autoregulation mechanism. Caution is needed in extrapolating our results to clinical situations where autoregulation may be impaired. Caution is also needed when interpreting the CBV result because its changes are rather small and the study may be underpowered in detecting the small change. Propofol and remifentanil were used in this study to maintain general anaesthesia because they preserve cerebral autoregulation,[23] cerebrovascular CO_2 reactivity,[24] and CBF–cerebral metabolic rate of oxygen ($CMRO_2$) coupling[25] and they do not possess an intrinsic cerebral vasodilating effect, which may occur with inhalation anaesthetic agents.[26]

In summary, this study demonstrates that a phenylephrine bolus results in a consistent but small decrease in Sct_{O_2} and CBV, and this decrease is intensified by hypocapnia and blunted by hypercapnia. The decrease in CO may not be solely responsible for the decrease in Sct_{O_2}. A decreased *A*:*V* ratio secondary to cerebral vasoconstriction may also account for the phenylephrine-induced decrease in Sct_{O_2}. The effect of phenylephrine treatment on Sct_{O_2} and CBV in individuals with injured nervous systems or receiving drugs that abolish autoregulation is not known.

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Declaration of interest

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

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NEUROSCIENCES AND NEUROANAESTHESIA

Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction

L. Tang[1], R. Kazan[1], R. Taddei[2], C. Zaouter[2], S. Cyr[1] and T. M. Hemmerling[1*]

[1] Department of Anaesthesiology, McGill University, Montreal General Hospital, 1650 Cedar Avenue, Montreal, Canada H3G 1A4
[2] University of Pisa, Pisa, Italy

* Corresponding author. E-mail: thomas.hemmerling@mcgill.ca

Editor's key points

- It is vital to understand the aetiology of postoperative cognitive dysfunction (POCD).
- Authors correlated cerebral oxygenation during thoracic surgery with POCD in 76 patients.
- Twenty-nine per cent of the patients had decreased Mini-Mental State Exam score 3 h after surgery.
- Importantly, even 5 min of cerebral oxygenation reduced to <65% led to cognitive dysfunction with odds ratio of 2.03.

Background. The objective of this prospective study is to determine cognitive dysfunction after thoracic surgery.

Methods. Seventy-six patients undergoing thoracic surgery with single-lung ventilation (SLV) of an expected duration of >45 min were enrolled. Monitoring consisted of standard clinical parameters and absolute oximetry ($S_{ct}O_2$). The Mini-Mental State Exam (MMSE) test was used to assess cognitive function before operation and at 3 and 24 h after operation. Data were analysed using Spearman correlation test; risks for cognitive dysfunction were expressed as odds ratios. $P<0.05$ and data are presented as median (interquartile range).

Results. One patient was excluded from the study. $S_{ct}O_2$ during SLV decreased to critical values of <65%, 60%, and 55% in 40 (53%), 15 (20%), and 5 patients (7%), respectively. Twenty-two patients (29%) had a decrease of MMSE>2 points 3 h after surgery, eight patients (10%) had a decrease of MMSE>2 points 24 h after surgery. Postoperative cognitive dysfunction correlated at $r^2=0.272$, 0.285, 0.297 with patient exposure times to $S_{ct}O_2<65\%$ ($P=0.018$), <60% ($P=0.013$), <55% ($P=0.010$), respectively. The odds ratios of developing early cognitive dysfunction ranged from 2.03 (95% CI: 0.74–5.59) for a short (<5 min) exposure to $S_{ct}O_2<65\%$ to a maximum of 9.56 (95% CI: 1.75–52.13) when $S_{ct}O_2$ was <60% for more than 30 min.

Conclusions. Early cognitive dysfunction after thoracic surgery with SLV is positively related to intraoperative decline of $S_{ct}O_2$.

Keywords: cerebral saturation; postoperative cognitive dysfunction; single-lung ventilation; thoracic surgery

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Monitoring cerebral oxygen saturation has become increasingly important in cardiac[1–6] and non-cardiac surgery.[7 8] Studies in cardiac surgery have shown that treating cerebral oxygen desaturations can improve postoperative cognitive function and reduce complications.[6]

There is a growing number of studies showing a significant incidence of cerebral oxygen desaturations in non-cardiac surgery, such as neurosurgery,[9–11] carotid surgery,[12–14] general surgery,[8 15 16] and thoracic surgery.[17–19] We have recently shown that the incidence of cerebral oxygen desaturations in patients undergoing thoracic surgery with single-lung ventilation (SLV) is similar to the incidence observed in cardiac surgery,[17] and that these desaturations increase the risk of poor postoperative outcome.[18 19]

To the best of our knowledge, there is no study published which investigates cognitive function after thoracic surgery. The determination of cognitive function after thoracic surgery is impaired by possible difficulty to determine long-term cognitive dysfunction in a patient population with limited survival rates. In addition, the routine use of continuous high thoracic epidural analgesia for up to 5 days after surgery (our institution) limits more extensive and repetitive tests of cognitive function after thoracic surgery. Some studies[15 20 21] have shown that evaluation of cognitive dysfunction only at 1 week after surgery—not immediately after surgery–might miss early cognitive dysfunction; therefore, tests seem necessary which can easily and reliably be performed at several time points within the first 24 h after surgery.

The Mini-Mental State Exam (MMSE)[22] is an easy test to do, and can be performed under the specific perioperative conditions of thoracic surgery. The test has been shown to be a valid and reliable method of cognitive screening widely used in both clinical and research settings.[22 23]

It was the objective of this prospective study to determine the possible correlation between cerebral oxygen desaturations during SLV and postoperative cognitive dysfunction (POCD) in patients undergoing thoracic surgery.

Methods

We conducted a prospective, observational, single-blinded study. After approval from the Local Ethics Committee and written informed consent, 76 patients, aged 18 yr or greater, undergoing elective thoracic surgery with SLV of an expected duration of more than 45 min were enrolled. Patients who had previous cerebral disease, dementia, severe problems in hearing and understanding, or who were unable to provide informed consent were excluded.

Before general anaesthesia, an epidural catheter was inserted at T4,5 or T5,6 level for perioperative administration of bupivacaine 0.1% and fentanyl 3 $\mu g\ ml^{-1}$. After radial arterial line placement, anaesthesia was induced with propofol 0.5–1.5 mg kg^{-1}, fentanyl 4–7 $\mu g\ kg^{-1}$, and rocuronium 0.6 mg kg^{-1}. A left-sided double-lumen tube was inserted under bronchoscopic assistance. Anaesthesia was provided using sevoflurane to maintain a bispectral index of 45 (BIS, Aspect A-2000 monitoring system, Aspect Medical System, MA, USA).

Rocuronium boluses were given at the discretion of the anaesthesiologist. Analgesia was maintained using 6–10 ml h^{-1} of bupivacaine 0.1%+fentanyl 3 $\mu g\ ml^{-1}$ commenced immediately after insertion of the epidural catheter. For surgery, the patient was placed in the left or the right lateral decubitus position. Intermittent positive pressure ventilation provided 100% oxygen to maintain an oxygen peripheral saturation of >90%; continuous positive airway pressure (CPAP) was applied for a limited time to the non-dependent lung when the peripheral saturation decreased below 90%.

Brain oxygen saturation was monitored continuously using the FORESIGHT cerebral oximeter (CAS Medical Systems, CT, USA) started before anaesthesia induction until extubation. After wiping the patient's forehead with an alcohol pad, the sensors were positioned bilaterally on the patient's forehead and covered in order to prevent ambient light to affect the measurements. Surgeons and anaesthesiologists were blinded to the measurement of cerebral oximetry (values were hidden), no anaesthetic decision was taken based on the absolute $S_{ct}O_2$ values. The average, left and right absolute $S_{ct}O_2$ values were collected every 5 min. Baseline absolute $S_{ct}O_2$ values were taken in the patient who is awake after 2 min of breathing 100% oxygen through a face mask. Standard monitoring variables such as peripheral oxygen saturation, BIS, mean arterial pressure (MAP), and heart rate were recorded every 5 min. In addition, arterial blood-gas analysis (pH, P_{CO_2}, P_{O_2}, Na^+, K^+, Ca^{2+}, glucose, lactate, haematocrit, haemoglobin, SO_2) was performed every 15 min.

The average, left and right absolute $S_{ct}O_2$, the highest and lowest values were used for analysis. Baseline $S_{ct}O_2$ value was defined as the average saturation value during a period of 1 min, obtained 5 min after administration of the sensors. The absolute $S_{ct}O_2$ decrease was calculated by subtracting the minimum absolute $S_{ct}O_2$ value during SLV from the baseline absolute $S_{ct}O_2$ value regardless of right, left, or average for each patient; the relative $S_{ct}O_2$ decrease was defined as the absolute $S_{ct}O_2$ decrease divided by the baseline $S_{ct}O_2$ value.[17 18] $S_{ct}O_2$ minutes and the area under the threshold (AUT) spent beneath the absolute threshold limits of 65%, 60%, and 55% were calculated for right, left, and average $S_{ct}O_2$ values. AUT was calculated based on this formula: AUT (present)=AUT (past)+($S_{ct}O_2$ threshold−$S_{ct}O_2$ value)×sample rate. AUT is 0 if the $S_{ct}O_2$ value is above the defined $S_{ct}O_2$ threshold.[24]

The MMSE tests neurocognitive functions, such as orientation, registration, attention, calculation, recall, and language.[22] This test combines high validity and reliability with brevity and ease of application, and suggests decline in cognitive function with repeated tests. The maximal score of MMSE is 30 points, and MMSE score≤23 is considered as abnormal. The MMSE was performed by a research assistant, not aware of intraoperative oximetry values, before surgery and then repeated twice, 3 and 24 h after surgery, respectively, to assess postoperative cognitive function. A decrease in MMSE score>2 points from baseline was defined as POCD.[8 15 16]

To calculate the sample size for this study, we hypothesized that the POCD is correlated with cerebral oxygen desaturations during surgery as defined by the exposure time spent beneath the absolute threshold limit of 65%. Thus, considering a coefficient correlation of 0.3 to be a fair correlation and consequently to be clinically relevant, we used an effect size of 0.3 for a one-sided type I error of 0.05, a statistical power of 80%, resulting in a sample size of 64 patients (Correlation Point Biserial Model, G*Power, v. 3.1.2, University Kiel, Germany). We planned to recruit 76 patients under the assumption that some would be excluded for protocol violation.

Data were analysed using SPSS (v. 15.0, SPSS Inc., Chicago, IL, USA) and presented as median [interquartile range (IQR); range] for continuous data and number (proportion) for nominal data. Spearman correlation test was used to test the correlation between POCD (defined as decrease in MMSE score>2 points from baseline) and age, SLV duration, relative maximum $S_{ct}O_2$ decrease, exposure time under threshold limits of $S_{ct}O_2$ of 65%, 60%, and 55% and other selected clinical parameters. Effects of exposure time under threshold limits of 65%, 60%, and 55% on cognitive dysfunction were calculated using risk-analysis and were expressed in terms of odds ratios. A P-value <0.05 was considered as statistically significant.

Results

A total of 76 patients were enrolled between August 2008 and February 2010 in Montreal General Hospital, Montreal, Canada. One patient was excluded from the analysis

Table 1 Patient data. Data are given as median (IQR; range) or values. SLV, single-lung ventilation; MMSE, Mini-Mental State Exam

	n=75
Age (yr)	64 (58, 76; 32, 86)
Sex (F/M)	35/40
ASA grade (I/II/III)	1/38/36
Duration of surgery (min)	175 (145, 210; 40, 435)
Duration of SLV (min)	135 (100, 170; 15, 405)
Baseline $S_{ct}O_2$ values (%)	79 (77, 84; 67, 96)
Baseline MMSE scores	28 (27, 29; 20, 30)
Type of surgery	
Lobectomy	45
Wedge resection	18
Pneumonectomy	10
Segmentectomy	2

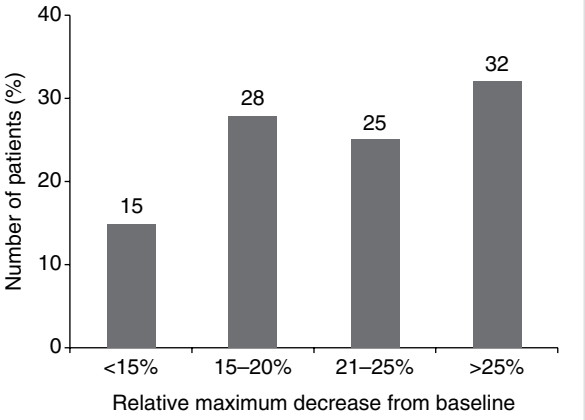

Fig 1 Number of patients with relative $S_{ct}O_2$—decreases of <15%, 15–20%, 21–25%, and >25% from baseline values.

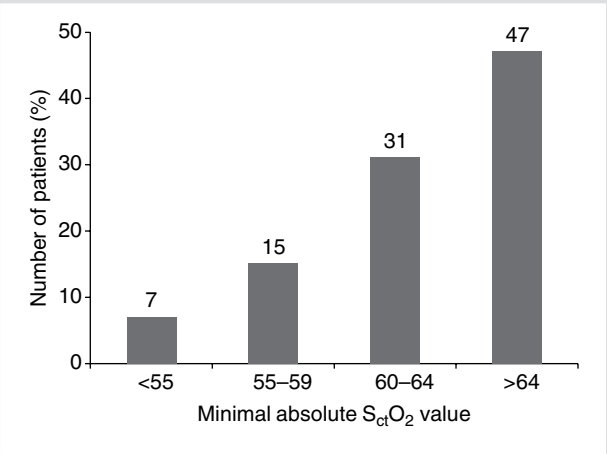

Fig 2 Minimal absolute $S_{ct}O_2$ values reached by patients (n=75) during SLV, with cutoff values of 55, 60, and 65.

because the patient was not willing to repeat the MMSE test after surgery. Data of 75 patients were taken into analysis. Characteristics of the patients, including age, sex, ASA grade, duration of surgery, duration of SLV, and type of surgery are listed in Table 1. No patient needed additional CPAP or oxygen insufflations. No surgical site infection, postoperative haemorrhage, or stump leakage were observed.

The patients had a baseline $S_{ct}O_2$ value [median (IQR; range)] of 79% (77, 84; 67, 96) in the awake state, which decreased to a minimum $S_{ct}O_2$ of 63% (59, 68; 33, 76) during SLV. This is equivalent to a decrease of $S_{ct}O_2$ by 21% (17, 27; 5, 54). Fifty-seven per cent of the patients had a relative maximum decrease of more than 20% in comparison with the baseline $S_{ct}O_2$ values (Fig. 1). The patients recovered to $S_{ct}O_2$ values of 69 (65, 73; 53, 86) within 5 min after the end of SLV. There was no significant difference between the $S_{ct}O_2$ of the site of surgery and the opposite site.

The minimal absolute $S_{ct}O_2$ values attained by patients during SLV are presented in Figure 2. The median exposure times to $S_{ct}O_2$ values of <65%, 60%, and 55% were 45, 45, and 15 min, respectively, which accounts for 30%, 25%, and 6% of the time of surgery, respectively. The integrals of $S_{ct}O_2$ under the specific threshold (AUT) of 65%, 60%, and 55% are presented in Table 2.

Patients showed a peripheral saturation of 99% (98, 99; 96, 100) when awake. During SLV, this value decreased to 98% (97, 99; 92, 100), then increased to 99% (98, 99; 97, 100) at the end of surgery. Arterial Pa_{O_2} started at 55 kPa (47, 65; 10, 78), then significantly decreased to 25 kPa (18, 31; 10, 72) during SLV, and recovered to 56 kPa (41, 63; 22, 80) at the end of the surgery. Changes in haemodynamic parameters, BIS, haemoglobin, and haematocrit during surgery are shown in Table 3.

The patients had a baseline MMSE value of 28 points (27, 29; 20, 30), which decreased to 26 points (25, 29; 13, 30) 3 h after surgery, then returned to 28 points (27, 30; 20, 30) 24 h after surgery. When tested at 3 h after surgery, a total of 22 patients (29%) had a decrease of MMSE>2 points. Out of these 22 patients, 10 patients (13%) showed a decrease of MMSE>3 points, and 6 patients (8%) a decrease of MMSE>4 points, respectively. When tested at 24 h after surgery, only eight patients (10%) still had a decrease of MMSE>2 points. Out of all the selected clinical parameters (age, duration of SLV less than surgery, relative decrease of haemoglobin, haematocrit, peripheral oxygen saturation, partial oxygen, carbon dioxide pressure in arterial blood, or MAP), only the exposure time spent below the $S_{ct}O_2$ thresholds of <65%, 60%, and 55% were found to be significantly correlated with POCD at r^2=0.272 (P=0.018), r^2=0.285 (P=0.013), and r^2=0.297 (P=0.01), respectively.

Table 4 demonstrates the odds ratios with 95% confidence intervals for POCD (decrease of MMSE>2 points) related to

Table 2 Exposure time and area under threshold (AUT) of 65%, 60%, and 55% of duration of surgery. Data are given as value (percentage) or median (IQR; range)

$S_{ct}O_2$ (%)	*n* (%)	Exposure time (min)	AUT (%–min)	Surgery time (min)	Time of $S_{ct}O_2$ (% surgery time)
<65	40 (53%)	45 (25, 115; 5, 350)	25 (13, 161; 5, 2323)	182 (150, 232; 86, 435)	30 (15, 64; 2, 95)
<60	15 (20%)	45 (15, 90; 5, 225)	32 (10, 125; 5, 1162)	200 (150, 250; 100, 435)	25 (13, 36; 3, 65)
<55	5 (7%)	15 (7, 67; 5, 100)	7 (5, 394; 5, 761)	265 (247, 362; 245, 435)	6 (3, 24; 2, 41)

Table 3 Standard monitoring parameters and selected blood-gas parameters throughout the three stages of thoracic surgery (pre-SLV, SLV, and the end of the surgery). Data are presented as median (IQR; range). SLV, single-lung ventilation; MAP, mean arterial pressure; BIS, bispectral index

	Pre-SLV	SLV	End of surgery
MAP (mm Hg)	76 (68, 83; 47, 115)	76 (71, 80; 57, 106)	76 (71, 83; 64, 123)
Heart rate (beats min^{-1})	68 (63, 77; 46, 105)	71 (63, 79; 42, 99)	72(64, 80; 44, 107)
BIS (0–100)	47 (41, 52; 29, 67)	46 (41, 49; 30, 86)	49 (44, 55; 30, 86)
Haemoglobin (g dl^{-1})	11.2 (10.9, 12.4; 8.1, 14.0)	11.0 (10.2, 11.7; 7.4, 13.3)	10.5 (9.6, 11.8; 7.4, 13.3)
Haematocrit (%)	37 (35, 40; 26, 45)	35 (32, 38; 24, 43)	34 (31, 38; 24, 43)

Table 4 Analysis of risk factors in relation to postoperative cognitive dysfunction (decrease in MMSE>2 points). Data are presented as values. OR, odds ratio; CI, confidence interval. *Unable to calculate odds ratio as the denominator is 0

	$S_{ct}O_2$<65%	$S_{ct}O_2$<60%	$S_{ct}O_2$<55%
>5 min	2.03 (0.74–5.59)	3.66 (1.06–12.58)	8.21 (0.80–83.82)
>10 min	2.38 (0.86–6.58)	4.48 (1.234–6.21)	5.20 (0.45–60.57)
>15 min	2.58 (0.93–7.16)	3.60 (0.97–13.41)	*
>20 min	2.5 (0.93–7.16)	4.59 (1.15–18.36)	*
>25 min	3.34 (1.19–9.38)	6.25 (1.40–27.89)	*
>30 min	3.04 (1.08–8.51)	9.56 (1.75–52.13)	*

the incremental exposure time of $S_{ct}O_2$ values under thresholds of <65%, 60%, and 55%.

MAP values throughout surgery for patients with or without significant cerebral oxygen desaturations were similar and are shown in Figure 3.

Discussion

This study confirms previous findings[17 18] of our group that a significant number of patients experience cerebral oxygen desaturations during SLV in thoracic surgery; one-third of the patients showed relative decreases of more than 25% from the baseline values. Half of the study patients had decreases of absolute $S_{ct}O_2$ values <65%, a threshold identified as indicative for an increased risk of postoperative complications.[24] Almost one-third of our patients showed a significant impairment of early (<3 h after surgery) postoperative cognitive function with 90% of them returning to normal cognitive function at 24 h after surgery. Even short periods of absolute $S_{ct}O_2$ values of <65% during SLV double the risk of POCD.

This study investigated patients undergoing thoracic surgery with SLV; in an initial small size study of 20 patients,[17] we found that 35% of the patients showed a significant relative decrease of more than 25% of cerebral oxygen saturation from the respective baseline values. In another study,[18] in 50 patients undergoing thoracic surgery with SLV, the significant incidence of cerebral oxygen desaturations was confirmed with more than half of the patients showing minimum $S_{ct}O_2$ values of <65%. In a cohort study by Tobias and colleagues,[19] in 40 patients undergoing thoracic surgery with SLV, 21% of the patients showed absolute changes of cerebral oxygen saturation of at least 20% less than the baseline values. Changes in cerebral oxygen saturation were presented in these former three studies in different ways, either as relative,[17] or absolute[18 19] changes from baseline. There is some inconsistency when it comes to the threshold of clinically relevant changes; this might be owing to different monitoring methods (relative or absolute oximetry), different types of surgery, and different ways to calculate these changes from baseline values. A consensus

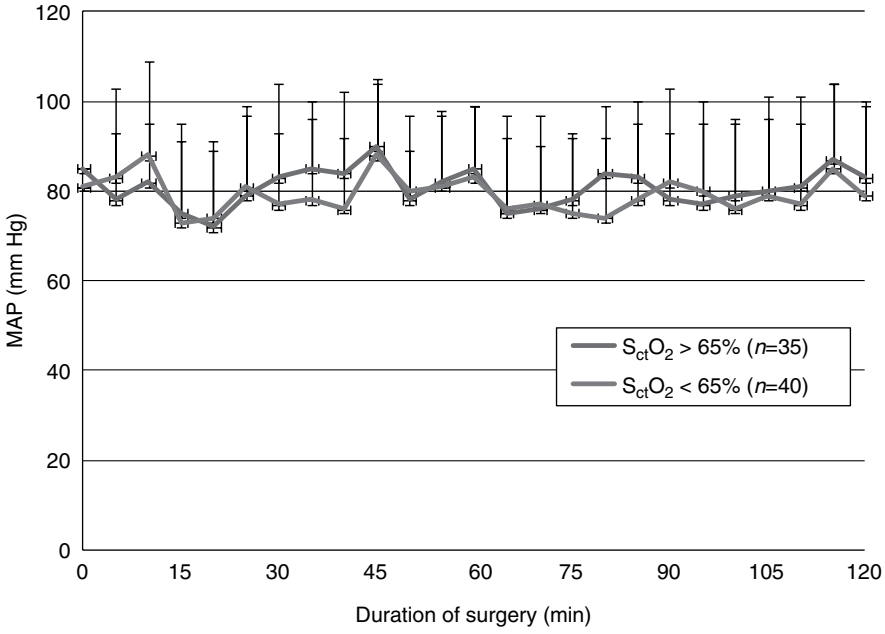

Fig 3 Comparison of mean arterial pressure (MAP) values throughout surgery in patients who showed cerebral oxygen desaturations below absolute $S_{ct}O_2$ values of 65% vs patients who did not reach absolute $S_{ct}O_2$ values of 65%. Data shown as median, bars represent interquartiles.

might be derived from two studies, one study used relative oximetry[25] and the other used absolute oximetry.[24] Samra and colleagues[25] determined the threshold of cerebral oxygen desaturations for the occurrence of neurological symptoms in patients undergoing carotid surgery in the awake state. This study found that a threshold of more than 20% of relative decrease from baseline was related to an increased incidence of neurological symptoms during carotid surgery. A more recent study by Fischer and colleagues[24] using absolute oximetry has shown that absolute $S_{ct}O_2$ values of $<65\%$ are related to an increased risk of postoperative complications in patients undergoing aortic arch replacement surgery.

As we used absolute oximetry to monitor cerebral oxygen saturation, we used Fischer's[24] thresholds to calculate the risk of developing POCD. We found that the risk was related to both the degree of desaturation and the duration during which these desaturations occurred. The risk of developing POCD ranged from two-fold even with a short (<5 min) exposure to $S_{ct}O_2$ concentrations of $<65\%$ to a 10-fold risk when desaturations of $<60\%$ occurred for more than 30 min. There is no other study which investigated the incidence of cognitive dysfunction after thoracic surgery, so our findings cannot be compared with other studies. However, there are studies determining the incidence and risk for cognitive dysfunction after non-cardiac surgery.

Few studies have looked at POCD after general anaesthesia in non-cardiac surgery. In one study, Casati and colleagues[15] studied cognitive dysfunction after abdominal surgery in elderly patients. Using the MMSE, he determined that 35% of 56 patients showed a significant decrease in cognitive function when tested 1 week after surgery. This dysfunction was significantly correlated with cerebral oxygen desaturation during surgery at $r^2=0.26$. The cerebral oxygen desaturations in that study were correlated significantly to an increased stay in the hospital highlighting the economic impact of intraoperative cerebral oxygen desaturations. It is interesting to note that the present study showed a similar positive correlation between intraoperative cerebral oxygen decline and POCD: the correlation coefficient ranged from $r^2=0.27$ to $r^2=0.3$ depending on the exposure time to increased degrees of desaturation. In another study involving 60 patients undergoing abdominal surgery, Casati and colleagues[16] confirmed the appearance of cognitive dysfunction—as determined using the MMSE—1 week after surgery only in patients with intraoperative cerebral oxygen decrease. Patients, who did not experience any desaturation during surgery, had a normal cognitive function 1 week after surgery. The desaturations were not correlated with the rate of complications, probably because of the small number of patients (a total of only 9 out of 60 patients showed complications after surgery). In one of our earlier studies in thoracic surgery,[18] we could show an increased risk of having postoperative complications—as determined using a modified SOFA and Clavien score—when cerebral oxygen decline occurred during SLV.

This highlights the importance of timing of cognitive dysfunction tests after non-cardiac surgery. In contrast to cardiac surgery, where patients usually stay intubated for a significant time and cognitive function tests can hardly be performed before 24 h after surgery, the rapid recovery of cognitive function after non-cardiac surgery allows the

detection of early cognitive dysfunction. Chen and colleagues[21] confirmed the importance of early cognitive function testing; they determined cognitive dysfunction after hip or knee arthroplasty in 70 patients without monitoring cerebral oximetry. When tested using MMSE 1 h after surgery, 51% of the patients showed a significant cognitive dysfunction, which disappeared in 85% of the patients at 3 h after surgery. When tested at 24 h after surgery, only one of 70 patients showed a cognitive dysfunction. These results agree with our findings with almost 90% of our patients showing normal cognitive function 24 h after surgery. In the present study, we also decided to determine early cognitive dysfunction and repeat MMSE tests at 24 h after surgery. Because of the specific nature of thoracic surgery—installation of patients in the PACU usually takes longer than in patients undergoing abdominal surgery, pain control might need some adjustments in the early periods of stay at the PACU—we designed the study for early testing of MMSE at 3 h after surgery. At that time, pain control was sufficient in all patients during MMSE testing, thus avoiding any pain-related bias. In order to exclude any bias from administration of systemic opioids, no patient received any opioids other than in the epidural infusion. However, there is a need for more studies indicating the impact of early cognitive dysfunction on general recovery from surgery, such as length of stay in the PACU or in the hospital.

One of the limitations of our study is that only one cognitive function test—MMSE—was used; this was based on the specifics of thoracic surgery, for example, an efficient epidural analgesia limits mobility of patients. Certain tests for cognitive function, such as the 6-min walk test or finger tapping test, can thus not be used in the immediate postoperative period. In order to maintain patients' cooperation for the cognitive function test in the early postoperative period after such a major surgery, it was decided to have them undergo only one test. Although we are aware that this test does not completely test mental function, studies in non-surgical subjects have shown that it reliably indicates the occurrence of cognitive dysfunction.[22 23]

At present, there is no study that has investigated the relationship between very early ($<$24 h after surgery) cognitive dysfunction with long-term cognitive function (more than 3 months), which will be the focus of future work and also to determine the clinical relevance of a two-point decline in MMSE after surgery.

Another limitation of this study is the fact that we did not assess the impact of the cognitive dysfunction on the duration of stay in either the hospital or in the PACU. Studies of such nature are very difficult to perform in our hospital setting—as in most hospital settings—because discharge from either PACU or hospital is influenced by various non-medical issues, such as bed shortage on the normal ward, nursing staff preferences, and other organizational issues. However, it needs to be pointed out that Casati and colleagues[15] have shown that intraoperative cerebral oxygen desaturations are significantly correlated with the length of hospital stay. As PACU nurses regularly assess the cognitive status in our hospital setting, it can be assumed that reduced cognitive function in the immediate postoperative period might lead to delayed discharge from the PACU.

We speculate that the significant cerebral oxygen desaturations during thoracic surgery with SLV could either be related to pathophysiological changes owing to changes in lung perfusion or ventilation or possible microemboli related to surgery. Future, more invasive studies will focus on revealing these mechanisms.

We conclude that 50% of patients undergoing thoracic surgery show cerebral oxygen desaturation during SLV of $S_{ct}O_2$ of $<$65%. These desaturations are positively correlated with early POCD. The risk of POCD after intraoperative cerebral oxygen desaturations ranges from two-fold to 10-fold, depending on the time and degree of the decline.

Declaration of interest

See Funding statement below.

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BJA

PAEDIATRICS

Effect of different quantities of a sugared clear fluid on gastric emptying and residual volume in children: a crossover study using magnetic resonance imaging

A. Schmitz[1]*, C. J. Kellenberger[2], N. Lochbuehler[2], M. Fruehauf[1], R. Klaghofer[3], H. Fruehauf[4] and M. Weiss[1]

[1] Department of Anaesthesia and [2] Department of Diagnostic Imaging, University Children's Hospital, Steinwiesstrasse 75, CH 8032 Zurich, Switzerland
[3] Statistics, Division of Psychiatry and Psychotherapy, University Hospital, Zurich, Switzerland
[4] Division of Gastroenterology and Hepatology, Department of Internal Medicine, Triemli Hospital, Zurich, Switzerland

* Corresponding author. E-mail: achim.schmitz@kispi.uzh.ch

Editor's key points

- Using MRI, this study compares gastric volume and emptying half-life during 1 h after 3 or 7 ml kg^{-1} sugared clear fluid intake.
- Gastric content volume 1 h after intake of 3 ml kg^{-1} syrup is significantly smaller than after 7 ml kg^{-1} and within the range of baseline.
- Emptying half-life is similar for different volumes of ingested liquid with identical caloric density.
- The findings underline the impact of the volumes of ingested liquid on residual gastric volumes in children.

Background. Gastric emptying in the first 2 h after 7 ml kg^{-1} of sugared clear fluid has recently been investigated in healthy children using magnetic resonance imaging (MRI). This study aims to compare gastric volume and emptying half-life during 1 h after 3 or 7 ml kg^{-1} sugared clear fluid intake.

Methods. Fourteen healthy volunteer children aged 11.1 (8.2–12.5) yr were investigated prospectively after administration of 3 and 7 ml kg^{-1} diluted raspberry syrup in a randomized order, after overnight fasting (baseline). Gastric content volume (GCV_w) was assessed with a 1.5 Tesla MRI scanner in a blinded fashion. Data are presented as median (range) and compared using the Wilcoxon test.

Results. Baseline GCV_w was 0.39 (0.04–1.00) and 0.34 (0.07–0.75) before intake of 3 and 7 ml kg^{-1} syrup, respectively (P=0.93). GCV_w was 0.45 (0.04–1.55)/1.33 (0.30–2.60) ml kg^{-1} 60 min after ingestion of 3/7 ml kg^{-1} syrup (P=0.002). Thus GCV_w had declined to baseline after 3 ml kg^{-1} (P=0.39) but not after 7 ml kg^{-1} (P=0.001) within 60 min. $T_{1/2}$ was 20 (10–62)/27 (13–43) min (P=0.73) after 3/7 ml kg^{-1}.

Conclusion. In healthy volunteer children, residual GCV_w 1 h after intake of 3 ml kg^{-1} syrup is significantly smaller than that after 7 ml kg^{-1} and within the range of baseline.

Keywords: children; fluids, oral; gastric emptying; preoperative fasting

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Existing guidelines recommend 2 h of preoperative fasting for clear fluids, which is a compromise between patient comfort, cooperation, and hydration on the one hand and safety with regard to the risk of pulmonary aspiration of gastric contents on the other hand.[1–3] Published data indicate that recommended fasting times are often exceeded.[4 5] This may be because of several reasons, one of which is organizational delay during routine operating programmes. For practical reasons, a 1 h period of fasting or stop of fluid on demand would be desirable.

The rapid emptying of gastric contents after ingestion of sugared clear fluid has recently been shown in healthy children using magnetic resonance imaging (MRI).[6] Residual gastric content volumes (GCV_w) at the hypothetical time of anaesthesia induction after 2 h were similar to baseline values after overnight fasting. However, 7 ml kg^{-1} is a rather large liquid meal volume. Extrapolating these results to smaller ingested liquid meal volumes with identical caloric density suggests that residual gastric volumes may decline to baseline levels within $\leq$1 but data to prove this are still required.

Therefore, the objective of the current study is to compare residual GCV_w and gastric emptying half-life 1 h after administration of 3 *vs* 7 ml kg^{-1} of a sugared clear liquid meal after overnight fasting in healthy volunteer children.

Methods

This prospective, blinded, randomized crossover trial was performed in healthy volunteer children. It was approved by the

local ethical committee (ref: KEK-ZH-Nr. 2009–0147, amendment 3) and registered with ClinicalTrials.gov (ref: NCT01133691). Inclusion criteria were age between 6 and 14 yr, ASA physical status class I or II and capacity to fast overnight and to lie still for 2–3 min in an MRI scanner. Exclusion criteria were gastrointestinal disease, gastrointestinal functional disturbance, claustrophobia, and any other psychiatric disorders. Children participated after being informed as adequate to their age with informed written parental consent and were rewarded with a gift voucher. All volunteers participated twice within a week under similar conditions and, at the same time, they were instructed to fast from midnight until the liquid nutrient test meal was administered perorally in the morning. The liquid nutrient test meal consisted of either 3 or 7 ml kg^{-1} clear fluid [noncarbonated commercially available raspberry syrup diluted with tap water, drinking solution with identical caloric density of 135 kJ dl^{-1} (0.32 kcal ml^{-1}) and carbohydrate concentration 8 g dl^{-1}] in a randomized sequence. The participants had to drink this fluid in <5 min, and no other fluid or food was allowed until the end of the investigation. The times of last meal or fluid in the evening were recorded.

To evaluate gastric volumes, MRI was performed after overnight fasting about 30 min before syrup ingestion ('baseline'), immediately after syrup ingestion ('0 min'), and exactly 30 and 60 min thereafter ('30 min', '60 min'). A 1.5 Tesla system (Signa Twinspeed HDxt, GE Medical Systems, Milwaukee, WI, USA) with an eight-channel, eight-element phased array coil, which covers the entire stomach, was used for acquisition of axial 5 mm slices as previously described.[6] Random string codes were used to identify the MRI scans and allow for blinded evaluation, which was performed by one investigator on a workstation with standard post-processing software under supervision by an expert radiologist. Gastric volumes were determined by tracing manually gastric fluid or solid content with bright signal and gastric air with dark signal on every slice. The respective areas were then added and multiplied with slice thickness to obtain absolute gastric content volume (GCV) and gastric air volume (GAV). GCV and GAV were divided by body weight to calculate the body weight-corrected volumes (GCV_w, GAV_w), with the body weight-corrected total gastric volume (TGV_w) as sum.

The study was powered to show a difference of 0.65 ml kg^{-1} in GCV_w (SD 0.85) measured 60 min after ingestion of between 3 and 7 ml kg^{-1} syrup with a two-sided α of 0.05 and a power of 0.8 in a crossover design, based on the results of previous examinations[6] and assuming a gastric emptying half-life of 30 min.

Data are presented as median (range) unless indicated otherwise. The Wilcoxon test was used to compare volumes pair-wise, considering a two-tailed *P*-value of <0.05 to designate statistical significance. Pearson's *R* was calculated for intra-individual correlation of GCV_w and overnight fasting times. Assuming an exponential (EXP) time course of GCVw after fluid intake, half-life, $T_{1/2}$, was obtained for each individual gastric contents emptying curve and for the decline of mean/median GCV_w values. $T_{1/2}$ was calculated as $T_{1/2}=\mathrm{LN}(0.5)\ B^{-1}$, with *B* as non-standardized regression coefficient from simple linear regression of the logarithms of GCV_w values and time. Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, WA, USA) and SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, USA) were used for data analysis.

Results

Fourteen volunteer school age children (for characteristics, see Table 1) participated in this study and completed all scheduled examinations, in total 112 MRI scans, without any adverse events or delays. Duration of overnight fasting from last food and fluid ingestion until baseline examination was similar on both occasions [12.3 (10.3–14.3) h/12.4 10.5–14.1] h, $P=0.26$, and 11.4 (9.5–13.8) h/11.7 (9.9–14.1) h, $P=0.13$, respectively, for 3/7 ml kg^{-1} group) and correlated intra-individually ($R=0.61$, $P=0.02$, and $R=0.63$, $P=0.02$).

GCV_w and TGV_w values for both occasions are compared in Table 2 (the corresponding parametric values may be found in the Supplementary material, Table S1). Baseline GCV_w values were similar ($P=0.93$) but showed no significant

Table 1 Characteristics of volunteering children (overall: $n=14$; female: $n=3$; male: $n=11$). *According to '2000 CDC Growth Charts for the United States: Method and development' (http://iea.de/perz/index.htm). †BMI, weight $height^{-2}$

Age	11.1 (8.2–12.5) yr
Weight	37 (23–50) kg
Percentile of weight*	51 (4–95)
Height	144 (129–157) cm
Percentile of height*	51 (15–97)
Body mass index (BMI)†	17.8 (13.8–21.1) kg m^{-2}

Table 2 Comparison of median (range) of body weight corrected gastric content/total gastric volumes (GCV_w/TGV_w) and gastric emptying half-lifes before ('baseline') and after either 3 or 7 ml kg^{-1} raspberry syrup. *Wilcoxon test

	3 ml kg^{-1} syrup	7 ml kg^{-1} syrup	*P**
Body weight-corrected gastric fluid volume (GCV_w) (ml kg^{-1})			
Baseline	0.39 (0.04–1.00)	0.34 (0.07–0.75)	0.93
0 min	3.19 (2.11–4.09)	7.08 (5.81–8.11)	0.001
30 min	1.02 (0.13–1.68)	2.80 (0.86–3.92)	0.001
60 min	0.45 (0.04–1.55)	1.33 (0.30–2.60)	0.002
Body weight-corrected total gastric volume (TGV_w) (ml kg^{-1})			
Baseline	1.01 (0.40–3.23)	1.14 (0.30–2.03)	0.25
0 min	4.47 (2.85–7.15)	8.34 (7.06–12.93)	0.001
30 min	1.48 (0.88–5.41)	3.56 (1.28–9.49)	0.001
60 min	1.23 (0.08–2.69)	2.12 (0.61–7.33)	0.005
Gastric emptying half-life $T_{1/2}$ (min)			
	20 (10–62)	27 (13–43)	0.73

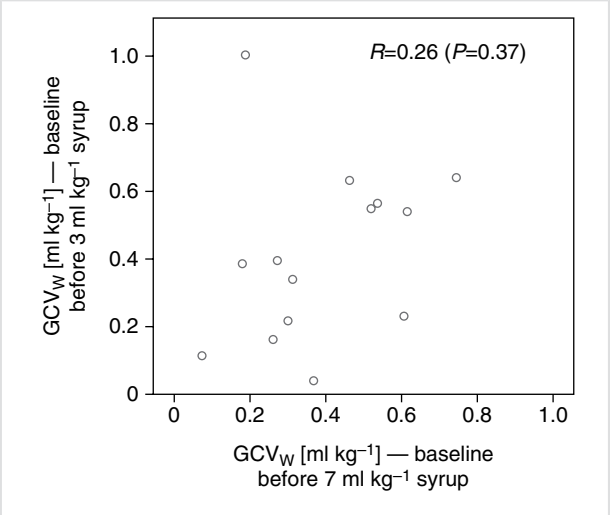

Fig 1 Scatter plot and intra-individual correlation of baseline body weight corrected gastric content volumes (GCV_w) after overnight fasting on 2 different days.

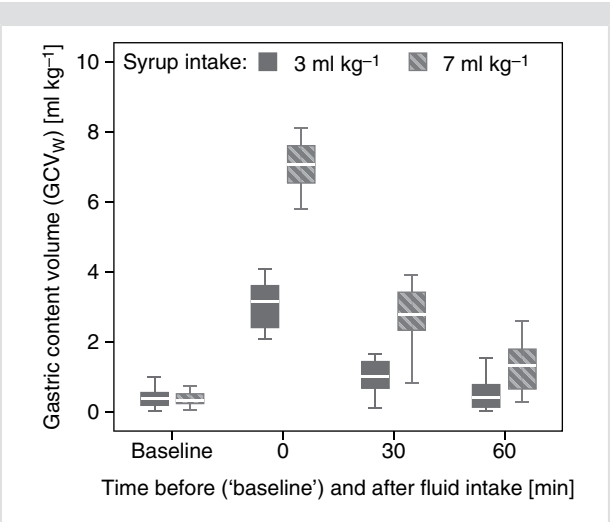

Fig 2 Box plot of body weight corrected gastric content volume (GCV_w) before ('baseline') and after clear liquid meal intake, comparing 3 and 7 ml kg^{-1} raspberry syrup.

intra-individual correlation (Fig. 1). Gastric emptying after ingestion of the liquid test meals is illustrated in Figure 2. After 60 min, GCV_w was still significantly smaller for 3 ml kg^{-1} when compared with 7 ml kg^{-1} ingested liquid volume. GCV_w had also declined into the range of baseline GCV_w after the 3 ml kg^{-1} liquid test meal volume (no difference between GCV_w at baseline and after 60 min, $P=0.39$) whereas 60 min after 7 ml kg^{-1} syrup intake, GCV_w was still significantly higher than the corresponding baseline value ($P=0.001$).

The gastric emptying half-lives calculated with mean and median GCV_w values were 23.9 min and 21.0 min, respectively, after 3 ml kg^{-1} liquid meal test volume, and with both mean and median GCV_w values 24.7 min after 7 ml kg^{-1}. The individual $T_{1/2}$ showed large variation and did not differ significantly between both liquid test meal volumes (Table 2).

The changes of TGV_w followed those of GCV_w (Table 2).

Discussion

The main finding of this pilot study was that the volume of residual gastric contents declined to baseline within 1 h after ingestion of the smaller liquid test meal volume of 3 ml kg^{-1}. GCV_w values were significantly higher after 7 than after 3 ml kg^{-1} ingested liquid volume 60 min after intake. The data obtained in this study group after ingestion of 7 ml kg^{-1} are basically in accordance with and confirm those previously obtained and published.[6]

It is highly desirable and of clinical relevance to achieve safe gastric residual volumes within 1 h after fluid ingestion. Prolonged preoperative fasting times occur in spite of liberal fasting rules (e.g. ASA guidelines),[3] which are related to organizational delays, lack of fluid administration by parents, or operation schedules that optimize utilization of operating theatre capacity rather than patient care. Preoperative timing and preparation could be considerably facilitated by reducing clear fluid fasting time to 1 h. The current practice of preoperative prescription could consecutively be replaced by a 'stop of fluid on demand' strategy.

The study findings underline the impact of the volumes of ingested liquid on residual gastric volumes, which have been used as a surrogate for the risk of pulmonary aspiration during anaesthesia induction.[1] The so-called risk volumes have been defined previously but of course other factors may be relevant[7] and the value of the gastric volume determination has been questioned.[8] Nevertheless, the current study indicates that it may be possible to choose drinking volumes reasonable for children's well-being and small enough to allow for gastric emptying to baseline values within 1 h. Although we do not know the 'real' risk volume for pulmonary aspiration, gastric volumes after overnight fasting and thus similar residual volumes after gastric fluid emptying may probably be considered as safe.

This study also showed that half-life of gastric emptying was similar after 3 and 7 ml kg^{-1} ingested liquid volume. Previous investigations in adults demonstrated different emptying rates for different fluids, with caloric load,[9] carbonation and carbohydrate levels,[10] and nutrient composition[11] as determining factors. Additional factors may be subject of future studies, such as the influence of solid food, perioperative drugs, preoperative stress, trauma, or pain on gastric emptying rate.

MRI has been shown to be a reliable method for assessment of gastric content and emptying.[5 12 13] While the current results are consistent with prior-reported baseline gastric contents volumes in healthy volunteer children, measurement in sedated children undergoing clinically indicated abdominal MRI have shown larger gastric residual volumes even after prolonged fasting.[5]

Thus, the presented preclinical results may be interpreted cautiously with regard to their application in clinical practice: only healthy school age children were investigated because a high degree of cooperation was required to perform the MRI measurements. The participants were not anaesthetized or undergoing any invasive procedure and received no medication whereas clinical patients may be stressed in the preanaesthetic period, suffer from pain and receive various perioperative drugs. Furthermore, the calculated half-lives should be regarded as approximation. A constant emptying rate was assumed to estimate half-life, although an exponential function may have limitations especially in the early postprandial phase[13]; however, the analysis of this early phase is not possible with our data because of 30 min intervals between subsequent measurements and because minor variations in drinking velocity cannot be excluded.

In conclusion, residual gastric content volume 1 h after ingestion of a sugared clear fluid depends on the amount of liquid volume ingested. In healthy volunteer children, GCV_w 60 min after intake of 3 ml kg^{-1} syrup is significantly smaller than after 7 ml kg^{-1} and within the range of baseline after overnight fasting. Emptying half-life is similar for different volumes of ingested liquid with identical caloric density.

Supplementary material

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

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Declaration of interest

None declared.

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BJA

RESPIRATION AND THE AIRWAY

Rapid sequence induction and intubation with rocuronium–sugammadex compared with succinylcholine: a randomized trial

M. K. Sørensen[1]*, C. Bretlau[2], M. R. Gätke[2], A. M. Sørensen[1] and L. S. Rasmussen[1]

[1] Department of Anaesthesia, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
[2] Department of Anaesthesiology, Copenhagen University Hospital, Herlev Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark

* Corresponding author. E-mail: martin@kryspin.dk

Editor's key points

- Succinylcholine is recommended for rapid sequence induction because of its quick onset and offset of actions.
- The offset of action of succinylcholine was compared with that of the rocuronium–sugammadex sequence.
- Sixty-one patients were studied in a randomized and blinded manner.
- Importantly, the rocuronium–sugammadex sequence had significantly quicker offset of neuromuscular blocking agent effect compared with succinylcholine.

Background. An unanticipated difficult airway may arise during rapid sequence induction and intubation (RSII). The aim of the trial was to assess how rapidly spontaneous ventilation could be re-established after RSII. We hypothesized that the time period from tracheal intubation to spontaneous ventilation would be shorter with rocuronium–sugammadex than with succinylcholine.

Methods. This randomized and patient- and observer-blinded trial was approved by the regional Ethics Committee and the Danish Medicines Agency. We included elective surgical patients undergoing general anaesthesia for RSII using alfentanil (10 μg kg^{-1}), propofol (2 mg kg^{-1}), and either succinylcholine (1 mg kg^{-1}) or rocuronium (1 mg kg^{-1}). Sugammadex (16 mg kg^{-1}) was given in the rocuronium group after tracheal intubation. The primary endpoint was the time from correct placement of the tracheal tube to spontaneous ventilation, defined as a respiratory rate of more than 8 bpm and a tidal volume of at least 3 ml kg^{-1} for 30 s.

Results. We included 61 patients; of whom, 55 were evaluated for the primary endpoint. The median time from tracheal intubation to spontaneous ventilation was 406 s with succinylcholine and 216 s with rocuronium–sugammadex ($P = 0.002$). The median time from tracheal intubation to 90% recovery of the first twitch in train-of-four (T_1 90%) was 518 s with succinylcholine and 168 s with rocuronium–sugammadex ($P < 0.0001$). Intubation conditions and time to tracheal intubation were not significantly different.

Conclusions. RSII with rocuronium followed by reversal with sugammadex allowed earlier re-establishment of spontaneous ventilation than with succinylcholine.

Keywords: anaesthesia, intravenous; intubation, intratracheal; neuromuscular block

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Rapid sequence induction and intubation (RSII) is performed when there is an increased risk of pulmonary aspiration of gastric contents. RSII consists of the following: optimal positioning of the patient, pre-oxygenation, injection of an opioid and a hypnotic i.v., injection of a fast-acting neuromuscular blocking agent (NMBA), cricoid pressure, and tracheal intubation.[1–3]

Succinylcholine has been for a long time the NMBA of choice for RSII, because of quick onset along with excellent intubation conditions.[4] However, it has been desirable to identify an alternative to succinylcholine because of its side-effects and the risk of delayed recovery of neuromuscular function. Spontaneous recovery of a succinylcholine-induced neuromuscular block may take too long to avoid desaturation in a 'cannot intubate, cannot ventilate' situation. In some patients, the hydrolysis of succinylcholine may be severely impaired as a result of genetic or acquired low cholinesterase activity.[5 6]

As an alternative to succinylcholine, the non-depolarizing NMBA rocuronium can be used for RSII.[7] The onset time of rocuronium 1 mg kg^{-1} is around 60 s.[7] Its duration of action is, however, 122 (33) min [from injection to recovery of first twitch of train-of-four (TOF) to 75% of baseline] for a single bolus dose of 0.9 mg kg^{-1}.[8] A new antagonist, sugammadex, binds the rocuronium molecules in a 1:1 ratio [9] without having an effect on the plasma cholinesterase

or on any receptor system in the human body.[10–14] Even profound neuromuscular block with rocuronium can be quickly antagonized with sugammadex.[15]

The aim of this trial was to assess the time from verified correct tracheal tube placement after RSII until regular and spontaneous ventilation was re-established. In addition, we assessed the intubation conditions and the duration of action of NMBA using acceleromyography. We hypothesized that the time from correct tracheal tube placement to spontaneous ventilation would be shorter with rocuronium followed by sugammadex, than with succinylcholine.

Methods

The Danish Medicines Agency and the Regional Ethics Committee approved the trial, which adhered to the standards of the International Conference on Harmonization Good Clinical Practice. The trial (NCT00953550) was registered at ClinicalTrials.gov before inclusion of the first patient. Written informed consent was obtained from all patients participating in this two-centre trial.

The patients were eligible if they were between 18 and 60 yr of age and undergoing RSII. We excluded patients with known allergic reactions to propofol, alfentanil, succinylcholine, rocuronium, or sugammadex, patients undergoing emergency surgery (operation scheduled $<$24 h), a BMI of above 35 kg m^{-2}, severe renal disease defined by S-creatinine $>$0.200 mmol litre^{-1}, New York Heart Association Functional Classification above II, a Canadian Cardiovascular Society Functional Classification of Angina above II, potassium $>$5.0 mmol litre^{-1}, untreated glaucoma, neuromuscular disease, a known disposition for malignant hyperthermia, female patients of child-bearing potential, and breastfeeding women.

Trial protocol

Patients were randomized 1:1 according to a computer-generated list (GraphPad QuickCalcs, GraphPad Software®, Inc., La Jolla, CA, USA). A total of 65 sealed and opaque envelopes were prepared for the trial by staff with no other involvement in it. The Regional Ethics Committee approved inclusion until 55 assessable patients for the primary endpoint (time to re-establishment of spontaneous ventilation) were collected, with a maximum of 65 included patients. Thus, enrolment was planned to be stopped when reaching 55 patients where the primary endpoint was assessed. The intervention allocation list was securely stored without access for the investigators, along with an allocation key.

The patients were randomized to receive either succinylcholine (1 mg kg^{-1}) or rocuronium (1 mg kg^{-1}) followed by sugammadex (16 mg kg^{-1}). The investigation was timed in a logged software program TOF-Watch® SX Monitor (Version 2.5 INT 2007, Organon, The Netherlands) from the start of pre-oxygenation.

The patients were monitored with a three-lead ECG, non-invasive arterial pressure measurement, and pulse oximetry. Hypnotic depth was assessed using BIS VISTA® (Aspect Medical Systems, Inc., Norwood, MA, USA). Neuromuscular monitoring was performed with acceleromyography using the TOF-Watch SX® (MSD, Glostrup, Denmark) connected to a computer in accordance with 'Good Clinical Research Practice in Pharmacodynamic Studies of Neuromuscular Blocking Agents II'.[16] The study arm was immobilized and the skin was cleansed before two paediatric electrodes (Cleartrode™, Conmed, Utica, NY, USA) were placed 3–6 cm apart over the ulnar nerve near the wrist. With Hand Adaptor® (MSD), a small preload was placed on the thumb for monitoring acceleration. After induction of anaesthesia, supramaximal stimulation was ensured using an automated calibration (CAL2). Every 15 s, a TOF pattern was delivered. The neuromuscular monitoring was performed until recovery of twitch responses in TOF had reached a plateau that was maintained for at least 2 min. A re-calibration was performed after ensuring that the first twitch (T_1) in TOF had reached the plateau. The plateau was defined as: little or no further increase in T_1-amplitude. The re-calibration was followed by TOF stimulation of at least three measurements with $<$5% variation in T_1 values. Measurements were discarded if they did not acquire this stable plateau. We also discarded measurements that did not reach $<$95% depression in T_1 after injection of succinylcholine. The palmar skin temperature was kept above 32°C and the central temperature was kept above 35°C.

The RSII procedure was conducted as described below (Fig. 1). After pre-oxygenation, alfentanil (10 μg kg^{-1}) and propofol (2 mg kg^{-1}) were given. Thereafter, propofol infusion was started. This was followed by calibration of TOF-Watch® SX and TOF nerve stimulation. Either succinylcholine (1 mg kg^{-1}) or rocuronium (1 mg kg^{-1}) was then given, followed by cricoid pressure and tracheal intubation. Upon verification of correct tracheal tube placement, sugammadex (16 mg kg^{-1}) was given to patients in the rocuronium group. Correct tracheal tube placement was confirmed by auscultation of the chest and epigastrium, visualization of thoracic movement, and the appearance of a typical capnography waveform.

Hypnotic level was kept in bispectral index (BIS) target range of 45–55 with a propofol infusion, starting at 3 mg kg^{-1} h^{-1}. Additional small bolus doses of propofol were given as required to maintain BIS within the target range. End-tidal P_{CO_2} was targeted to just below 7.0 kPa with gentle ventilation at low frequency to avoid excessive hypercapnia and also desaturation.

The patient and the investigator evaluating the primary endpoint were blinded to the investigated drug. The investigator (in all cases, an anaesthesiology consultant) was blinded by only being allowed to enter the operating theatre after correct placement of the tracheal tube had been verified. The personnel doing the statistical evaluation were blinded to the allocation by being presented the allocation list without the key. After statistical evaluation, an abstract and a conclusion were written in two copies, one for each allocation possibility. After completion of the abstracts, the allocation key was revealed. The staff in the

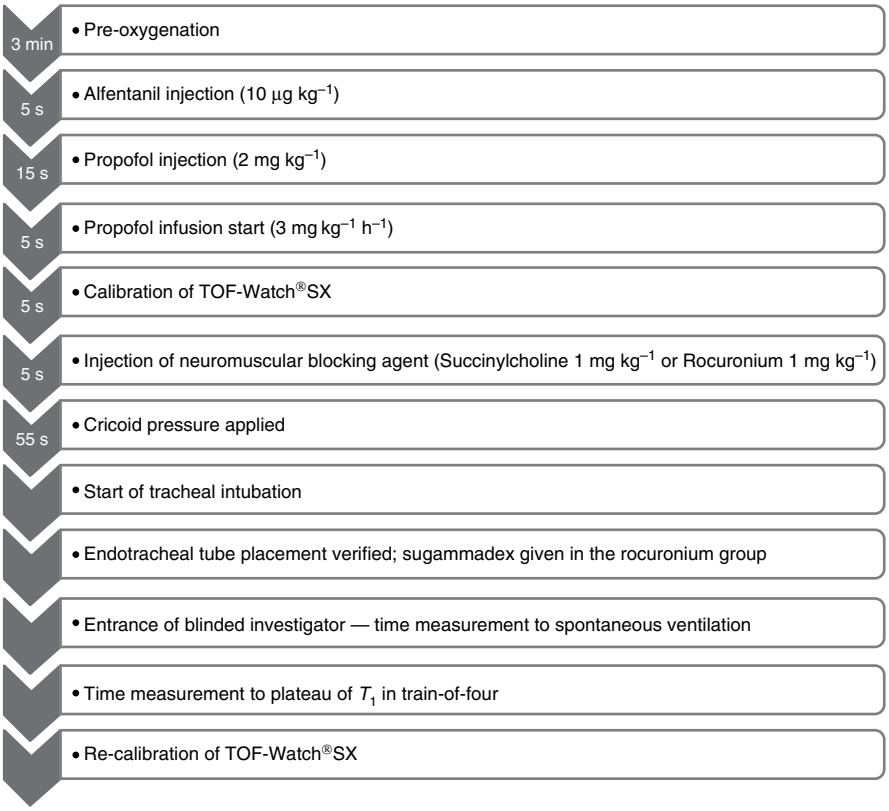

Fig 1 Flow diagram of RSII.

operating theatre could not be blinded. Neuromuscular data from 17 patients randomized to the succinylcholine group had their butyrylcholinesterase genotype analysed along with the enzyme activity for another study.[17]

The primary outcome variable was the time from correct placement of the tracheal tube (confirmed by auscultation after intubation) until re-establishment of spontaneous ventilation, defined as a respiratory rate of 8 bpm, a tidal volume above 3 ml kg^{-1}, and an arterial oxygen saturation of above 90%, for 30 s. Tidal volume was measured using the built-in spirometer in the anaesthetic machine.

Secondary outcomes were duration of action of NMBA measured with TOF-Watch SX® from start of injection of the NMBA to recovery of T_1 in TOF to above 90% (T_1 90%) and from tracheal intubation to recovery of T_1 to 90%. The T_1 90% value was calculated as 90% of the T_1-max value, which was the second of three consecutive T_1 values in the TOF, after T_1 had reached a plateau. The T_1-max value evaluation was done independently by two investigators; in the case of discrepancy, a third investigator judged what observation to report or whether the measurement should be discarded. Intubation difficulty scale (IDS)[18] and intubation conditions[16] were also assessed. Adverse events were reported by a non-blinded investigator, and the possibility of awareness was evaluated after operation after discharge from the postoperative care unit and again within 24 h after surgery by a modified Brice interview for all randomized patients[19 20] along with an assessment of generalized muscle ache.

Statistical analysis

The sample size calculation was based on a pilot protocol with 10 included patients. The data from the pilot indicated that a presumed standard deviation of 80 s would be realistic for return of spontaneous ventilation. A difference of 60 s in time to spontaneous ventilation was considered to be clinically relevant. Based on this, we calculated a sample size of 55 patients for the primary endpoint, assuming a power of 0.80 at the 5% significance level.

Patient characteristic data and continuous variables were presented as median values (inter-quartile range). The primary endpoint and other continuous variables were compared using the Mann–Whitney rank-sum test. Proportions were compared using a χ^2 test or Fisher's exact test. $P<0.05$ was considered statistically significant. We made an 'intention to treat' analysis on all randomized patients who received an intervention using SAS® statistical software version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Between September 2009 and January 2011, we enrolled 61 patients at two centres (Fig. 2). A total of 55 patients were

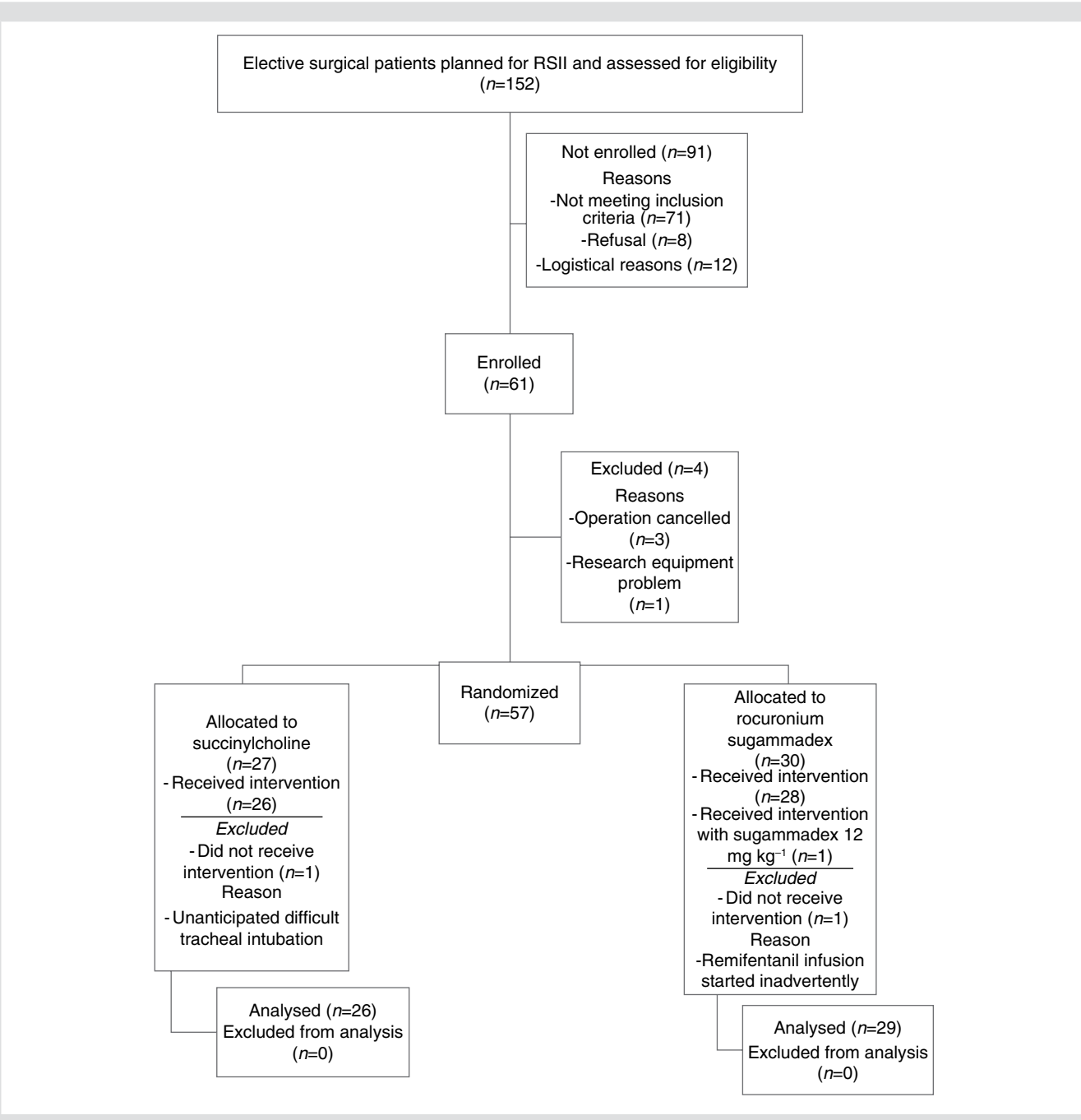

Fig 2 Trial profile.

evaluated in the 'intention to treat' analysis. Patient characteristic data are given in Table 1. All patients had an increased risk of aspiration. Two patients were excluded after randomization because of a protocol violation: one due to an unanticipated difficult airway, which resulted in the use of a NMBA out of protocol to re-paralyse the patient, and in the other, a remifentanil infusion was started inadvertently.

The median time from intubation to spontaneous ventilation was 406 s with succinylcholine and 216 s with rocuronium–sugammadex ($P=0.002$, Table 2). The median time from tracheal intubation to T_1 90% was 518 s with succinylcholine and 168 s with rocuronium–sugammadex ($P<0.0001$, Table 2). The median time from injection of NMBA to recovery of T_1 90% was 719 s with succinylcholine and 282 s with rocuronium–sugammadex ($P<0.0001$, Table 2). Eleven patients were not included in the analysis of acceleromyography measurements due to a calibration error (Table 2). Intubation conditions and time to tracheal intubation were not significantly different.

In the succinylcholine group, we observed: desaturation to 80% ($n=1$), bronchospasm ($n=1$), severe generalized

Table 1 Characteristics for elective surgical patients given either succinylcholine or rocuronium–sugammadex for RSII. Values are median (inter-quartile range). ASA PS class, American Society of Anesthesiologists physical status class; BMI, body mass index

	Patients given succinylcholine ($n=26$)	Patients given rocuronium and sugammadex ($n=29$)
Age (yr)	49 (46–53)	53 (48–56)
Gender (male/female)	6/20	11/18
Weight (kg)	76 (68–80)	79 (72–85)
BMI (kg m^{-2})	26.8 (23.7–28.9)	25.5 (24.1–27.7)
ASA PS class		
I	5 (19%)	9 (31%)
II	19 (73%)	18 (62%)
III	2 (8%)	2 (7%)
Mallampati score		
1	15 (57%)	18 (62%)
2	9 (35%)	9 (31%)
3	2 (8%)	2 (7%)
Neck movement		
$\leq 90^{\circ}$	0 (0%)	0 (0%)
$>90^{\circ}$	26 (100%)	29 (100%)
Ability to prognath		
Yes	26 (100%)	27 (93%)
No	0 (0%)	2 (7%)
Indication for RSII		
Gastrooesophageal reflux disease	20 (76%)	21 (73%)
Hiatus hernia	1 (4%)	7 (24%)
Nausea or vomiting within 24 h of surgery	3 (12%)	0 (0%)
Previous gastric bypass	1 (4%)	1 (3%)
Oesophageal diverticulum	1 (4%)	0 (0%)
Type of surgery		
Abdominal	2 (8%)	2 (7%)
Breast	3 (12%)	2 (7%)
Ear–nose–throat	4 (15%)	3 (10%)
Gynaecological	7 (27%)	4 (14%)
Orthopaedic	4 (15%)	6 (21%)
Plastic	4 (15%)	8 (27%)
Urological	2 (8%)	4 (14%)
Co-morbidity		
Hypertension	8 (31%)	3 (10%)
Other cardiovascular disease	1 (4%)	2 (7%)
Pulmonary disease	3 (12%)	3 (10%)
Excessive alcohol consumption, >48 g per day	0 (0%)	2 (7%)
Other	2 (8%)	4 (14%)

muscle ache ($n=2$), and unanticipated difficult tracheal intubation, defined by an IDS value above 5 ($n=3$; one patient excluded after randomization). Adverse events of importance during induction in the rocuronium–sugammadex group were: urticaria in the surgical zone after chlorhexidine application ($n=1$) and tachycardia to above 100 bpm ($n=3$). Recall was not suspected in any of the patients within 24 h after operation. No patient has contacted an investigator describing memories or events suggestive of awareness during induction or intraoperatively.

Discussion

We found that spontaneous ventilation was re-established significantly earlier using rocuronium–sugammadex instead of succinylcholine for rapid sequence induction. The difference in the median values was around 3 min, and an even greater difference was found in the recovery of neuromuscular function. The trial was conducted on two well-matched groups of patients undergoing RSII, which was performed in a standardized regimen. The primary endpoint was evaluated by a blinded investigator and the tidal volume of 3 ml kg^{-1}

Table 2 Tracheal intubation conditions, time to reappearance of a spontaneous ventilation, and recovery of neuromuscular function in surgical patients randomized to either succinylcholine or rocuronium–sugammadex for RSII. Values are median (inter-quartile range), *n*=number of patients. The T_1-max value was the second value of three consecutive T_1 values in the TOF, after T_1 had reached a plateau with little or no further increase in its amplitude. The T_1 90% value was calculated as 90% of the T_1-max value

	Succinylcholine (1 mg kg^{-1}) (*n*=26)	**Rocuronium (1 mg kg^{-1}) Sugammadex (16 mg kg^{-1}) (*n*=29)**	***P*-value**
Time from start of procedure to tracheal intubation (s)	330 (313–351)	324 (312–343)	0.45
Intubation conditions			0.13
Excellent	20 (76%)	27 (93%)	
Good	6 (24%)	2 (7%)	
Poor	0 (0%)	0 (0%)	
Intubation difficulty score			0.23
≤5	24 (92%)	28 (100%)	
>5	2 (8%)	0 (0%)	
Time from tracheal intubation to spontaneous ventilation (s)	406 (313–507)	216 (132–425)	0.002
Time from tracheal intubation to T_1 90% (s)	518 (451–671) (*n*=17)	168 (122–201) (*n*=27)	<0.0001
Time from injection of NMBA to T_1 90% (s)	719 (575–787) (*n*=17)	282 (242–319) (*n*=27)	<0.0001

and respiratory rate of 8 bpm kept for 30 s must be considered conservative when concluding the presence of spontaneous ventilation after RSII. We studied patients with increased risk of aspiration and we assessed recovery of spontaneous ventilation, which we consider as a more clinically important endpoint than evaluating recovery of neuromuscular function alone.[15]

We included only elective patients. This was done for practical and research ethical reasons since it would be difficult to strictly standardize the anaesthetic procedure in emergency patients who could have compromised haemodynamic status and fluid deficits necessitating a reduction in the propofol and alfentanil doses. Patients with significant heart disease were excluded, and a reduction in the induction dosages would be needed in some of these patients as well. Our findings are not applicable in obese patients, because the intubation dose of rocuronium should not be 1 mg kg^{-1} according to total body weight.[21] RSII in elderly patients would have to be based on different doses as propofol especially needs to be given in a reduced dose.[22 23] A propofol infusion was given after intubation to avoid awareness. This may have prolonged the time to spontaneous ventilation, but we do not suspect that it has caused a difference between the two groups. The tracheal tube kept the airway open, and even little diaphragmatic movement can create airflow in this situation because the diaphragm is relatively resistant to NMBAs.[24] This limitation is known to us, but due to ethical considerations, it would not have been possible to leave these research patients in apnoea and *not* to intubate the trachea because of the risk of aspiration. Another limitation of the study was that onset of spontaneous ventilation could be influenced by even gentle ventilation as this may lower the respiratory drive. The observer was effectively blinded, but onset of spontaneous ventilation was the primary endpoint. Still, we consider this approach appropriate in this clinical trial to avoid desaturation and excessive hypercapnia. In a study aimed at investigating reversal of profound neuromuscular block, when comparing succinylcholine 1.0 mg kg^{-1} with rocuronium 1.2 mg kg^{-1} and sugammadex 16 mg kg^{-1}, Lee and colleagues[15] demonstrated a recovery to T_1 90% in 10.9 min (mean value) from the start of injection of succinylcholine. This is in accordance with our finding of 12.0 min (median value). The automated calibration (CAL2) of the TOF-Watch® SX was not successful in all patients in our study due to a narrow time frame in which it had to succeed between onset of the hypnotic and of NMBA. If calibration was obstructed or the equipment was defective, this was not known until the algorithm of the procedure was running. We compensated for these errors by re-calibrating the equipment after full recovery of the neuromuscular block in all patients. This was done to verify that the true plateau in the T_1 values was in fact reached.

In the rocuronium group, intubation conditions tended to be better and a lower IDS was observed. This tendency is in contradiction with the conclusion of a systematic Cochrane review reporting succinylcholine to be superior to rocuronium (all doses) in creating optimal intubation conditions.[4] The reason for this discrepancy could be that we used 1 mg kg^{-1} rocuronium and that the timing of NMBA administration in our study favours rocuronium as the intubation attempt was done as late as 60 s after the drug had been given. The choice of using 1 mg kg^{-1} rocuronium was based on the recommendation by the Scandinavian Society of Anaesthesiology and Intensive Care Medicine[2] and it reflects our practice. All patients received 2 mg kg^{-1} propofol, which most likely improved intubation conditions when compared with a smaller dose or a different hypnotic. An advantage of using rocuronium is the fact that intubation conditions will be favourable until reversal with sugammadex is initiated.

The most serious adverse effects of succinylcholine are bradycardia, asystole, elevation of the plasma potassium concentration, and malignant hyperthermia.[25] Other adverse effects include muscle ache. Sugammadex has a low incidence of adverse effects and the profile of the adverse events has so far not been serious.[26 27]

Unassisted spontaneous ventilation in patients administered succinylcholine may not occur sufficiently soon after failed intubation to avoid desaturation.[5] The genotype of the butyrylcholinesterase is known to be of importance for the ability to metabolize succinylcholine.[6] This might explain the variability in time to recover from succinylcholine-induced block. Recent studies have shown that succinylcholine was associated with a more rapid desaturation than rocuronium during RSII.[28 29] Patients with a BMI of 25–30 kg m^{-2} had a 46 s difference in time to desaturation to 92% between succinylcholine and rocuronium.[28] A study in patients with an average BMI of ~24 kg m^{-2} showed similar results.[29] The reason is probably the skeletal muscle fasciculation that increases oxygen consumption induced by the depolarizing effect of succinylcholine,[30] whereas rocuronium does not have this effect. Thus, RSII using rocuronium seems to be associated with later onset of desaturation and better intubation conditions due to the prolonged duration of action. Desaturation to 95% has been reported ~7 min after injection of rocuronium 1 mg kg^{-1} in patients carefully pre-oxygenated[27] and sugammadex should therefore be expected to allow re-establishment of spontaneous ventilation before profound hypoxemia occurs. In our study, however, sugammadex was given much sooner than in a real clinical situation where several tracheal intubation attempts will usually be done before a decision to wake the patient. Our study did not include this delay, but it is difficult to see how a research protocol could reflect an emergency situation in a more realistic way.

The price of an escape bolus of sugammadex (16 mg kg^{-1}) for a 75 kg patient with intense neuromuscular block is approximately €760 in Denmark. It is an expensive drug, but an escape dose of sugammadex is needed in only very few patients. If the possible complications of prolonged apnoea in a high-risk patient during induction can be avoided, then the cost of the drug is not important.[31] Unanticipated prolonged apnoea will make most anaesthesiologists to begin forced bag-valve ventilation at some point to avoid desaturation, although this increases the risk of aspiration considerably, especially in patients already categorized as being at high risk of aspiration.

The safety of RSII can probably be enhanced when using rocuronium if sugammadex is available as an escape drug. We recommend a strict RSII protocol, where the escape sugammadex dose is calculated, the drug is readily available in the operating theatre, although not drawn up, and syringes are prepared for emergency draw up, before initiation of RSII.[32] In conclusion, RSII with rocuronium followed by sugammadex allowed earlier re-establishment of spontaneous ventilation than with succinylcholine.

Declaration of interest

None declared.

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Aspen and the Health Minister cycle "from the front" for children's healthcare

Aspen Group Chief Executive, Stephen Saad, and Minister of Health Dr Aaron Motsoaledi gave new meaning to the phrase "leading from the front" when they participated in the demanding inaugural 240 kilometer Aspen Trans Karoo mountain bike challenge from Ceres to Sutherland in the Western Cape. This race is recognized as one of the most grueling in the country, by virtue of the terrain and distance that needs to be traversed.

Saad and the Minister were raising funds for the newly established Sifiso Nxasana Paediatric Trust for the Children of Africa, created by Aspen following the untimely death of Sifiso Nxasana, son of Aspen's chairwoman, Dr. Judy Dlamini and her husband Sizwe Nxasana, CEO of FirstRand Ltd.

"The Minister demonstrated his commitment to raising funds for quality healthcare for the children of South Africa in the most practical and impressive way possible," comments Saad. "He led the field of cyclists and proved his enthusiasm and passion for public-private partnerships in addressing the shortage of paediatric healthcare in our country."

"South Africa has only one paediatric hospital in comparison with Canada's 23 and Australia's 19 and that is the Red Cross Children's Hospital in Cape Town," Saad points out. "The Trust will be raising funds for the Nelson Mandela Children's Hospital and the KwaZulu Natal Children's Hospital."

The Trans Karoo race was the first phase of the fund-raising campaign and reached the encouraging sum of R10 million. "We urge both local and foreign organisations and enterprises with interests in Africa to support the Trust," says Dr Motsoaledi. "If we truly believe the children are our future then we have a responsibility to ensure that all our youngsters, irrespective of culture or background, should have access to quality paediatric care in South Africa."

The race was won by former South African Iron Man, Raynark Tissink, with Hannele Steyn being the first woman across the finishing line.

Saad completed the course in just under 16 hours, expressing the great pleasure he experienced knowing that significant results had been achieved for children's healthcare.

Dr. Aaron Motsoaledi, Minister of Health; Stephen Saad, Aspen Group Chief Executive

From left to right: Sizwe Nxasana, CEO FirstRand Ltd; Dr. Aaron Motsoaledi, Minister of Health; Dr. Judy Dlamini, Aspen Group Chairwoman; Stephen Saad, Aspen Group Chief Executive; Stavros Nicolaou, Senior Executive, Aspen Pharmacare

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Pfizer announces co-promote deal with Specpharm

Described as a uniquely South African deal, Pfizer South Africa's Biopharmaceutical Division together with Specpharm announced that the no.3 ranked pharmaceutical multi-national in South Africa has contracted the services of Specpharm to co-promote a total of 22 of its pharmaceutical products within the private market. Pfizer, the US based multi-national, indicated that Specpharm was a likely match as the company exhibited a strong local presence as well as displayed the necessary expertise in the following therapeutic areas of Central Nervous System (CNS); Genitu-Urinary; Cardio-vascular (CV) and Anti-microbials.

The deal is intended to rake in revenues in the region of R120m per annum over a five year contractual period. Pfizer South Africa's Biopharmaceutical Division's CEO & Country Manager, Brian Daniel explains that this deal was carefully considered as part of enhancing Pfizer's marketing portfolio in South Africa. "Over a few months towards the latter part of 2011, a number of companies were invited to make representations to Pfizer as part of this opportunity and I am happy to announce that given Specpharm's presentation, the fit was evident."

At a specially arranged signing ceremony to announce this deal, Specpharm's Managing Director, Eugene Lottering, applauded Pfizer for its vision in this regard. "Pfizer has now provided us the opportunity to partner with a multi-national pharmaceutical giant which is intent on enhancing its local presence. Our ambition is to ensure that this five year partnership has the potential to lead to other synergies in time to come." Lottering further added: "Given Specpharm's national footprint and strong local manufacturing presence, Pfizer perceived our offering as an obvious opportunity."

As part of this deal, Pfizer will remain the dossier holders of the relevant pharmaceutical products and Specpharm has been contracted to market the 22 products on Pfizer's behalf.

"The opportunity to employ additional people as part of this initial phase is a significant benefit to both Pfizer and Specpharm. Furthermore, Pfizer will assist in the training and up-skilling of essential resources as part of this process over the period of contract. Part of this training will be centred around ensuring that Specpharm is up-skilled in the areas of adverse event reporting and Pfizer compliance systems," concluded Brian Daniel.

For additional information contact:

1. Ms Leigh Gunkel-Keuler: Public Affairs, Policy & Communications Director, Pfizer South Africa's Biopharmaceutical Division on Leigh.Gunkel-Keuler@pfizer.com and 011 320 6168.
2. Ms Usheema Maraj: Marketing Manager, Specpharm on umaraj@specpharm.co.za or on 011 652-0410.

L-R: Leigh Gunkel-Keuler; Public Affairs, Policy & Communications Director, Pfizer South Africa's Biopharmaceutical Division; Jacques Mare, Business Intelligence & Development Manager, Pfizer South Africa's Biopharmaceutical Division; Karen Hulett, Established Products/Pharmacia Director, Pfizer South Africa's Biopharmaceutical Division; Brian Daniel, CEO & Country Manager, Pfizer South Africa's Biopharmaceutical Division; Dr Eugene Lottering; Managing Director, Specpharm; Nkosi Gugushe; BEE Shareholder, Specpharm; Linda Lombaard, Operations Director, Specpharm; Pieter Engelbrecht, Financial Director, Specpharm and Usheema Maraj, Marketing Manager, Specpharm

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Facilities for tracheal intubation & maintenance of pulmonary ventilation & adequate arterial oxygenation must be available. Monitoring of neuromuscular function is recommended in order to individualise dosage requirements. Must not be administered into the infusion line of a blood transfusion. ICU Patients: In animals, high concentrations of laudanosine, a metabolite of cisatracurium, was associated with hypotension and, in some species, cerebral excitation. **DOSAGE AND DIRECTIONS FOR USE:** Refer to package insert for full details on dosage recommendations. **Use by intravenous bolus injection. Dosage in adults:** *Tracheal intubation:* The recommended dose is 0.15 mg/kg, providing good to excellent conditions for tracheal intubation 120 seconds following injection. Higher doses will shorten the time to onset of neuromuscular block. *Maintenance:* A dose of 0.03 mg/kg provides approximately 20 minutes of additional clinically effective neuromuscular block during opioid or propofol anaesthesia. *Spontaneous Recovery:* Once spontaneous recovery from neuromuscular block is underway, the rate is independent of the dose. *Reversal:* Neuromuscular block is reversible with standard doses of anticholinesterase agents. **Dosage in paediatric patients aged 1 month to 12 years:** *Tracheal intubation:* The recommended dose is 0.15 mg/kg administered rapidly over 5 to 10 seconds, providing good to excellent conditions for tracheal intubation 120 seconds following injection. NIMBEX® has a shorter clinically effective duration and a faster spontaneous recovery profile than those observed in adults under similar anaesthetic conditions. *Maintenance:* A dose of 0.02 mg/kg provides approximately 8 minutes of additional clinically effective neuromuscular block during halothane anaesthesia. *Spontaneous Recovery:* Once recovery from neuromuscular block is underway, the rate is independent of the dose administered. *Reversal:* Neuromuscular block following administration is reversible with standard doses of anticholinesterase agents. **Use by intravenous infusion. Dosage in adults and children aged 2 to 12 years.** An initial infusion rate of 3 µg/kg/min (0.18 mg/kg/hr) is recommended to restore 95 - 99% T_1 suppression following evidence of spontaneous recovery. After an initial period of stabilisation of neuromuscular block, a rate of 1 - 2 µg/kg/min (0.06 – 0.12 mg/kg/hr) should be adequate to maintain block in this range in most patients. Reduction of the infusion rate by up to 40% may be required when administered during isoflurane or enflurane anaesthesia. Steady rate continuous infusion is not associated with a progressive increase or decrease in neuromuscular blocking effect. Following discontinuation of infusion, spontaneous recovery proceeds at a rate comparable to that following administration of a single bolus. **Dosage in elderly patients, renal impairment and hepatic impairment:** No dosing alterations required. **Dosage Recommendations in patients with cardiovascular disease and in ICU patients:** Refer to package insert. **For details on compatibility and dilution:** Refer to package insert. **SIDE-EFFECTS AND SPECIAL PRECAUTIONS:** Cutaneous flushing or rash, bradycardia, hypotension and bronchospasm, severe anaphylactic reactions have been reported. There have been some reports of persistent muscle weakness and/or myopathy following prolonged use in severely ill patients in the ICU. Great caution should be exercised in patients who have shown allergic hypersensitivity to other neuromuscular blocking agents. NIMBEX® has no clinically significant effect on heart rate and will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery. Patients with myasthenia gravis and other forms of neuromuscular disease have shown increased sensitivity to non-depolarising blocking agents. An initial dose of not more than 0.02 mg/kg is recommended in these patients. Severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to neuromuscular blocking agents. **Interactions:** *Increased effect:* enflurane, isoflurane and halothane, ketamine, other non-depolarising neuromuscular blocking agents. For other drugs, refer to package insert. *Decreased effect:* Prior chronic administration of phenytoin or carbamazepine, administration of suxamethonium to prolong the effects of non-depolarising neuromuscular blocking agents may result in a prolonged and complex block which can be difficult to reverse with anticholinesterases. Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to non-depolarising neuromuscular blocking agents might result. Refer to package insert for a list of such drugs. **MANAGEMENT OF OVERDOSAGE:** Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage. It is essential to maintain pulmonary ventilation and arterial oxygenation until adequate spontaneous respiration returns. Full sedation will be required since consciousness is not impaired. Recovery may be accelerated by the administration of anticholinesterase agents once evidence of spontaneous recovery is present. **APPLICANT:** GlaxoSmithKline South Africa (Pty) Ltd., (Co. reg. no. 1948/030135/07), 57 Sloane Street, Bryanston, 2021. Marketed by Aspen Pharmacare, Building 12, Healthcare Park, Woodlands Drive, Woodmead, 2191. www.aspenpharma.com Medical Information Hotline: 0800 118 088. March 2010. NI/0310/065. A11055 03/10.

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