

CORRESPONDENCE

Zero-heat flux thermometry

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Published online 10 December 2015

Editor,

We read with interest the recent evaluation of the 3M SpotOn thermometer by Iden *et al.*¹ Encouragingly, their results in noncardiac surgical patients were generally similar to ours in cardiac surgical patients.² There are nonetheless several aspects of their report where clarification might be helpful.

Perhaps, the most striking aspect of Iden *et al.* is that 37 of 120 enrolled patients, very nearly a third, were excluded from analysis. Granted, two patients were switched to spinal anaesthesia and the SpotOn thermometer malfunctioned in four others. But 19 patients were eliminated because of ‘calibration failure of the sublingual probe’. That an electronic sublingual probe would fail in more than 15% of cases seems remarkable. After all, oral thermometers are standard hospital equipment and rarely fail in normal use. Twelve additional patients were excluded because surgery did not last long enough to obtain the final planned temperature measurement at 75 min.

The protocol specifies that ‘patients with unexpected blood loss, haemodynamic instability . . . , and the need for postoperative ventilation were excluded’. At least two of these could only be determined during or after surgery, thus well after enrolment. However, no patients appear to have been excluded for these reasons. Did none of 120 enrolled patients meet any of these exclusion criteria?

The general rule in clinical research is to analyse data from all enrolled patients to avoid data-selection bias. There is no compelling reason to exclude patients with missing sublingual temperatures from comparisons to nasopharyngeal temperature (which is anyway the more reliable temperature-monitoring site). Similarly, the initial measurements could perfectly well be evaluated in patients whose final temperatures were missing.

The nasopharyngeal sensor is described as being ‘inserted through a nostril just posterior to the soft palate’. How far was the probe actually inserted? Probe insertion distance may be important because sublingual temperatures are reported as being ‘greater’ than both nasopharyngeal and SpotOn temperatures by about a third of a degree Celsius. This is an unusual pattern since the nasopharynx, as a reliable core temperature-monitoring site, should be warmer than the mouth.

When assessing agreement between two methods, it is important to report the average difference or bias. However, the variability of the individual differences is even more important as even wildly variably thermometers might well look good on ‘average’. Clinicians need to be confident that any ‘single’ measurement well reflects actual core temperature. It would thus be helpful if the authors presented the mean bias ± 2 SD range for each measurement for all enrolled patients, along with the fraction of SpotOn measurements that were within the $\pm 0.5^\circ\text{C}$ they describe as ‘adequate for temperature monitoring’.

The authors claim that SpotOn temperatures were ‘almost identical’ to nasopharyngeal temperatures, and report a mean bias of 0.07°C and *P* value for a paired *t* test of 0.14. However, paired *t* tests are not the right way to assess agreement as they evaluate mean bias, rather than agreement amongst individual pairs which is what we need to know. When used to assess agreement, as in Iden *et al.*, a *t* test can be misleading. For example, a *t* test will fail to reject (and thus claim ‘good agreement’) when the average difference is zero, even when within-pair differences are large. It will also reject the null and claim ‘poor agreement’ in the presence of excellent agreement (i.e. tiny differences) coupled with low variability (e.g. all difference of similar magnitude). Paired *t* tests were simply the wrong analysis tool.

Bland and Altman³ developed their now-famous methods for assessing agreement in the 1980s specifically to combat the misuse of paired *t* tests and correlation coefficients for such studies. The authors did include a Bland-Altman method – which should have been their primary analysis. However, they used the wrong version. Specifically, they used the original method which is only applicable for studies with a single set of measurements from each patient, with all pairs being independent. Their analysis, though, included data from three distinct time points for each patient, thus introducing within-patient correlation across time. The proper tool would thus have been the repeated-measures version of the technique.⁴

Furthermore, graphical and numerical displays of the data should have highlighted the three time intervals, rather than lumping them together, since agreement and accuracy may have varied over time.

As paired *t* tests should never have been used, it is obvious that the authors' sample-size estimate based on *t* tests is faulty. The estimate instead should have been based on having sufficient data to precisely estimate the standard deviation of the differences or the proportion of pairs within the *a priori* defined clinically acceptable limits of $\pm 0.5^{\circ}\text{C}$. For example, assuming that 70% of differences were expected to fall within the acceptable limits, they would have needed $n = 150$ patients to have a 95% confidence interval width of 0.15 for the proportion and $n = 350$ for a width of 0.10.

The authors incorrectly refer to the Spearman correlation coefficient (*r*) as the 'coefficient of determination'. Actually, the coefficient of determination is R^2 , the proportion of variance of one measure explained by the other, and would be obtained by squaring the Pearson correlation coefficient. As the authors only report the Spearman correlation, the coefficient of determination should not have been mentioned. Much more importantly, though, the Spearman rank-order correlation and Pearson correlation do not assess agreement, only the strength of the association. Either correlation can therefore be high even when agreement between two measures is terrible.

The proper test would have been Lin's concordance correlation coefficient.⁵ Lin's concordance is a standard measure of agreement for continuous data which indicates how closely the pairs are to the 45° line of agreement in a scatterplot of two methods. Intuitively, it is a function of both the perpendicular distance from the 45° line of agreement and the strength of association measured by Pearson correlation (*r*). So for data strongly correlated ('tight' on the scatterplot, with high '*r*') but with poor agreement (i.e. off of the 45° line), the Lin's concordance will be low, appropriately indicating poor agreement.

As the authors defined two comparisons of interest (SpotOn to nasopharyngeal, and SpotOn to sublingual), a Bonferroni correction should have been applied rather than defining ' $P < 0.05$ ' as significant and using it for each comparison. Another mistake is that the authors specify that 'power (β) = 95%'; however, power is $1 - \beta$. Finally, as Iden *et al.* were comparing to a gold standard temperature, they could have also reported the slope and intercept of the regression line of gold standard on 3 M SpotOn. To the extent that the slope differed from 1.0, there might be a predictable relationship between device and gold standard that could be used to improve device calibration. For example, for sublingual temperature, the slope in their Fig. 3 appears to be less than 1.0.

In summary, proper methods for assessing agreement between two continuous measures include a Bland-

Altman comparison of differences versus the mean of two measures, Lin's concordance correlation coefficient, the proportion of differences falling within predefined limits and the mean difference (or bias) and its standard deviation. Iden *et al.* attempted a Bland-Altman analysis, but used the wrong version. And they failed to use the other methods at all. We encourage Iden *et al.* to use the proper statistical analysis and include all available data. Although unlikely to substantively change the authors' conclusions, doing so would improve readers' confidence in the authors' conclusions.

And finally, we were surprised that the authors report no conflicts of interest as Berthold Bein apparently serves on a 3 M advisory board.

Acknowledgements related to this article

Assistance with the letter: none.

Financial support and sponsorship: none.

Conflicts of interest: the Department of Outcomes Research is funded by 3 M (manufacturer of the SpotOn thermometer) and various other temperature monitoring and management companies. DIS serves on advisory boards for 3 M and the 37Company, and consults for other temperature-related companies. He donates all temperature-related payments to charity.

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DOI:10.1097/EJA.0000000000000365

Reply to: zero-heat flux thermometry

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Published online 10 December 2015

Editor,

We appreciate the interest and the comments by Sessler and Mascha¹ on our study 'Intraoperative temperature

Eur J Anaesthesiol 2016; **33**:140–155

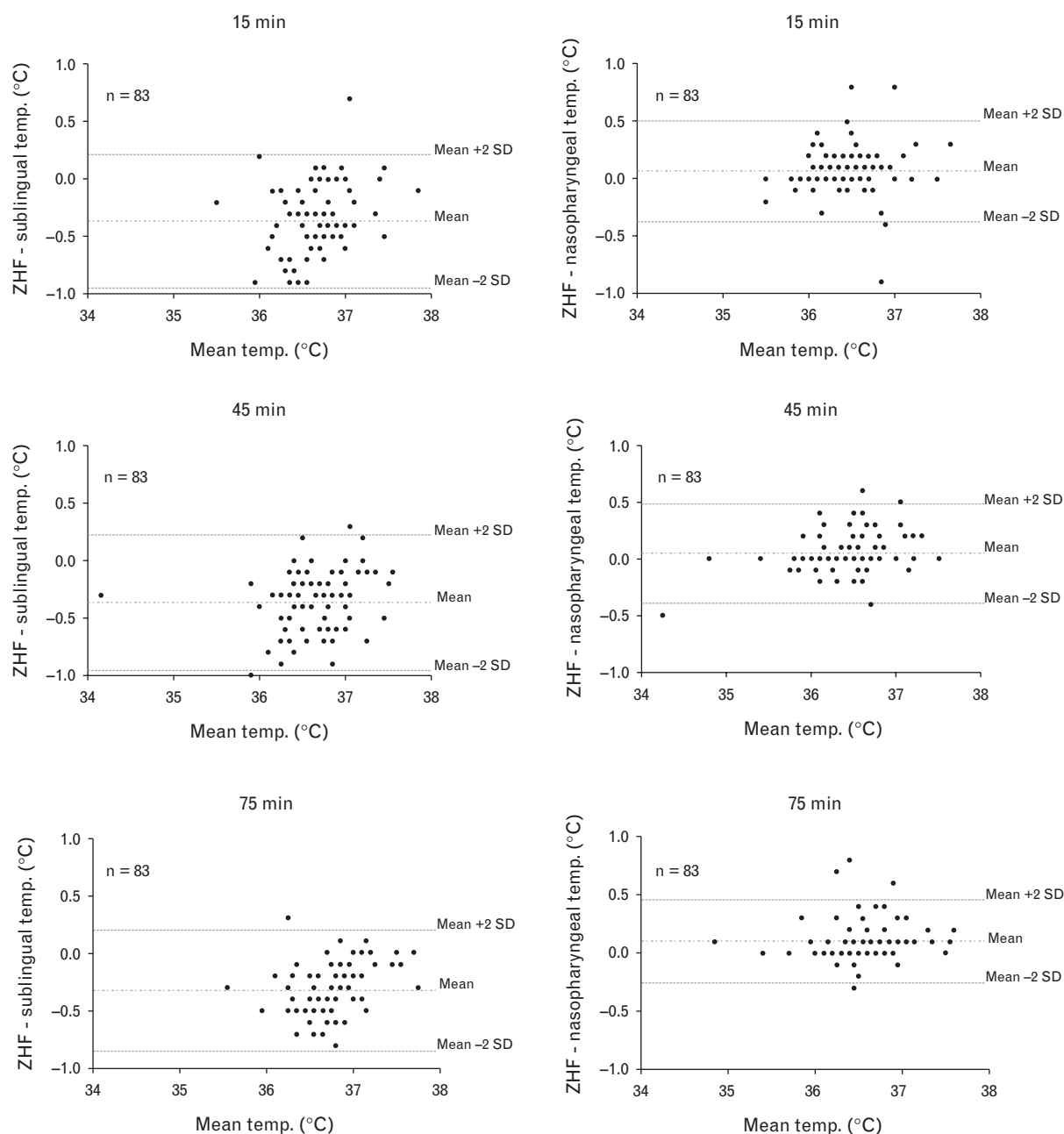
monitoring with zero heat flux technology (3M SpotOn sensor) in comparison with sublingual and nasopharyngeal temperature'.²

Indeed, in our study, a relatively large number of patients were excluded from the final analysis because of a calibration failure of the sublingual probe. For this study, we bought a new probe with optimised accuracy. Unfortunately, the initial temperature data obtained were fluctuating and unreliable. A technical

check-up of the device revealed a 'calibration failure' malfunction. Therefore, we decided to exclude these 19 patients from the final analysis, which is stated clearly in the article.

We studied elective patients undergoing orthopaedic surgery (mainly arthroscopic surgery of the shoulder, hip or knee), or gynaecological surgery (mainly laparoscopic interventions). Among these American Society of Anesthesiologists (ASA) status 1 and 2 patients included

Fig. 1



Bland-Altman analyses for different time points.

in the final analysis, none had to be excluded because of postoperative need for ventilation, unexpected blood loss (need for blood transfusion) or haemodynamic instability defined by the need for continuous norepinephrine infusion. This result is comparable with our clinical experience regarding this type of surgery and patient cohort.

Regarding the statistical methodology, we confirm that the Bland-Altman plot was the primary analysis in our study. However, additional analyses are reasonable and provide supplementary information to interpret the results. The primary intention of the study was to assess agreement of temperatures at three different time points reflecting different clinical situations because 'agreement and accuracy may have varied over time' as Sessler and Mascha¹ state in their letter. Therefore, we analysed the data from each time point separately using the 'conventional' Bland-Altman analysis.³ In fact, results were presented in the text including the mean bias $\pm$ standard deviations, and the 95% limits of agreement as required. Owing to limited space, we presented a condensed plot which included data for all three time points together instead of six separate plots (Fig. 1). However, we were surprised that in a previous study by Kimberger *et al.* published in 2009, evaluating accuracy and precision of a novel noninvasive core thermometer,⁴ the 'conventional' Bland-Altman analysis³ instead of the repeated-measures version⁵ as requested by Sessler and Mascha was used to analyse 1287 temperature measurement pairs obtained at 5 min intervals from 36 patients.

Paired *t* tests were not the 'wrong' analysis tool but allowed a comparison of the means of the different methods of temperature assessment. Spearman correlation coefficient is the more popular and frequently applied analysis of correlation in comparison to Lin's concordance correlation coefficient. However, we agree that Lin's concordance correlation coefficient may have been a valid alternative in this setting as, in contrast to the Pearson and Spearman correlation coefficient, it measures only the correlation with respect to the 45° line through the origin and not to an arbitrary line. A Bonferroni correction as a consequence of performing two comparisons of interest was applied as described in the text and the reported *P* values were adjusted accordingly. Indeed, the 'coefficient of determination' is R^2 not r which is a mistake in the abstract. However, in the text, the correct term 'correlation coefficient' r was used consistently. In the absence of a genuine gold standard temperature in our study, as was discussed in the manuscript, a calculation of the 'slope and intercept of the regression line of gold standard' is not possible.

Finally, all potential conflicts of interest including the 3 M advisory board membership of Berthold Bein were

declared to the *Journal* on separate forms. However, we regret that we have overlooked these declarations in the Acknowledgements section of the published article and have requested an erratum in the *Journal* to correct the omission.

Acknowledgements related to this article

Assistance with the reply: none.

Financial support and sponsorship: none.

Conflicts of interest: BB has received consulting fees and/or travel support from CSL Behring, Air Liquide, 3 M, GE Healthcare and Deltex. He is a member of the 3 M, Pulsion Medical Systems, Orion Pharma and Ratiopharm advisory boards. JH has received payments for lectures from 3 M, The Surgical Company, Moelnlycke and Abbvie.

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DOI:10.1097/EJA.0000000000000364

Preoxygenation by spontaneous breathing or noninvasive positive pressure ventilation with and without positive end-expiratory pressure

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Published online 14 November 2015

Editor,

We read with great interest the study by Hanouz *et al.*¹ and commend the authors on their work. The study addresses an important aspect of emergency anaesthesia and critical care practice and contributes to the evidence available on preoxygenation. However, there are several

issues with the trial and conclusions that we feel are worthy of comment and further discussion.

The authors present findings of a comparison of time taken to reach a point of satisfactory preoxygenation prior to tracheal intubation, as identified by an end-tidal oxygen fraction of 90%, using three different techniques. They concluded that preoxygenation with positive pressure ventilation, both with and without the application of positive end expiratory pressure, led to shorter preoxygenation times in patients undergoing elective surgical procedures compared with spontaneous ventilation via a mask. The authors proceed to highlight the importance of this finding in populations wherein rapid airway control – such as emergency surgery and haemodynamically unstable critically ill patients – is desirable.²

This is a pertinent area to study, but we perceive several issues regarding patient selection and exclusion criteria for the trial, and question the transferability of findings from this trial to contemporary practice.

The authors only included American Society of Anesthesiology physical status I and II patients undergoing elective surgical procedures in their study.¹ In fact, the strict inclusion criteria prevented enrolment of patients from most clinical situations in which thorough and rapid preoxygenation would be desirable – such as rapid sequence induction of anaesthesia and emergency tracheal intubations – and also in patients with potentially difficult airways. As a result, the reader is left questioning whether the patient population selected is appropriate for the clinical question posed. It is certainly clear that the patients studied are not representative of emergency surgical or critically ill patient populations, and thus it is difficult to justify extrapolating the findings of this study to those particular groups.

We would also question the authors' use of noninvasive positive pressure ventilation without the application of positive end-expiratory pressure as a method of preoxygenation. Bilevel noninvasive ventilation, in which both positive end-expiratory pressure and positive pressure ventilation are applied, has been demonstrated to improve gas exchange in a wide variety of clinical situations, including in preoxygenation prior to tracheal intubation.³ The application of positive end-expiratory pressure – or continuous positive airway pressure – alone has also been demonstrated to improve oxygenation and measured indices of respiratory function in a wide range of patients in the perioperative period.⁴ The use of positive pressure ventilation without positive end-expiratory pressure, however, is an infrequently used modality of ventilatory support, and it seems curious that the authors chose to study this mode of support rather than continuous positive airway pressure. It would be interesting and useful to learn if the addition of positive pressure ventilation to a basic level of positive

end-expiratory pressure had a favourable effect on preoxygenation, and unfortunately in this regard, we feel that this study represents something of a missed opportunity.

The time taken from tracheal intubation to desaturation to oxygen saturations of 93% was used as a secondary endpoint in this study and no significant difference was found between the three methods of preoxygenation. However, we would question the relevance of this finding to clinical practice. Rapid desaturation as a complication of intubation is a common and difficult problem in emergency situations.⁵ However, the study population display few, if any, of the risk factors for desaturation following intubation, and thus no real conclusions can be drawn on the efficacy of any of the methods of preoxygenation in preventing this significant clinical problem.

So where does this study leave us in terms of guiding our clinical practice? The authors make no reference at all in their discussion of the study population being very different to that highlighted in both the introduction and discussion as the population of interest. Is this a feasibility study for trialing the technique before its use in sicker patients more in need of rapid and efficient preoxygenation? If not, it does not provide robust evidence to suggest that we should be changing our clinical practice with regard to preoxygenation and high-risk inductions. Further work – perhaps comparing continuous positive airway pressure, bilevel noninvasive ventilation or oxygen delivered by high flow nasal cannulae⁶ to standard mask preoxygenation – in emergency and critically ill patients is warranted.

Acknowledgements related to this article

Assistance with the letter: none.

Financial support and sponsorship: none.

Conflicts of interest: none.

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DOI:10.1097/EJA.0000000000000380

Reply to: preoxygenation by spontaneous breathing or noninvasive positive pressure ventilation with and without positive end-expiratory pressure

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Published online 14 November 2015

Editor,

We thank Drs Glossop and Esquinas for their interest in our study¹ and the opportunity to discuss the results. They highlight that the patients included in our study were not representative of emergency surgical or critically ill patients in whom rapid airway control and hence rapid and efficient preoxygenation was required.² We fully agree. However, the endpoints of our study (primary endpoint: time from face mask positioning to expired oxygen fraction >90%; secondary endpoint: time to peripheral O₂ saturation = 93%) did not enable us to include emergency surgical and critically ill patients. Especially, the time until peripheral O₂ saturation decreased to 93% was not considered ethical in emergency care and critically ill patients. We definitely believe that the time to desaturate must be studied. At the present time, our results may support the design of specific studies aimed at comparing different preoxygenation methods in emergency anaesthesia and critical care. We agree that such studies must be the next step.

They also questioned the use of noninvasive positive pressure ventilation without positive end-expiratory pressure. At the present time, most anaesthesia ventilators include a noninvasive positive pressure ventilation mode. One hypothesis of the study was that positive inspiratory pressure *per se* could result in faster preoxygenation compared with spontaneous breathing, at least from direct and indirect mechanisms. First, positive pressure ventilation requires perfect positioning of the face mask which could focus practitioner care on face mask position. Second, positive inspiratory support could prevent inward air leaks avoiding dilution of inspired oxygen, thus increasing the efficacy of preoxygenation. Third, positive pressure ventilation increases end-expiratory

lung volume through the recruitment of collapsed alveoli and increases tidal volume resulting in a more efficient washing out of nitrogen. And fourth, positive pressure ventilation requires monitoring of airway pressure, tidal volume and inspiratory and expiratory gases. Thus, we wished to study a group with positive pressure ventilation without positive end-expiratory pressure. The results of our study support this hypothesis since the time to achieve preoxygenation was comparable between groups with positive pressure ventilation and with positive end-expiratory pressure. We fully agree with Drs Glossop and Esquinas that adding positive pressure ventilation to continuous positive airway pressure during preoxygenation could be valuable but we think that it should be comparable to the positive pressure ventilation and positive end-expiratory pressure group included in our study.

We think that our study supports the use of positive pressure ventilation with or without positive end-expiratory pressure during preoxygenation of patients whatever their condition. Beyond decreasing the time to achieve preoxygenation, the most important benefit could be an increased efficiency and reproducibility of preoxygenation which has been shown to remain a major issue.³ A single study will never answer all questions but could in fact raise some more questions. We thank Drs Glossop and Esquinas for highlighting some limits of our study¹ and opening the way to further studies on preoxygenation.

Acknowledgements relating to this article

Assistance with the letter: none.

Financial support and sponsorship: this work was supported by CHU de Caen, Caen, France.

Conflicts of interest: none.

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DOI:10.1097/EJA.0000000000000381

Delayed diagnosis of anaphylaxis secondary to ondansetron

A case report

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Published online 7 November 2015

Editor,

A 66-year-old man attended for routine day-case arthroscopic subacromial decompression on an afternoon operating list. He had no significant past medical history and was essentially fit and well. He had undergone two uneventful general anaesthetics for shoulder arthroscopies in the past.

Following induction of anaesthesia, he developed severe hypotension and tachycardia with a SBP of 55 to 60 mmHg. This hypotension was unresponsive to large intravenous fluid boluses and intermittent boluses of metaraminol. He required repeated adrenaline boluses and a noradrenaline infusion. His ECG at the time suggested nonspecific anterolateral ST-segment depression. Surgery was abandoned and the patient was transferred to the high dependency unit for further investigations and resuscitation. His cardiovascular parameters normalised and ECG changes resolved, although the 12-h troponin was modestly elevated at 87 ng l^{-1} . He was discharged home the following day and a cardiology referral was made for further investigations. A subsequent transthoracic echocardiogram was normal and a diagnostic coronary angiogram revealed entirely unobstructed coronary vessels. As a result, the troponin-positive cardiac episode was attributed to profound hypovolaemia and hypotension.

Six months later, the patient was listed for the same operation as an inpatient. He was preloaded with 1000 ml Hartmann's solution and general anaesthesia was induced using midazolam, fentanyl and propofol. He was then transferred on to the operating table and positioned in the left lateral position. Once surgery had commenced, he received intravenous dexamethasone, ondansetron and paracetamol. Ten minutes later, a drop in blood pressure was noted which quickly progressed to cardiac arrest with the ECG showing pulseless electrical activity. The operation was abandoned. He was successfully resuscitated following a brief period of cardiopulmonary resuscitation and was transferred to the intensive care unit.

With a working diagnosis of anaphylaxis, all pertinent investigations were sent after consultation with the immunology team. The immunology results showed significant elevations in serum tryptase levels at 0 h (67.6 mg l^{-1}), 1 h (89.3 mg l^{-1}) and 24 h (8.7 mg l^{-1}) (normal range 2 to 14 mg l^{-1}). Total immunoglobulin E concentration was mildly elevated at 162 kU l^{-1} . Skin prick testing to neat ondansetron (2 mg ml^{-1} concentration) was negative; however, intradermal testing to ondansetron diluted 1:50 in 0.9% isotonic saline showed a 2.5-fold increase in wheal diameter. The result was also positive at 1:250 dilution with a two-fold increase in wheal diameter. The above tests to dexamethasone, propofol, midazolam, glycopyrronium, diamorphine, fentanyl, latex and betadine were all negative. Complement and mannose-binding lectin assays were normal.

The patient made a full recovery and was discharged to go home on the third postoperative day.

Six months later, he returned for the same procedure, which was performed using regional anaesthesia in the form of an interscalene block with propofol sedation. He was discharged on the same day. He was pleased with the outcome of the surgery and gave his written consent for the publication of this case report.

The incidence of anaphylaxis in anaesthesia has been estimated at between 1:10 000 and 1:20 000.^{1,2} It can be a very challenging condition to manage and is fatal in 10% of cases.

There were two serious events which ultimately led to the final diagnosis of anaphylaxis. A multidisciplinary meeting was initiated following the first hypotensive episode. The panel, which comprised several consultant anaesthetists, thought the cause of hypotension was cardiac in nature because of the nonspecific anterolateral ST-segment depression. The cardiology team confirmed that there was no underlying coronary disease or evidence of left ventricular dysfunction and attributed the hypotension to profound hypovolaemia. This was attributed to the prolonged preoperative fasting period (nil by mouth since 18:00 the evening prior to surgery) and the fact that the patient had gone for a morning jog on the day of surgery. A differential diagnosis of anaphylaxis was not considered at that time. The patient was reviewed on two other occasions by anaesthetic consultants. Both were satisfied with the cardiology investigations and did not feel the need to consider other potential causes for the previous hypotensive episode.

The first episode of hypotension observed in our patient was most likely because of his sensitivity to ondansetron, which he had safely tolerated on two previous occasions. Neat ondansetron skin prick test is usually negative in most cases,^{3,4} as it was in our case, and should not be used to exclude allergy. In our patient, the test was positive

down to 1:250 dilution. A 1:50 dilution is the minimum necessary dilution to consider ondansetron allergy and was positive in none of the 10 healthy controls reported by Fernando and Broadfoot.³

Ondansetron, a selective 5-hydroxytryptamine receptor antagonist, is widely used as an antiemetic because of its efficacy and safety profile. Life-threatening reactions have been uncommonly reported. Fernando and Broadfoot³ reported a reaction that consisted of marked hypotension without skin rash or bronchospasm, as was the case in our patient. Unexplained hypotension during anaesthesia should always be investigated with serial tryptase estimations and ondansetron should be included in the list as a potential agent amongst other drugs if used. It is the responsibility of the anaesthetist to appropriately report, refer and follow-up these patients. A suspected 'allergy under anaesthesia' pack containing all relevant paperwork required to make referrals is now available in every theatre in our hospital.

Anaesthetists are probably the clinicians who are most likely to encounter anaphylaxis during their routine practice. As such, they should be wary of overlooking the diagnosis when the patient presents with atypical features, as this is the most common contributor to diagnostic errors.⁵ In a Scandinavian study,⁶ 42 anaesthetists were tested on a high fidelity simulator and not one made the diagnosis of anaphylaxis within 10 min.

In conclusion, this case reinforces the following statement highlighted by the Association of Anaesthetists of Great Britain and Ireland⁷:

'... during anaesthesia when a fall in blood pressure, change in heart rate or difficulty with ventilation are noticed, anaphylaxis is so rarely the cause that inevitably treatment is given for another diagnosis before anaphylaxis is recognised; the response to this treatment has commonly delayed or even prevented recognition of the true cause.'

Acknowledgements relating to this article

Assistance with the article: the authors would like to thank Dr Amolak Bansal, Consultant Immunologist, who helped conduct the immunological tests at St Helier's Hospital.

Financial support and sponsorship: none.

Conflicts of interest: none.

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DOI:10.1097/EJA.0000000000000372

Xenon anaesthesia in a patient with susceptibility to malignant hyperthermia

A case report

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Published online 9 July 2015

Editor,

Malignant hyperthermia is a rare pharmacogenetic disorder of skeletal muscle tissue that can be triggered by volatile anaesthetics, haloperidol, depolarising muscle relaxants and, in rare cases, by strenuous exercise and heat exposure.

Once malignant hyperthermia is triggered, an abnormally high release of calcium from the sarcoplasmic reticulum is initiated, resulting in a hypermetabolic state. This leads to tachycardia, muscle rigidity, hypercapnia, hyperthermia, hypoxia and lactate acidosis.¹ The use of a well tolerated anaesthetic technique is vitally important for patients susceptible to malignant hyperthermia. Currently, the only alternative proposed in the literature to inhalational anaesthesia for a patient with a known sensitivity to malignant hyperthermia is the use of total intravenous anaesthesia (TIVA).¹

Xenon, an inert noble gas with beneficial anaesthetic properties, could be helpful in this condition.^{2,3} Xenon has been investigated in susceptible swine as well as in-vitro human muscle strips without showing malignant hyperthermia type reactions. With the consent of our patient, we report on the use of xenon to induce and maintain anaesthesia in a patient with a positive test result for malignant hyperthermia.

In April 2014, a 31-year-old man (height 180 cm, weight 76 kg) was scheduled for a Hartmann's colonic resection for perforated diverticulitis and, in June 2014, for a reconstruction of intestinal continuity with colo-colonic

Eur J Anaesthesiol 2016; **33**:140–155

anastomosis and cholecystectomy. He was transferred to our hospital for a suspected iatrogenic bile duct injury and underwent a laparotomy.

The patient reported a family history of malignant hyperthermia. The diagnosis of malignant hyperthermia was made in 2003 through muscle biopsy and an in-vitro contracture test for caffeine-halothane. The pre-operative evaluation classified the patient as American Society of Anesthesiologists' (ASA) physical status 2. Before the procedure, the operating room was prepared according to the Malignant Hyperthermia Association of the United States guidelines.⁴ The patient refused epidural anaesthesia for postoperative pain control. One hour before surgery, two intravenous cannulae (18-gauge) were inserted and we administered antibiotic prophylaxis and premedication with midazolam 0.04 mg kg^{-1} , atropine 0.01 mg kg^{-1} and ondansetron 4 mg. In the operating room, general anaesthesia was induced with a target-controlled infusion (TCI) of propofol with a target blood concentration of $4 \mu\text{g ml}^{-1}$ and remifentanyl $0.01 \mu\text{g kg}^{-1} \text{ min}^{-1}$, titrated according to clinical and haemodynamic parameters (blood pressure and heart rate $>20\%$ of baseline) (Fig. 1a). In addition to remifentanyl, sufentanil $10 \mu\text{g}$ was used as premedication, at induction and after 180 min of surgery. Rocuronium 0.6 mg kg^{-1} was used as a muscle relaxant after calibration and monitoring of train-of-four (TOF) at the start of the procedure. The introduction of xenon was preceded by a phase of 'denitrogenation' by administration of oxygen at a high flow rate for 10 min. This step is crucial in order to limit the amount of xenon when inducing anaesthesia. Xenon was administered using a closed circuit breathing system. The hypnotic concentration of xenon (40 to 45%) stabilised after about 2 min, reaching the desired concentration of approximately 60 to 70% in 8 min (Fig. 1b). The infusion of propofol was modified according to the bispectral index (BIS) and was stopped when the concentration of xenon reached 40%. Maintenance of anaesthesia was augmented by an infusion of remifentanyl 0.01 to $0.04 \mu\text{g kg}^{-1} \text{ min}^{-1}$, a mixture of oxygen 30% and xenon 60%, and rocuronium 0.07 mg kg^{-1} (according to TOF). During surgery, the patient was monitored using a five-lead ECG, noninvasive arterial pressure monitor, pulse oximeter, capnograph, BIS, analgesia nociception index (ANI), urine output and bladder temperature (Fig. 1c,d). For haemodynamic monitoring, we used a noninvasive cardiac output monitor (NICOM; Cheetah Medical, Boston, Massachusetts, USA) that recorded the following parameters: cardiac output (CO), cardiac index (CI), stroke volume variation (SVV) and stroke volume index (SVI) (Fig. 1e). Hydration was ensured by administration of intraoperative crystalloid $2 \text{ ml kg}^{-1} \text{ h}^{-1}$. No episode of intraoperative or postoperative haemodynamic instability occurred. Arterial

blood gas samples were taken 140 min into surgery and showed no abnormality.

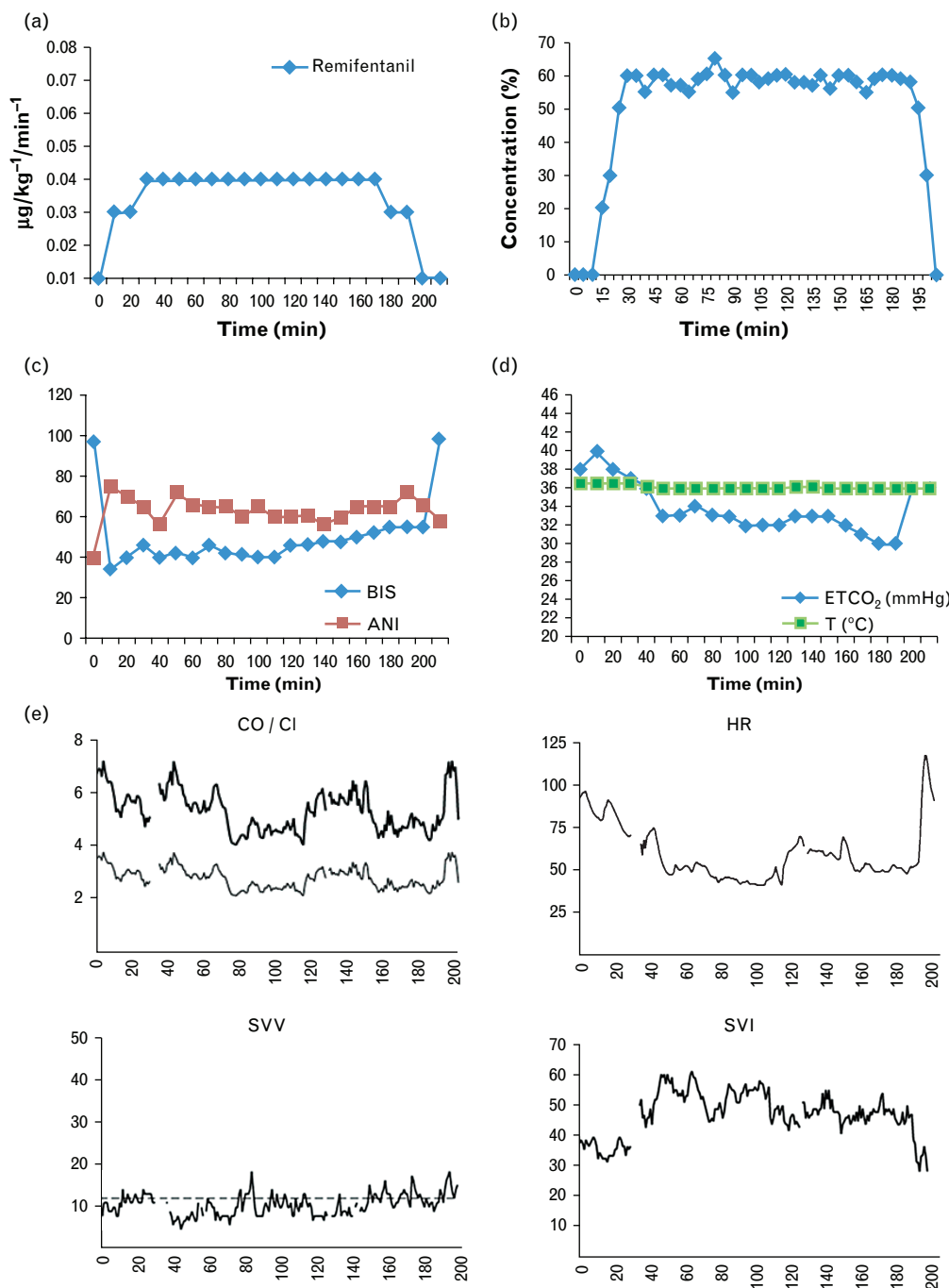
At the end of the surgery, which lasted 210 min, sugammadex 2 mg kg^{-1} was administered on reappearance of T2. The trachea was extubated at a TOF ratio of 100%, and when upper airway reflexes were fully recovered and respiratory function was adequate.

The patient was observed in the operating room until full orientation and was then taken to the postanesthetic care unit (PACU) for further surveillance for the first 24 h. Postoperative analgesia was provided using an elastomeric pump with ketorolac 180 mg, tramadol 500 mg, ranitidine 300 mg and ondansetron 8 mg. Postoperative pain was assessed regularly using a numerical rating scale (NRS). Rescue analgesia was provided (NRS ≥ 4) with ketorolac 30 mg because the patient reported an allergy to paracetamol. Two hours after anaesthesia, blood gas analysis showed no abnormality. Blood gas analysis remained normal throughout the postoperative period. In PACU, the patient was afebrile (peak body temperature 37.5°C), did not show haemodynamic instability and only presented moderate impairments of laboratory parameters, compatible with surgical stress. Postoperative evaluation did not show any adverse events or signs of intolerance and the patient was admitted to the ward during the first postoperative day.

Our purpose is to report on the use of xenon in a malignant hyperthermia susceptible patient undergoing laparotomy. In animal models, malignant hyperthermia sensitive swine initially anaesthetised with pentobarbital and then ventilated with 70% xenon in oxygen for 2 h did not develop malignant hyperthermia.⁴ Xenon exposure did not induce any changes in metabolic and haemodynamic parameters nor elevations of plasma catecholamine concentrations indicative of malignant hyperthermia. In contrast, in all animals, within 20 min after starting administration of halothane and succinylcholine, fulminant and fatal malignant hyperthermia episodes were reported.⁵ Furthermore, xenon 70% did not cause an increase in baseline tension of any malignant hyperthermia susceptible human muscle specimens, in contrast to halothane and caffeine.⁶

To our knowledge, this is the first case report describing the use of xenon in a patient with established susceptibility to malignant hyperthermia. We chose to use xenon because of its availability in our hospital (a referral centre for xenon anaesthesia), its safety profile in previous in-vitro and animal studies and its haemodynamic stability. Our patient had already undergone a reconstruction of intestinal continuity with a colo-colonic anastomosis, and an open Roux-en-y hepato-jejunal anastomosis, and had a high risk of bleeding and haemodynamic instability. Given the patient's condition and the risks associated with the planned surgery, we chose to use an anaesthetic

Fig. 1



Variables during anaesthesia. (a) Remifentanyl infusion rate. (b) The averaged value of inspired and expired xenon concentration during anaesthesia. (c) Bispectral index (BIS) and analgesia nociception index (ANI). (d) End-tidal carbon dioxide tension (ETCO₂) and temperature. (e) Haemodynamic monitoring. CI, cardiac index ($\text{l min}^{-1} \text{m}^{-2}$); CO, cardiac output (l min^{-1}); HR, heart rate (beats per min); SVI, stroke volume index (ml m^{-2}); SVV, stroke volume variation (%).

strategy with the greatest hemodynamic stability. Xenon, compared with volatile anaesthetics and propofol, allows a remarkably 'stable' circulation with a higher arterial blood pressure.⁷ Indeed, xenon avoids vasodilatation and does not suppress cardiovascular feedback loops.⁷

However, the use of TIVA remains a well tolerated alternative for general anaesthesia in a haemodynamically stable patient with known sensitivity to malignant hyperthermia. The noble gas xenon offers many characteristics of an ideal anaesthetic including haemodynamic

stability and rapid induction and emergence from anaesthesia regardless of its duration. In this case, under general anaesthesia with xenon, values of CO , SVI and heart rate were consistent. Furthermore, body temperature and end-tidal CO_2 remained in the proper ranges.

In conclusion, the special characteristics of xenon may offer a new approach for well tolerated anaesthesia in a patient with susceptibility to malignant hyperthermia.

Acknowledgements relating to this article

Assistance with the article: none.

Financial support and sponsorship: none.

Conflicts of interest: none.

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DOI:10.1097/EJA.0000000000000302

Falsely reduced bispectral index during light anaesthesia in the elderly

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Published online 16 June 2015

Editor,

The validity of bispectral index (BIS) monitoring in the elderly remains unclear, as the database that was used to develop the BIS algorithm did not contain any electroencephalogram (EEG) data from the elderly.¹ The characteristics of the EEG are known to change with increasing age and we have often experienced some uncertainty regarding the accuracy of BIS monitoring, particularly in the elderly. In the present case report, an unsynchronised EEG during light anaesthesia was falsely evaluated as indicating a BIS value less than 20, because

the small EEG amplitude typically seen in the elderly was mistakenly interpreted as burst suppression.

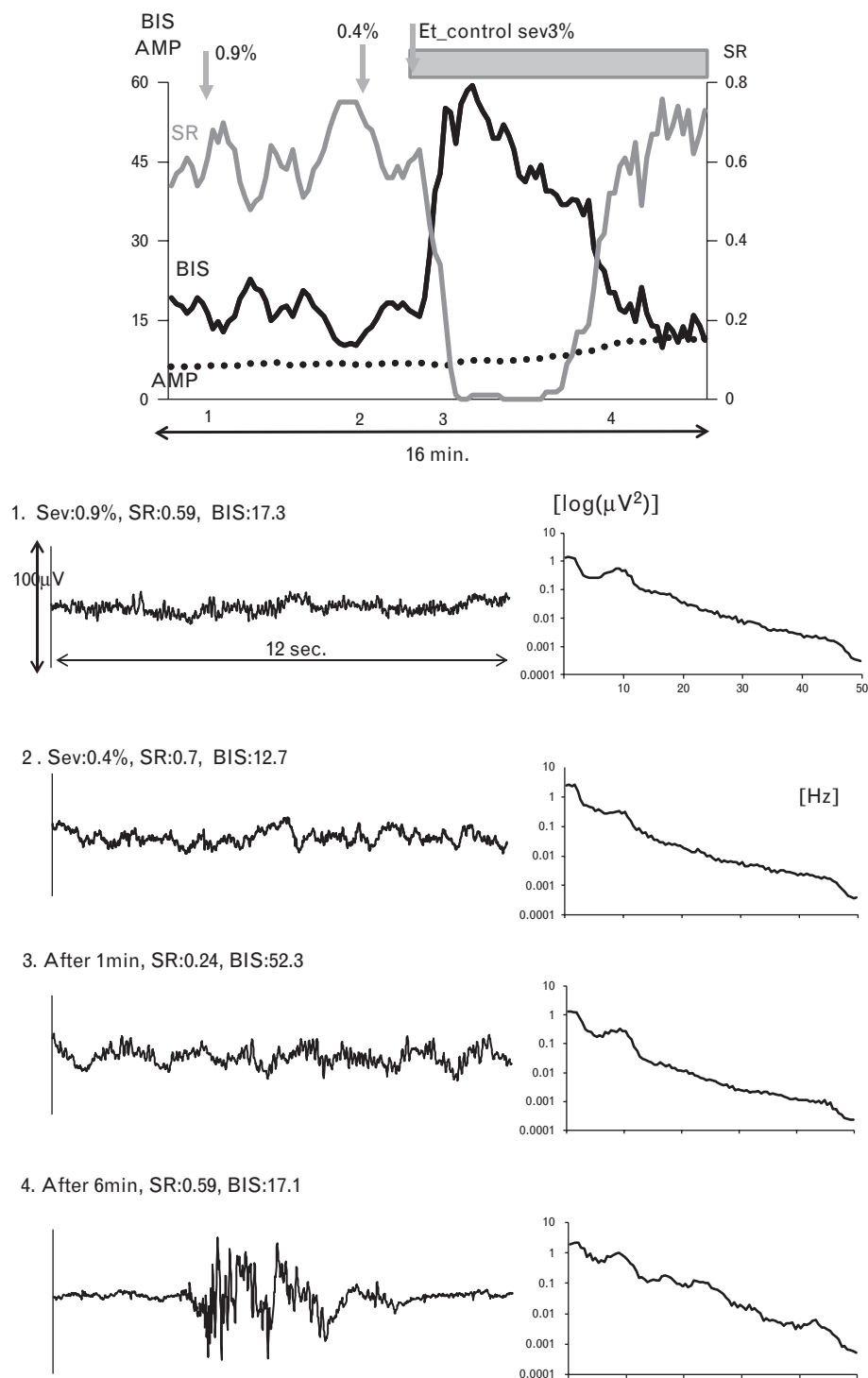
Written informed consent for publishing this case was obtained from the patient and her daughter.

An 82-year-old woman with hypothyroidism was scheduled for surgery for humeral bone fracture. No antipsychotics had been prescribed and she showed no evidence of dementia. Anaesthesia was induced using propofol and remifentanyl and was maintained using sevoflurane and remifentanyl. The EEG was monitored and recorded using an Aspect A-2000 BIS monitor (version 4.0; Aspect Medical Systems, Natick, Massachusetts, USA).

About 45 min after inducing general anaesthesia, BIS values suddenly decreased from 40 to 60 to 10 to 20, despite there being no changes or additions to the anaesthetic (Fig. 1, Point 1). Expiratory sevoflurane concentration was maintained at 0.9% and remifentanyl was continuously administered at $0.2 \mu\text{g min}^{-1} \text{kg}^{-1}$. Circulatory dynamics were stable (SBP was kept between 90 and 130 mmHg, heart rate was 50 to 60 beats min^{-1}). Although the expiratory sevoflurane concentration was reduced to 0.4%, BIS values remained below 20 (Fig. 1, Point 2). We checked the raw EEG data and found that the EEG amplitude was very small but included many waves, and that the appearance of the EEG was somewhat different from what is referred to as a suppressed EEG. We then set the expiratory sevoflurane concentration to 3%. About 1 min later, the BIS values suddenly returned to more than 50 (Fig. 1, Point 3). About 6 min after the expiratory sevoflurane concentration was set to 3%, BIS values again decreased abruptly to less than 20, accompanied by burst suppression (Fig. 1, Point 4). During that period, SBP was maintained above 90 mmHg using phenylephrine and heart rate was always above 50 beats min^{-1} . After surgery, the patient woke up immediately and did not show any neurological complications. She had no experience of perioperative awakening.

Postoperative EEG analysis using BSA version 3.22B2 software (Bispectrum Analyser for A-2000BIS monitor)² revealed that the EEG with an uncharacteristically low BIS index (Point 1) had a low amplitude of about 6 to $7 \mu\text{V}$ and the burst suppression ratio was 0.5 to 0.6. However, the EEG (Point 1) actually differed from the suppressed EEG at the time of real burst suppression (Point 4). The EEG (Point 1) consisted of numerous small waves and its power spectrum resembled the power spectrum associated with intermediate BIS values (Point 3), which had a peak alpha component. The burst phase was also not observed. As for the EEG when BIS increased markedly (Point 3, about 1 min after changing the expiratory sevoflurane concentration to 3%), the suppression ratio was reduced to less than 0.1 because the EEG with slightly increased amplitude was no longer considered to be a suppressed EEG.

Fig. 1



Time course of anaesthesia during 16 min from the appearance of abnormally low bispectral index values (BIS <20) to 8 min after setting the expiratory sevoflurane concentration to 3%. AMP, EEG amplitude; Sev, sevoflurane; SR, suppression ratio. See text for details.

The BIS algorithm employs a suppression ratio that quantifies the isoelectric activity of the burst suppression pattern to calculate the level of deep anaesthesia (particularly levels wherein BIS index is <30).^{3,4} Although

suppression ratios less than 0.4 are not adequately reflected in the BIS index, deep anaesthesia causing suppression ratios more than 0.4 have been reported to be linearly correlated with BIS values in the range 0 to

30.⁴ The sudden recovery in BIS (i.e. from BIS <20 to BIS >50) described in the present report caused by a reduction in suppression ratio from 0.5 to 0.6 was consistent with a previous report.⁴

Concerning the detection of the suppression ratio, suppression is considered to occur when the EEG voltage does not exceed approximately +5.0 μ V for periods longer than 0.50 s.^{3,4} Generally, 5 μ V is used for the threshold value for suppression. However, in the elderly, low-amplitude, unsynchronised EEG near 5 μ V during light anaesthesia might be misinterpreted as a suppression EEG, causing extremely low BIS values.

The ageing process is characterised by neuronal apoptosis and a loss of both synaptic density and neurotransmitters in various regions of the brain. It also causes a general reduction in EEG voltage, altering the functional neural networks of the brain.⁵ The physiology of unsynchronised, low-amplitude EEG in the elderly under light anaesthesia differs markedly from that associated with suppression processes, which are effected by strong, synchronised thalamic discharges to the unresponsive cortex wherein a depletion of extracellular cortical Ca^{2+} causes dysfunction of synaptic transmission.^{6,7}

The elderly can easily be exposed to cerebral ischaemia and hypoperfusion because of a high incidence of cardiovascular complications, which can cause severe reductions in BIS values. However, this report indicates another possibility when extremely low BIS values are monitored in the elderly.

Acknowledgements relating to this article

Assistance with the letter: we thank Satoshi Hagihira for supplying BSA software.

Financial support and sponsorship: none.

Conflicts of interest: none.

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DOI:10.1097/EJA.0000000000000276

Sevoflurane-induced reduction of bispectral index does not affect human cerebral microcirculation

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Published online 16 June 2015

Editor,

Sevoflurane was introduced into clinical practice in 1990 and is commonly used for the maintenance of general anaesthesia. The favourable pharmacokinetic and pharmacodynamic characteristics of sevoflurane include a limited impact on cerebral macrocirculation, pressure autoregulation and carbon dioxide vasoreactivity. However, knowledge of the microcirculatory effects of sevoflurane on the human brain remains limited. It has been proposed that sevoflurane and other anaesthetics may affect the homeostasis of organ microcirculation, potentially influencing clinical outcome.^{1,2}

The aim of this study was to investigate the effects of deeper sevoflurane anaesthesia, when monitored by increased end-tidal sevoflurane concentration (etSevo) and bispectral index (BIS), on the cerebral microcirculation in both 2 mm (grey matter) and 8 mm (white matter) brain tissue. The measurements were obtained using a novel probe combining white light spectrometry and laser Doppler flowmetry (O₂C-device; Lea Medizintechnik GmbH, Giessen, Germany) that was applied directly to the brain surface during craniotomy. The following variables were measured: regional capillary venous cerebral blood flow (rvCBF); regional capillary venous cerebral oxygen saturation (srvO₂); and regional capillary venous cerebral haemoglobin amount (rvHb). From these, arteriovenous difference in cerebral oxygen concentration (avDO₂) and approximated cerebral metabolic rate of oxygen, (aCMRO₂) were estimated as measures of cerebral metabolism.^{3,4} The effects of interest, analogous to the effects of sevoflurane on cerebral macrocirculation, were as follows:

- (1) increases in rvCBF (increased cerebral vasodilatation) and srvO₂ (elevated rvCBF);
- (2) decreases in avDO₂ (reduced oxygen extraction fraction) and aCMRO₂ (suppression of cerebral metabolism).

Ethical approval for this study [Ref: 837.136.05 (4794)] was provided by the Ethical Committee of the State of Rhineland-Palatinate (Landesärztekammer Rheinland-Pfalz, Deutschhausplatz 3, 55131 Mainz, Germany) on 11 May 2005. The study was conducted from 3 January 2008 until 8 August 2010. After written informed consent on the day before neurosurgery, patients ($n = 24$) scheduled for routine craniotomy were included in the randomised crossover study. A BIS electrode was placed at the forehead contralateral to the site of craniotomy (A-2000; Aspect Medical, Norfolk, Massachusetts, USA). etSevo was adjusted so as to produce 'adequate' (etSevo 1.5 %vol/vol) or 'deeper' (etSevo 2.5 %vol/vol) sevoflurane anaesthesia. At steady-state cardiopulmonary conditions, the sterile O₂C-probe was placed onto macroscopically healthy brain tissue. Measurements were performed during stable haemodynamic and respiratory conditions at target etSevo concentrations. Data were recorded as follows: srVO₂ in %; rvHb; and rvCBF in arbitrary units (AU). Mixed linear models and paired Student's *t*-tests were performed to determine the effects of etSevo concentrations on rvCBF, srVO₂, rvHb, avDO₂, aCMRO₂ and BIS. Data were analysed using the software R (R Foundation for Statistical Computing, Vienna, Austria) with *P* value less than 0.05 considered significant.

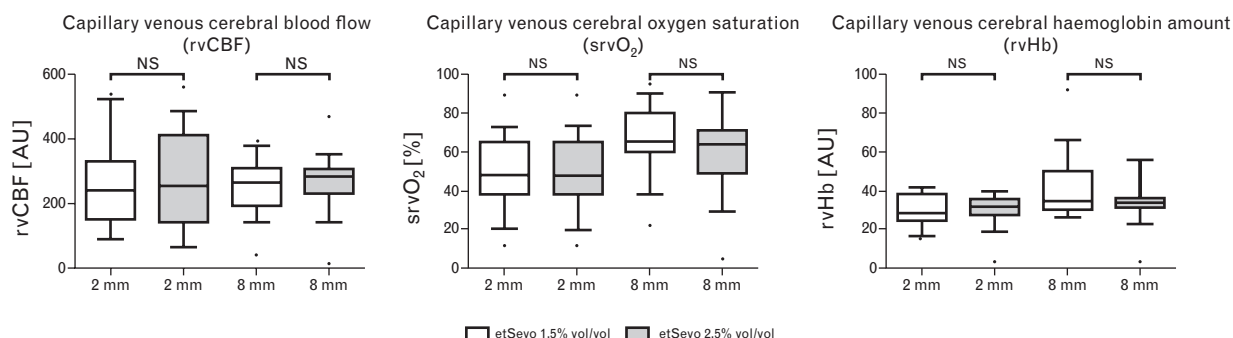
Measurements were successfully completed in 20 patients (sequence A: adequate followed by deeper sevoflurane anaesthesia $n = 11$; sequence B: deeper followed by adequate sevoflurane anaesthesia; $n = 9$). In four patients, no O₂C data could be recorded because the size of the craniotomy was too small. There were no signs or symptoms of raised intracranial pressure. Cerebral measurements were performed at the frontal ($n = 7$), temporal ($n = 6$), parietal ($n = 6$) and occipital ($n = 1$) lobes depending on the location of craniotomy. Important physiological variables with an impact on cerebral

circulation remained unchanged during measurements. No adverse effects attributable to the positioning of the O₂C-probe (e.g. bleeding, infection, cerebral tissue damage or severe neurological dysfunction) occurred before the patients were discharged.

Results are presented as median with interquartile range (Fig. 1). O₂C measurements were performed at etSevo concentrations of 1.5 (1.3 to 1.7) %vol/vol and 2.5 (2.2 to 2.8) %vol/vol ($P < 0.001$). BIS levels were 30 (27 to 38) at deeper and 42 (40 to 47) at adequate etSevo concentrations ($P < 0.001$). Eight of 20 patients showed an 'insufficient' BIS reduction (< 15 BIS units) and four patients showed a 'paradoxical' BIS increase with higher sevoflurane concentrations. Paradoxical BIS increases have previously been reported when increasing sevoflurane MAC levels.⁵ rvCBF, rvHb, srVO₂ and the calculated variables, avDO₂ and aCMRO₂, did not differ at etSevo 1.5 and 2.5 %vol/vol, nor at cerebral depths of 2 and 8 mm (Fig. 1). A previous study showed that srVO₂ decreased during increasing propofol anaesthesia when BIS was altered from 40 to 21.³ Although this and our studies are observational, it may be that propofol and sevoflurane exhibit specific effects on human cerebral microcirculation and oxygenation, an assumption that needs to be investigated in detail with regard to organ homeostasis on a microregional scale.

Low srVO₂ values (e.g. 45.9% in 2 mm cerebral depth during etSevo 1.5 %vol/vol) and high avDO₂ values (e.g. 8.3 ml dl⁻¹ in 2 mm cerebral depth during 2.5 %vol/vol) represent a high oxygen extraction of brain tissue during sevoflurane anaesthesia. These values seem reasonable, as pericapillary partial pressure for oxygen gradients for grey matter are steep due to the high metabolic activity in this area.⁶ Clinical studies using cortical photospectroscopy showed similar capillary venous haemoglobin oxygen saturations (40 to 70%) when measured directly

Fig. 1



Regional capillary venous cerebral blood flow, regional capillary venous cerebral oxygen saturation and regional capillary venous cerebral haemoglobin amount in brain tissue depths of 2 mm (grey matter) and 8 mm (white matter) at end-tidal sevoflurane concentrations (etSevo) of 1.5 and 2.5 %vol/vol. Box-whisker plots show median, 25th and 75th percentiles (box) with 10th and 90th percentiles (whiskers).

at the cerebral cortex.^{3,4} In the present study, unaltered rvHb values at varying BIS levels suggest that the cerebral capillary blood filling and emptying remained stable and that a microcirculatory flow problem in the cerebral capillary bed was unlikely.

In conclusion, our findings suggest that the microcirculatory environment (rvCBF, srvO₂, rvHb, avDO₂, aCRMO₂) remains unchanged at two different concentrations of sevoflurane anaesthesia (etSevo 1.5 and 2.5 %vol/vol) during routine craniotomy.

Acknowledgements relating to this article

Assistance with the study: none.

Financial support and sponsorship: the study was supported by a research grant from the German Society of Anaesthesiology and Intensive Care Medicine (DGAI e.V.).

Conflicts of interests: none.

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DOI:10.1097/EJA.0000000000000278

Measuring regional cerebral oxygen saturation during surgery in the prone position

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Published online 16 June 2015

Editor,

Near-infrared spectroscopy (NIRS) is a technique that measures regional cerebral oxygen saturation (rScO₂). By using one detector near, and one or more distant, from the light source, it is theoretically possible to subtract the

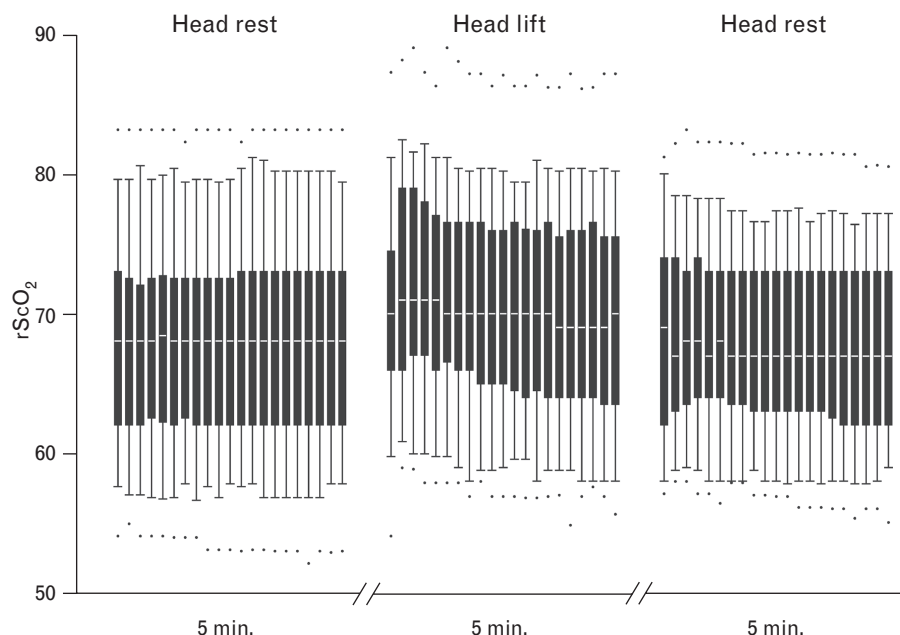
signal from superficial layers and obtain a signal from the cerebral tissue with limited extra-cerebral contamination.¹

To be able to rely on such measurements carried out with the patient in the prone position as, for example, during spine surgery, it is important to know whether the rScO₂ readings are affected by the external pressure on the forehead sensor in this position. In a previous study, it was suggested that in patients placed in the prone position, a relieved pressure on the extra-cranial tissues below the sensor (head lift from the head support) might distort the rScO₂ value on the monitor.² The aim of the present study was to confirm and quantify this in a protocolled study. The primary endpoint was the increase in rScO₂.

The prospective study was approved by the Danish Regional Scientific Ethics Committee of the Capital region (approval number: H-4-2013-FSP 78) as a quality assurance project on 5 September 2013 (chief Adviser Lone Gundelach) and was registered at Clinical Trials.gov (ID NCT01971996). The study was approved by The Danish Data Protection Agency. Written and informed consent was obtained from all patients. Patients scheduled for lower back surgery were enrolled. Inclusion criteria were age above 18 years and free painless extension of the neck. Exclusion criteria were known disease of the cervical spine.

A self-adhesive NIRS pad (Adult SomaSensor; Covidien, Troy, Michigan, USA) was attached on the right side of the forehead, 1 to 2 cm above the eyebrow and at least 2 cm lateral to the midline so that the diode and optodes were clear of the frontal sinus. The pads were connected to an INVOS oximeter model 5100C (Covidien, Troy, Michigan, USA). A cerebral state monitor (CSM, Danmeter, Denmark) was used to register the depth of anaesthesia during the measuring period. Anaesthesia was induced and maintained with propofol and remifentanyl. After tracheal intubation, the lungs were ventilated using a volume controlled mode with a 1:1 oxygen air mixture. The patient was then placed in the prone position. The head was supported on the forehead, the cheek and the jaw by a foam head support (Proneview Helmet, Dupaco, California, USA). Steady-state anaesthesia was defined as obtained when there had been no change in positioning of the operating table or in the inspiratory oxygen fraction (F_iO₂), no use of vasoactive drugs or inotropes and no change in drug infusion rate for a period of at least 30 min. During steady-state anaesthesia, measurements were carried out in three series of 5 min, one with the head resting in the head support, one with the head lifted a few mm to alleviate pressure and one with the head again resting in the head support. During each series, the NIRS values were registered every 15 s; cerebral state index (CSM) was registered every minute, and blood pressure, heart rate (HR), SpO₂ (all measured on an Intelli Vue, MP70, Philips,

Fig. 1



Regional cerebral oxygen saturation (rScO₂). The median, 25 and 75% quartile (boxes) and 10 and 90% percentiles (whiskers) are shown. The dots denote values in the 5 to 10% and 90 to 95% intervals.

Denmark) and EtCO₂ (Primus, Dräger, Germany) were registered immediately before and after each 5 min series.

Using a type I error of 0.05 and a type II error of 0.8, the sample size was calculated using data from the above-mentioned study and 10% was chosen to be a clinically relevant change.¹ Fifty-seven patients completed the study. The results of the NIRS measurements are shown in Fig. 1. A transient increase in rScO₂ was observed when the head was lifted from the support. The maximum difference in median value was 5 rScO₂ units (7%). There was no difference between the rScO₂ values obtained in the two series of measurements during head rest ($P=0.4$). SpO₂, mean arterial pressure, HR EtCO₂ and cerebral state index were all constant during the three measurement series.

We found no difference between the rScO₂ values obtained in the two series of measurements during head rest ($P=0.4$), but a transient increase in rScO₂ was seen during head lift. The change in measurement is largest in the beginning of the head lift and decreases within a few minutes. Such an initial response is supportive of the idea that there is some ischaemia in the scalp followed by hyperaemia as the pressure on the sensor is relived, and

that this is responsible for the signal differences. The gradual shift back to baseline values that we observed during the head lift might support this hypothesis.

On the basis of the relatively small changes in the rScO₂ readings induced by the head lift, we conclude that the prone position and the concomitant pressure on the tissue at the NIRS pad do not change rScO₂ to a clinically relevant magnitude.

Acknowledgements relating to this article

Assistance with the study: we would like to thank all the dedicated anaesthesia nurses for their assistance with the study.

Financial support and sponsorship: the Toyota foundation is thanked for the donation of the NIRS monitor.

Conflicts of interest: none.

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DOI:10.1097/EJA.0000000000000289