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ABSTRACTS

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*(The name of the author presenting the paper is shown in bold type. *Indicates non-member. All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.)*

Evaluation of modified early warning scores as a predictor of outcome in obstetric admissions to critical care units: secondary analysis of the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Program (CMP) database

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The latest CEMACH report[1] recommends the use of modified early warning scores (MEWS) to assist in identifying the obstetric patient at risk of deterioration. By using critically ill obstetric patients from the Case Mix Program (CMP) data set and examining their unit mortality, we aim to evaluate the ability of various pre-existing MEWS to identify the obstetric patient at risk.

After ethical approval, all female admissions (aged 16–50 yr) during the 13 yr study period were extracted from the CMP database. The data (n=71 107) were randomly split into two sets. All analyses have been carried out on set 1. Set 2 was reserved for future analysis. Cases with an obstetric cause as their primary or secondary reason for admission (direct obstetric admissions) were identified. A variety of MEWS scores were selected for evaluation. These included published, unpublished, general, and obstetric specific scores. Using physiological data collected within the first 24 h of admission, we calculated nine different MEWS for each direct obstetric admission. The ability of the nine MEWS to predict outcome (unit mortality) was evaluated. Discrimination was assessed using area under ROC curves.

Within 'set 1', 2240 direct obstetric admissions were identified. Unit mortality was 1.7%. ROC curve analysis (Table 1) showed that all nine MEWS were able to distinguish, with varying degrees of discrimination, intensive care survivors from non-survivors within the study group. The 'obstetric' MEWS did not confer any additional benefit.

Our obstetric data set (n=2240) comprises parameters measured *after admission* to critical care. Ideally, to evaluate a MEWS, the parameters in the period *before admission* should be used. An estimated 0.06% of maternities require critical care.

Table 1 ROC curve analysis of direct obstetric admissions (n=2240). *Specific obstetric MEWS. H, Heart rate; R, respiratory rate; T, temperature; A, AVPU; U, urine output; B, systolic arterial pressure (B); S, Sp_{o_2}; D, diastolic arterial pressure

	Area under ROC curve	95% CI	Parameters included
MEWS 1	0.980	0.967–0.993	H, R, T, A, B, U
MEWS 2	0.980	0.967–0.993	H, R, T, A, B, U, S
MEWS 3	0.985	0.974–0.995	H, R, T, A, B, U
MEWS 4	0.979	0.969–0.990	H, R, T, A, B
MEWS 5	0.971	0.952–0.991	H, R, T, A, B, U, S
MEWS 6	0.981	0.969–0.992	H, R, T, A, B, U
MEWS 7*	0.981	0.971–0.992	H, R, T, A, B, U, S
MEWS 8*	0.967	0.947–0.987	H, R, T, A, B, U, S, D
MEWS 9	0.971	0.954–0.989	H, R, T, A, B, S

Prospective data collection of a similarly sized data set is unfeasible as it would require participation by all the CMP units over a 6 yr period. Our findings confirm that the MEWS studied can be used to predict unit mortality among obstetric admissions and identify the at risk obstetric patient.

Keywords: obstetrics; obstetric labour complications; critical illness

Reference

1 Lewis G, ed. *The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom*. London: CEMACH, 2007

Use of preparative fluorescence-activated cell sorting (FACS) to profile opioid receptor and peptide mRNA expression on human granulocytes, lymphocytes, and monocytes

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Expression of μ-opioid receptors (MOP) on immune cells is controversial with several papers showing expression in varying experimental protocols.[1 2] We have failed to demonstrate MOP receptors on peripheral blood mononuclear cells using endpoint and quantitative PCR, radioligand binding, and antibody binding.[2] We are also unable to show MOP on polymorphs.[3] In contrast, the receptor for nociceptin/orphanin FQ (N/OFQ) or NOP (a member of the opioid family) and N/OFQ precursor ppN/OFQ are found on these cell types using PCR.[4] In this study, we have separated human immune cells into granulocytes, lymphocytes, and monocytes using fluorescence-activated cell sorting (FACS) and probed for MOP, ppN/OFQ, and NOP mRNA by quantitative PCR.

Leucocytes from 10 ml of lysed (BD Pharm Lyse) whole blood were sorted into lymphocyte, monocyte, and granulocyte populations using a Becton Dickinson FACSAria II, based on forward and side scatter characteristics.[5] Total RNA was isolated from cell populations using a mirVana RNA isolation kit according to the manufacturer's protocol. To remove gDNA, $\leq$2.5 μg of RNA was processed with a DNase enzyme; samples were converted to cDNA using a reverse transcriptase and assessed for gene expression using TaqMan probes (for MOP, NOP, ppN/OFQ, and the housekeeper GAPDH) and the StepOne real-time PCR system (Table 2).

These data confirm that human immune cells do not express MOP and the search for site(s) of opioid immunomodulation should move elsewhere. In contrast, the N/OFQ-NOP system is present and represents an interesting target for further work in situations involving immunomodulation. On the basis of small numbers, NOP expression appears relatively consistent, but there is some variation in ppN/OFQ with granulocytes expressing the lowest quantity. Studies to separate granulocytes into neutrophils, basophils, and eosinophils and measure functional protein are underway.

Keywords: opioid receptors; immune cells; polymerase chain reaction; fluorescence activated cell sorting

Table 2 Granulocytes, monocytes, and lymphocytes express NOP and ppN/OFQ but *not* MOP mRNA. Data are median (range) from four volunteers and are expressed as the difference in cycle threshold (C_t) between the housekeeper and gene of interest (ΔC_t large number equates to small amount of mRNA). One volunteer had a repeat sample to examine reproducibility, for example, NOP C_t values for granulocytes first:second assay of 8.92:8.19, monocytes 7.02:6.21, and lymphocytes 6.03:4.86. In one sample, ppN/OFQ was not detected in granulocytes

	MOP ΔC_t	NOP ΔC_t	ppN/OFQ ΔC_t
Granulocytes	Not detected	5.93 (2.44–8.92)	10.37 (6.50–11.29)
Monocytes	Not detected	6.33 (5.07–7.99)	8.37 (6.95–10.27)
Lymphocytes	Not detected	6.78 (5.64–9.26)	6.28 (5.05–11.45)

Acknowledgement

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5 Murihead KA, *et al. Ann N Y Acad Sci* 1986; **468**: 113–27

A preliminary investigation into the effects of opioids in patients with and without pain

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Opioids are commonly used in the management of pain and substance misuse. The varied incidence and severity of opioid side-effects is postulated to be due to altered neurobiology and variations in genetic makeup among individuals. Chronic opioid use may also be associated with opioid-induced hyperalgesia (OIH). This work is preliminary data from a larger long-term study, aiming to investigate the prevalence and severity of opioid side-effects and of OIH in neurobiologically diverse patient populations. It aims to assess if neurobiological state may influence the response to opioids.

Patients with chronic non-cancer pain (CNP) and cancer pain (CP) using strong opioids for pain relief and subjects with a history of opioid misuse on opioid maintenance therapy (OMT) were included in the study. The assessment included obtaining information regarding opioid use and incidence of side-effects. The sensory-discriminative component of pain was tested using Quantitative Sensory Testing in index and control areas. Affective and cognitive components of pain were tested using appropriate assessment tools. Statistical analysis was carried out using χ^2 test and Fisher's exact test.

Nineteen patients were included in the preliminary analysis. The number of patients included in each group was CNP (n=11), CP (n=4), and OMT (n=4). Subjects in all groups had been taking a total daily dose equivalent of 60 mg of morphine or greater for at least 3 months. Six of 11 (54.5%) in the CNP and four of four (100%) in the CP group had Self-completed Leeds Assessment of Neuropathic Symptoms and Signs score of >12, suggesting that their pain was of predominantly neuropathic origin. The mean values for the Brief Pain Inventory scores did not differ significantly between the CNP and CP groups. The mean mechanical pain threshold (MPT) values showed a trend that, both in the control and index areas, the CNP group had a lower

MPT value than the CP group which was lower than the OMT group. The CNP group also had a higher mean MPT VAS-score than the OMT for both index and control areas. Three of 11(27%) subjects from the CNP group were identified as constipated in spite of being on laxatives. None of the patients from other groups was constipated. Three of eight (37.5%), four of four (100%), and one of four (25%) in the CNP, CP, and OMT groups, respectively, had total Hospital Anxiety and Depression Score scores above 14 and would thus be considered distressed. Mean Mini-Mental State Examination scores were significantly better in the CNP group when compared with the OMT group and the difference [7.88 (1.08, 14.67, 95% CI)] was statistically significant ($P<0.05$).

Patients in the CNP group have lower mean MPT values and higher MPT-VAS scores when compared with those in the other two groups. Patients in the CNP group also showed increased incidence of severity and number of side-effects due to opioid use. Subjects on OMT having no pain did not have any side-effects from opioid use. The exact mechanism of why patients with chronic CNP would have lower pain thresholds in the control area and increased incidence and severity of side-effects is not known. Various factors including neurobiological variations, genetic susceptibility, and psychological and affective circumstances may have had an influence on this. A larger sample size will be able to throw further light on the findings of these preliminary data.

Keywords: pain; analgesics, opioid; adverse effects

Use of non-depolarizing neuromuscular blocking drugs and markers of severity of malignant hyperthermia reactions

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As part of a retrospective analysis of patients investigated for malignant hyperthermia (MH) susceptibility, we have examined whether the use of non-depolarizing neuromuscular blocking drugs affected the speed of onset of the metabolic features of the MH reaction, the maximum serum creatine kinase (CK) concentration after the crisis, or both.

The records of patients tested for susceptibility to MH at the Leeds MH unit between 1990 and 2009 were identified. From these, the records of index cases (probands) who were confirmed to be MH susceptible by diagnostic muscle biopsy were isolated manually. The available anaesthetic and perioperative records of each proband were reviewed. An anonymized database was constructed with fields including details of drugs used during anaesthesia, and also the course of clinical variables associated with MH. The speed of onset of the metabolic features of the MH reaction was defined as the time from induction of anaesthesia to the development of two of the following: evidence of increasing end-tidal carbon dioxide, increasing heart rate, increasing core body temperature.[1] The maximum CK concentration in a sample taken at any time after the onset of the reaction was also recorded. The data were summarized graphically and analysed using non-parametric statistical tests.

Of the 566 probands investigated at the Leeds MH unit during the period 1990–2009, 101 patients were excluded because of inadequate information within the records. Out of the 465 probands included, 62% were male and 38% were female. After a diagnostic muscle biopsy, 214 (46%) were found positive for MH and 251 (54%) tested negative. Out of the 214 patients tested positive for MH, 88 had received non-depolarizing neuromuscular blocking drugs: 34 of these had received succinylcholine before administration of the non-depolarizing neuromuscular blocking drug. Patients who received non-depolarizing neuromuscular blocking drugs had a delayed time to onset of the MH reaction (median 60, IQR 30–112 *vs* 42, 11–53 min: $P=0.02$) and lower maximum CK concentrations (3780, 829–17 216 *vs* 12 113, 2087–30 150 IU litre^{-1}: $P=0.002$) compared with those who did not receive non-depolarizing neuromuscular blocking drugs.

MH reactions are associated with a slower onset and a lower maximum CK concentration when non-depolarizing neuromuscular blocking drugs are used as part of the general anaesthesia technique.

Keywords: malignant hyperthermia

Reference

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Origin of abstracts published in the *British Journal of Anaesthesia*

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There have been significant changes to the way research is conducted in the UK over the last 30 yr.[1 2] We were interested to see if the geographical origin of anaesthesia publications has also changed during this period.

We reviewed all meeting abstracts published online in the *British Journal of Anaesthesia (BJA)*. For each abstract, we recorded the submitting hospital, strategic health authority (for England), and country of origin. The region was determined as being that of the first listed hospital except when the senior author's hospital was different. For abstracts originating from multiple specialities, the origin of the anaesthetic related component was recorded. Abstracts published in 1983–7 were compared with those from 2005 to 2009. The percentage of journal pages containing abstracts was also calculated.

A total of 806 abstracts were reviewed. Of these, more than 90% were from meetings of the Anaesthesia Research Society. The number of abstracts published nearly halved between the two time periods (515 *vs* 291), although the percentage of

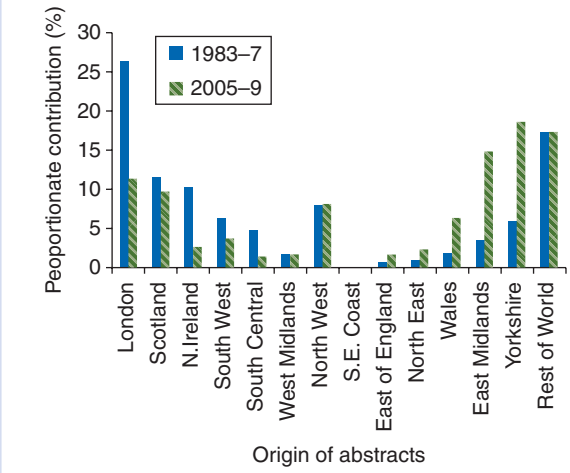

Fig 1 Origin of abstracts published in *BJA*.

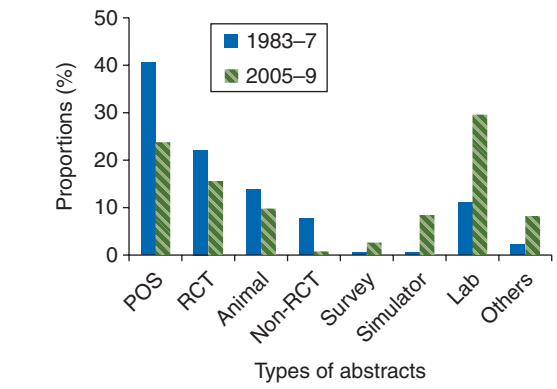

Fig 2 Proportions of the types of abstracts published in the *BJA*.

journal pages containing abstracts was unchanged (3.6%). As shown in Figure 1, there was a three- to four-fold increase in contributions from East Midlands, Yorkshire and Humber, and Wales. Conversely, contributions from Northern Ireland, South Central, and London declined.

The proportion of abstract publications in the *BJA* may be an indicator of changing patterns of research activities of anaesthetic departments. The data for the UK show a geographic redistribution over time. Many factors determine the research activities of individual departments. It may be interesting to see whether the increased proportion of output from the East Midlands, Wales, and Yorkshire is associated with changes in these regions that promote and prioritize anaesthesia research.

Keywords: abstracting and indexing as topic

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Types of abstracts published in the *British Journal of Anaesthesia*

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There have been significant changes to the way research is conducted in the UK over the last 30 yr.[1] We were interested to see if there had been an alteration in the type of anaesthetic research being conducted.

We reviewed all the anaesthesia meeting abstracts published online in the *British Journal of Anaesthesia* (*BJA*) and compared the periods from 1983 to 1987 and 2005 to 2009. We categorized each abstract as either an animal study, laboratory study, randomized controlled clinical trial (RCT), non-randomized controlled clinical trial (Non-RCT), prospective observational study (POS), simulator study, survey, or other. To minimize bias, the two authors reviewed alternate years' data.

A total of 806 abstracts were reviewed. Eighteen abstracts were excluded, as insufficient information was available to categorize the paper. The number of abstracts published nearly halved from 498 to 290. A higher proportion of Laboratory, Simulator studies, and Surveys were published in the second period. The proportion of POS, RCT, Non-RCT, and Animal studies declined. The proportions of the types of study are shown in Figure 2.

The trend towards fewer publications of interventional trials, Animal and Observational studies could be attributed to increasing difficulty in obtaining ethical approval and greater strictures on clinical trials. This premise is reinforced by the shift towards increased Laboratory-based and Simulator studies.

Keywords: periodicals as topic

Reference

1 Langford RA, Huang GH, Leslie K. *Anaesthesia* 2009; **64**: 60–4

Prediction of arterial partial pressure of oxygen in mechanically ventilated patients: validation of a novel formula and comparison with use of the PF ratio

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The ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen ($Pa_{O_2}/F_{I_{O_2}}$: the PF ratio) is widely used to predict Pa_{O_2} in response to $F_{I_{O_2}}$ adjustment, based on the assumption that PF ratio is independent of $F_{I_{O_2}}$. In the present study, we evaluate its accuracy in predicting Pa_{O_2} after a change in $F_{I_{O_2}}$ and compare it with a newly developed formula to predict the resulting Pa_{O_2} ($_{new}Pa_{O_2} = {}_{new}F_{I_{O_2}} \times {}_{old}Pa_{O_2}/{}_{old}F_{I_{O_2}} \times k$), *where* $k = 1 - ({}_{old}F_{I_{O_2}} - {}_{new}F_{I_{O_2}})/2$.

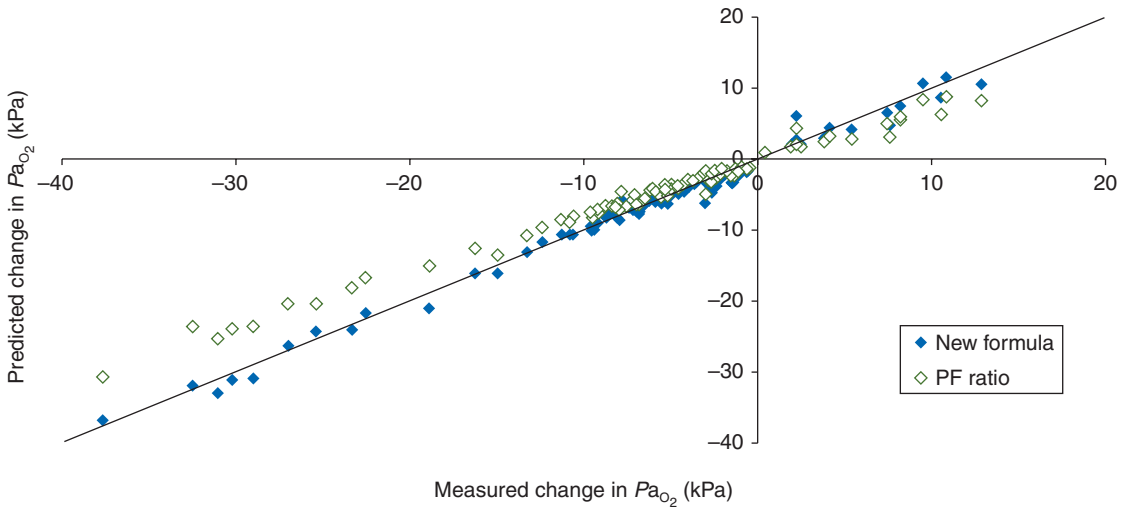

Fig 3 Predicted *vs* measured changes in Pa_{O_2} using the new formula and the PF ratio. The line of equality is shown (diagonal), where all points would lie if prediction was perfect.

One hundred and six data sets were collected from randomly selected, mechanically ventilated patients in the critical care unit, before and 20 min after $F_{L_{O_2}}$ adjustment. Each data set comprised $F_{I_{O_2}}$, ventilatory frequency (bpm), tidal volume (ml), positive end-expiratory pressure (cm H_2O), haemoglobin (g dl^{-1}), and arterial pH, Pa_{O_2}, and Pa_{CO_2}. The resulting Pa_{O_2} was predicted using the conventional $Pa_{O_2}/F_{I_{O_2}}$ formula ($_{new}\ Pa_{O_2} = {}_{new}\ F_{I_{O_2}} \times {}_{old}\ Pa_{O_2}/{}_{old}\ F_{I_{O_2}}$) and using the new formula (above). All data are presented as mean (SD) unless stated otherwise.

Inspired oxygen fraction decreased, on average, from 0.6 (0.21) to 0.5 (0.16). Pa_{O_2} decreased, on average, from 22.9 (14.3) to 17.5 (7.9) kPa. The 95% limits of agreement between measured and predicted magnitude of changes for Pa_{O_2} were −1.45 (3.81) kPa using the conventional PF ratio and 0.08 (1.95) kPa using the new formula. Predicted and measured changes in Pa_{O_2} are shown in Figure 3.

The data indicate that prediction of Pa_{O_2} after a change in $F_{I_{O_2}}$ using the PF ratio loses accuracy as the magnitude of change increases. The new formula improves upon this. It possesses sufficient accuracy and consistency to be used in clinical settings and its simplicity may facilitate its adoption.

Keywords: oxygen; hypoxemia; estimation techniques

Is on table continuous spirometry a marker for recovery room respiratory complications in ultra-fast-track coronary artery bypass patients?

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This paper describes the immediate changes in minute volume and tidal volume in an ultra-fast-track cardiac anaesthesia technique where spontaneous ventilation is established as soon as the sternum is closed. Tracheal extubation then occurs in the recovery room. The benefits of a fast-track pathway to reduce intensive care admissions have previously been described.[1] The data are taken from an ongoing prospective randomized trial using single-dose i.v. acetaminophen at close of surgery.

Fifty-four patients were anaesthetized using a standardized technique. Patients were transferred to recovery breathing via a t-piece. Continuous spirometry was collected from close of the sternum via a Datex AS3 monitor. Staff were blinded to spirometry recordings and performed tracheal extubation according to our usual criteria.[2] Respiratory complications (RCs) were defined as 'poor respiratory pattern', hypoxaemia Pa_{O_2} <9.5 kPa or hypercarbia Pa_{CO_2} >7.5 kPa (two successive readings).

Eight patients had RCs. Mean (SD); age, body mass index, and bypass times for RC *vs* normal extubation groups were 61.7 (7.13) *vs* 62.4 (5.66) yr, 28.5 (3.3) *vs* 30.7 (4.43), and 80 (20.6) *vs* 71.4 (19.7) min, respectively, and did not differ ($P>0.05$). Median (range) time to extubation was significantly longer 89 (28–319) min for the RC *vs* normal group of 23 (5–99) min ($P=0.001$). The RC group minute volume was significantly reduced after 2 min of spontaneous ventilation ($P<0.05$). Tidal volume in the two groups was similar for 25 min. The mean of 5.45 (1.13) ml kg^{-1} became less than the value of the uncomplicated group 6.97 (1.91) ml kg^{-1}, $P=0.03$ at 30 min (Fig. 4).

As tidal volume is unchanged for 25 min, respiratory rate is the major contributor to lowered minute volume in the RC group. This different pattern emerges before surgery has ended but appears to pre-empt RCs in recovery.

Keywords: continuous spirometry; fast track cardiac

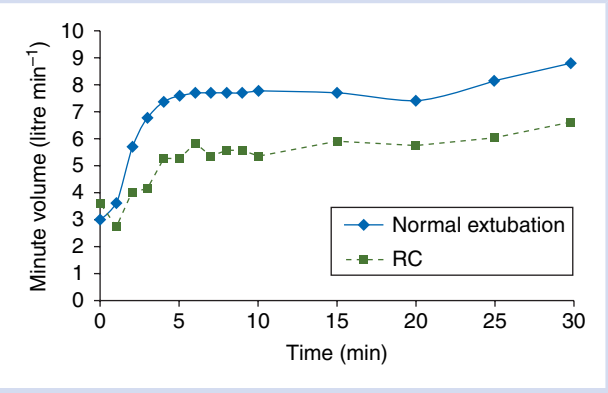

Fig 4 Changes in minute volume for normal extubation and those with RCs. Minute volume is lower and remains so from as early as 2 min of spontaneous ventilation in the RC group, with a high degree of significance $P<0.03$ at all the subsequent time points.

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Does on table spirometry correlate with recovery room extubation time in spontaneously ventilating ultra-fast-track coronary artery bypass patients?

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Continuous spirometry is a simple but effective measure of respiratory function. This paper investigates the relationship between minute volume (MV), tidal volume (TV), end-tidal carbon dioxide ($F_{E'_{CO_2}}$), and time to tracheal extubation in 54 self-ventilating patients after coronary artery bypass surgery. The data are taken from an ongoing, prospective, randomized trial using a single-dose acetaminophen at close of surgery.

Fifty-four patients were anaesthetized according to a standardized technique which involves establishing spontaneous ventilation as soon as the sternum has been closed and while the patient is still in theatre. Patients are subsequently transferred to the recovery room and extubated according to clinical criteria.[1] Spirometry recordings were collected from the point of spontaneous ventilation until tracheal extubation. Data were analysed using PASW18. Non-parametric correlations were made with Spearman's coefficient.

The mean (SD) age was 61.9 (6.8) yr, body mass index was 28.8 (3.5) kg m^{-2}, bypass time was 79 (20) min, and aortic clamp time was 46 (12.53) min. Time to establish spontaneous ventilation was 64 (32.5) s and time from spontaneous ventilation to recovery was 28 (5.8) min. Median (range) extubation time from recovery was 40 (314) min. Mean (SD) MV increased from the time zero value of 3.01 (2.60) to 8.52 (3.13) litre min^{-1} in 30 min. Over the same time, TV changed from 2.76 (3.11) to 6.47 (1.64) ml kg^{-1}. $F_{E'_{CO_2}}$ increased from baseline 4.58 (0.83) to a peak of 6.23 (0.89) kPa at 25 min declining slightly at 30 min. The correlation at three time points between extubation time, MV, TV, and $F_{E'_{CO_2}}$ is shown in Table 3.

MV correlates most strongly with tracheal extubation time and is more sensitive than blood gas analysis. TV does not correlate after the initial 5 min of the study period. The weak positive correlation at 5 min is unexpected. $_{E'_{CO_2}}$ exhibits a weak positive correlation. Continuous spirometry may be a valuable indicator for tracheal extubation decision-making in recovery as an adjunct to established extubation criteria. It is also hoped that it may be a convenient method of comparing anaesthetic techniques for respiratory depression in ultra-fast-track patients.

Keywords: continuous spirometry; fast track cardiac

Reference

1 Khalil MW, Chaterjee A, MacBryde G, Sarkar PK, Marks RRD. *Br J Anaesth* 2006; **96**: 171–8

Plasma concentration of ropivacaine after ultrasound-guided transversus abdominis plane block for open retropubic prostatectomy

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Table 3 Spearman's correlation coefficient for the relationship between tracheal extubation time and MV, TV, and $F_{E'_{CO_2}}$ at 5, 10, and 30 min time points after spontaneous ventilation was established. MV is negatively correlated with extubation time at all three time points. End-tidal carbon dioxide also exhibits a weak positive correlation with time to extubate. TV is not strongly correlated and shows a weak positive correlation with extubation time at 5 min. Also shown is the correlation between tracheal extubation and arterial carbon dioxide partial pressure

Time (min)	Minute volume		Tidal volume		$F_{E'_{CO_2}}$		Pa_{CO_2}	
	Coef.	*P*-value	Coef.	*P*-value	Coef.	*P*-value	Coef.	*P*-value
5	−0.518	0.0001	0.332	0.016	0.411	0.0002	0.424	0.01
10	−0.544	0.0001	−0.237	0.088	0.497	0.0001		
30	−0.60	0.001	−0.241	0.082	0.521	0.0001	0.417	0.002

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The transversus abdominis plane (TAP) block is a novel approach for blocking the abdominal wall where local anaesthetic is injected into the neurovascular plane between the transversus abdominis and internal oblique muscles.[1] This new method allied with ultrasound guidance[2] can improve not only analgesic efficacy for lower abdominal incision pain, but also safety, because of direct visualization of the needle and the spread of local anaesthetic. However, information regarding the pharmacokinetics of local anaesthetics after TAP block is lacking. In this present study, we have measured plasma concentrations of ropivacaine after preoperative TAP block in open retropubic prostatectomy using increasing concentrations of ropivacaine (0.25–0.75%) with or without epinephrine.

With ethical committee approval and informed consent, 65 patients were randomly allocated to five groups for bilateral TAP block with 20 ml solution (ropivacaine 0.25, 0.5, 0.75, and 0.5% containing lidocaine with or without 3.3 g μg ml^{-1} epinephrine). Arterial plasma samples were collected 15, 30, 45, 60, 90, 120, and 180 min after completion of TAP. Plasma ropivacaine concentrations were measured by gas chromatography mass spectrometry (GC/MS) (inter- and intra-assay coefficient of variation and minimum sensitivity were 3.6%, 3.7%, and 10 ng ml^{-1}, respectively).

Maximum plasma concentrations occurred after a mean time of 23 (range, 15–60), 23 (15–60), 21 (15–45), 44 (15–90), and 18 (15–30)min, respectively, for each group. The groups had mean maximum ropivacaine concentrations of 0.41 (SD, 0.14; range, 0.20–0.70), 0.89 (0.55; 0.35–2.36), 1.56 (0.50; 0.90–2.71), 0.64 (0.27; 0.29–1.21), and 1.01 (0.33; 0.58–1.76) μg ml^{-1}, respectively. No signs of central nervous system or cardiac toxicity were observed.

After TAP block, the C_{max} of ropivacaine is dose-dependent with rapid absorption compared with rectus sheath block.[3] With the addition of epinephrine, C_{max} and T_{max} were suppressed or delayed. TAP block is safer with the addition of vasoconstrictor to prevent the possibility of local anaesthetic toxicity.

Keywords: anaesthetic techniques, regional; transversus abdominis plane block; anaesthetics local, ropivacaine; analgesic techniques

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Development of a model to investigate high-frequency jet ventilation in a simulated broncho-pleural fistula

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High-frequency jet ventilation (HFJV) is a form of mechanical ventilation used to ventilate patients with a broncho-pleural fistula (BPF). The precise mechanisms of HFJV are not fully understood and the optimal frequency and pressure for ventilation of a patient with BPF are not established. The aim of this study was to investigate the effects of variations in ventilator frequency on delivered gas flow and pressure and air entrainment using a simulated BPF fistula.

We used an Acutronic Monsoon HFJV ventilator to ventilate a manikin including a Test lung (Intersurgical, Berkshire, UK) and recorded total measured flow, entrained flow, and airway pressures with differential and gauge pressure sensors (Freescale MPX10DP and MPX10GP) attached to a laptop-based four-channel oscilloscope (Picoscope 4464, Picotech UK, UK). Frequency of ventilation was varied between 60 and 350 bpm. Experiments were repeated using a test lung with a distal hole of 1 cm diameter to simulate a BPF.

Tidal volume and entrained fraction decreased as anticipated and in agreement with previous work[1 2] with little variation between repeated readings (Fig. 5).

Tidal volumes are lower with a BPF with the largest differences seen at lower ventilator frequencies. Further work is planned to investigate mechanisms.

Keywords: high frequency jet ventilation; fistula

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Insights from a systems analysis of a cerebral blood flow simulation

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A first-principles simulation model proceeds by assembly of the key equations that govern the constitutive processes, each with its own uncertain parameters. Large simulation models are complex non-linear systems for which optimization techniques can provide additional validation and insight, both by mapping the relationships between key parameters and the model's output and by testing the model's conformity to expectations. A previously described model of cerebrovascular behaviour was therefore examined via several optimization algorithms designed to drive the model to the extremes of its behaviour. For speed of implementation, standard Matlab algorithms were used, along with a simple Monte Carlo analysis. A first objective was to investigate the relationship between input and output parameters: driving the model to its extremes

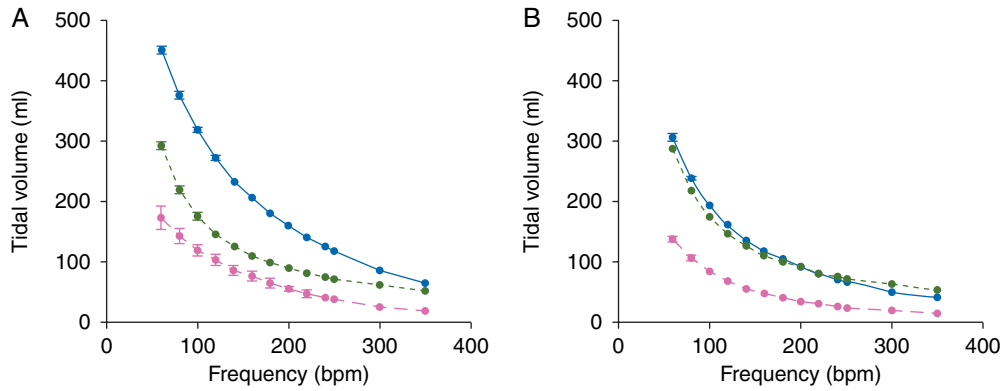

Fig 5 Effect of HFJV frequency on mean (SD) measured (continuous blue line), entrained (dashed pink line), and machine (dotted green line) tidal volumes without (A) and with (B) a simulated BPF.

identifies which input parameter or combination of input parameters has the greatest impact on each output value (for this, each output parameter must be tested in isolation). A second objective was to validate the range of the model domain itself.[1] Input parameters tested were: MAP (mean arterial pressure), arterial partial pressure of carbon dioxide (Pa_{CO_2}), arterial oxygen saturation (E'_{CO_2}), and intracranial compliance (IC). Output parameters were: intracranial pressure (ICP), middle cerebral artery flow velocity, index of static autoregulation (SAR), and carbon dioxide reactivity.

This model previously performed well in matching standard plots from the medical literature,[1 2] but optimization analysis reveals some limitations. ICP range was limited, and SAR achieved values above 1 (~1.3). Reduced blood flow for increased MAP is clearly non-physiological and indicates a region where the model fails to perform (Fig. 6).

These results do not necessarily demonstrate a flawed simulation design, but do indicate that further model adjustment is needed. The optimization results themselves may assist with this.

In summary, these results demonstrate how a physiological model that otherwise performs well may fail under optimization analysis and how the results of this analysis may be used to improve the model's design and tuning.

Keywords: cerbral blood flow, simulation

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Gene expression profiling in skeletal muscle tissue of malignant hyperthermia patients

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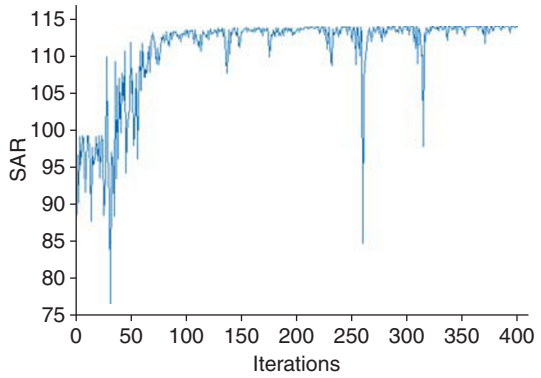

Fig 6 SAR analysis. MAP, 109 and 119; Pa_{CO_2}, 6; IC, 0.2; Sa_{O_2}, 0.8.

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Using mRNA microarray technology, it is now possible to determine simultaneously the level of expression of 30 000 genes thought to encompass the entire genome. We are applying this technology to examine gene expression in skeletal muscle tissue from patients attending for investigation of malignant hyperthermia (MH) susceptibility by diagnostic muscle biopsy and *in vitro* contracture tests (IVCTs). This study represents a preliminary analysis to determine if it is possible to use differences in gene expression to distinguish between skeletal muscle from MH-susceptible and normal patients. We also investigated whether the gene expression profile from samples of patients with genotype–phenotype discordance (lacking a familial ryanodine receptor gene, *RYR1*, mutation but with positive IVCT) clustered with that of susceptible or normal individuals.

Thirty muscle samples were chosen for this study: 12 from MH-susceptible patients with identified *RYR1* mutations, 12 from patients tested normal (MH negative), and six from genotype–phenotype discordant individuals. Total RNA was

extracted from muscle samples that had been frozen and stored in liquid nitrogen. The concentration and quality of obtained RNA was checked using a bioanalyzer (Agilent). Samples with an RNA integrity number <8.0 were excluded from further analysis. Affymetrix HG_U133Plus2 microarrays were used to examine gene expression in muscle samples. RNA labelling, hybridization, and image acquisition were done according to the standard Affymetrix protocol at the Microarray and DNA Analysis Section, Faculty of Biomedical and Life Sciences, University of Glasgow. Using commercially available bioinformatic pipeline software GeneSpring GX (Agilent), we compared the gene expression profiles of the different diagnostic groups.

We noticed that patient sex had a strong influence on muscle gene expression. Even so we were able to demonstrate clear clustering that completely segregated MH-susceptible from normal individuals using a panel of genes with >1.2-fold difference in gene expression between the groups. Interestingly, the discordant samples clustered with the MH-susceptible samples.

This preliminary analysis, if validated, suggests that it may be possible to identify a typical gene expression profile in skeletal muscle from patients with MH.

Keywords: malignant hyperthermia

Acknowledgement

This study was supported by a grant from The Wellcome Trust.

Anaesthetic experiences of patients tested negative for malignant hyperthermia susceptibility

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Patients who have negative *in vitro* contracture test results when attending for diagnosis of malignant hyperthermia (MH) susceptibility are advised that they can receive potent inhalation anaesthetics and also succinylcholine without risk of developing MH. We conducted a survey to ascertain whether such patients experienced any problems when they subsequently presented for surgery.

Six hundred patients who were diagnosed negative for MH susceptibility at the Leeds MH investigation unit between 2000 and 2005 were sent a questionnaire by post with a covering letter explaining the purpose of the survey. The first question asked whether the patient or any relative whose negative MH status was presumed from the same result had required surgery since the MH test. If so, further questions were asked including the nature of the procedure and whether it was performed under a general or local anaesthetic. They were also asked if they thought their history of screening for susceptibility to MH had resulted in them being treated any differently from normal, despite informing the anaesthetist and other staff of their negative diagnosis.

Two hundred and forty-three (41%) questionnaires were returned, of which nine had to be discarded. Of 132 patients who had not required surgery, six reported relatives being treated as MH positive for nine operations. The other 102 patients had a total of 166 procedures, 129 with general anaesthesia. Twenty-six patients had been treated as MH positive and 76 as MH negative. Three patients said that they had complications, but none was related to MH. Of these 102 patients, 13 reported that they experienced difficulties in terms of how they were treated by medical staff and six reported similar problems when relatives required anaesthesia.

Diagnostic thresholds for IVCTs for MH susceptibility were set with the intention of avoiding false-negative results,[1] albeit at the possible expense of a reduction in specificity: a validation study was consistent with 100% sensitivity.[2] Our survey suggests that a significant minority of patients were treated as susceptible to MH, despite being tested negative and 12% experienced some problem when they presented for routine surgery. It would be interesting to know the reasons underlying these findings.

Keywords: malignant hyperthermia

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Desensitization of human Urotensin II receptors does not involve protein kinase C

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Urotensin II (UII) is an 11 amino acid peptide that binds irreversibly to the UII receptor (UT).[1] UII produces inotropic and vasoconstrictor effects and, with UT, is up-regulated in diseases that may end in intensive care admission (e.g. heart failure).[1] Typical of G_q G-protein-coupled receptors, UT activation increases Ca^{2+}, and activates protein kinase C (PKC).[1] In this study using human embryonic kidney cells expressing recombinant human UT (HEK_{hUT}), we examined the effects of prestimulation of endogenous G_q-coupled M_3 muscarinic receptor with carbachol on UII increases in Ca^{2+} and the role of PKC in the response.

HEK_{hUT} cells were incubated with 5 μM of the Ca^{2+} indicator dye Fura2 and intracellular Ca^{2+} measurements made as described.[2] Cells were initially pre-stimulated with carbachol (1–100 μM) for 2 min then a full concentration response curve to UII (10 pM–1 μM) was constructed. In some experiments, the PKC inhibitors GF109203X (0.3 or 1 μM for 0–30 min preincubation) and staurosporine (0.3 μM for 30 min preincubation) or the PKC activator phorbol dibutyrate (PDB 1 μM for 15 min) were included. We also examined the ability of UII and carbachol to activate PKC by measuring

the translocation from membrane to cytosol of the PKC substrate eGFP-MARCKS protein via confocal microscopy.[3]

In control cells without carbachol challenge, UII increased Ca^{2+} with potency (pEC_{50}) and efficacy (E_{max}) of 8.22 (0.04) and 371 (18) nM [mean (SEM), $n=5$], respectively. Initial stimulation with carbachol produced concentration-dependent reduction (desensitization) in pEC_{50} and E_{max} which was significant from 3 to 10 μM [at 10 μM: UII pEC_{50} and E_{max} were 7.55 (0.09) and 179 (27) nM, $P<0.05$]. Both 10 μM carbachol and 1 μM UII enhanced [0.78 (0.15) and 2.19 (0.37) fold basal, respectively, from 12 to 14 cells] the translocation of eGFP-MARCKS protein indicative of PKC activation. However, preincubation with either PKC inhibitor at either concentration did not affect the ability of carbachol to desensitize the UII response. Moreover, activation of PKC with PDB *per se* did not desensitize the UII response.

These data describe a heterologous desensitization of the human UT expressed in HEK cells. Although PKC is activated by carbachol (and UII), PKC does not appear to be involved in this desensitization. Other potential targets include Ca^{2+}-calmodulin kinase and casein kinase.

Keywords: urotensin II; desensitization; intracellular calcium

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A pilot study in the use of sono-elastography to visualize regional anaesthesia

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Despite the undoubted benefits of regional anaesthesia, there remain possible serious clinical side-effects which suggest the need for optimum methods of application of the anaesthetic. In ultrasound-guided regional anaesthesia, in particular, the need to visualize the tip of the needle and anaesthetic flood has been highlighted.[1]

A high-quality medical ultrasound imaging system is used (Zonare Inc., CA, USA) with an early implementation of sono-elastography to visualize the flow of anaesthetic agent. The anechogenic nature of the injection liquid means that it cannot be visualized by elastography, unlike surrounding tissue. Sono-elastography is thus able to enhance contrast between it and tissue.

The outcome of this work has been evaluated in Thiel cadavers which have proved particularly suitable for ultrasound imaging and have been shown to be a valid model.

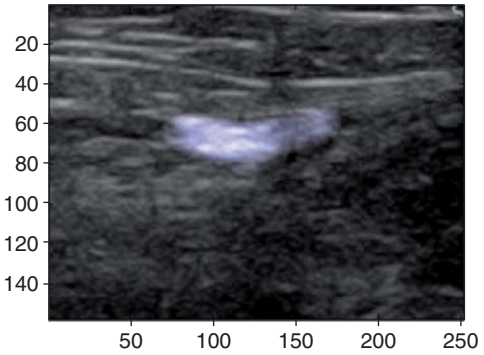

Fig 7 Enhanced elastography overlaid with B-Mode.

The study was performed with interscalene, femoral, and median nerve-blocks on Thiel cadavers, each representing a typical clinical anaesthesia approach.

Results have shown that it is possible to improve the hydro-localization method by processing the echo-elastography data using MATLAB®. This involves the identification of a region of interest and adaptive filtering of the data map to increase the contrast of the liquid volume. An adaptive filtering algorithm for enhanced elastography is realized through the acquisition of a dynamic elastography noise profile which is subtracted from the regular elastography frame. Furthermore, an additional two-dimensional median filter is applied to reduce unwanted elastography image artifacts. The map of this restricted area can then be superimposed on the B-scan image highlighting and corresponding to the area of fluid (anaesthetic) spread (Fig. 7).

The image processing is carried out in real time and displayed on a computer screen positioned adjacent to the ultrasound imaging system. This enables very sensitive verification of the needle tip position. The necessary confirmation volume can be reduced to 0.25 ml. This sensitivity also means that it is possible to see if the local anaesthetic spreads in the wrong direction and reposition the needle accordingly.

Keywords: ultrasound; elastography

Reference

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Ability of patients to retain and recall new information in the post-anaesthetic recovery period: a prospective clinical study in day surgery

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The amnesic effect of hypnotic drugs is well known and has been extensively researched. In the immediate post-

Table 4 Recall and retention data in day-surgery patients. *$P<0.0001$ for comparisons between the groups; $^{\$}P=0.035$; #after leaving theatre

	Early	Late	Control
Objects recalled/5* [mean (SD)]	1.75 (1.45)	3.38 (1.29)	4.4 (0.81)
Objects recalled/5 [median (IQR)]	2 (0–3)	4 (3–4)	5 (4–5)
Unable to remember being given task	23/100	1/100	0/100
Duration of anaesthesia$^{\$}$ (min)	30.37 (1.99)	37.21 (2.33)	N/A
Time# until information given (min)	17.6 (1.61)	58.1 (1.65)	N/A
Opioid# given before information	1/100	16/100	N/A
Opioid# given before recall test	7/100	20/100	N/A

anaesthetic recovery period, declining levels of residual drugs will be present with attendant effects. Within the day surgery setting patients are often given new information about their treatment in the postoperative period which may include fundamental information such as what operation was actually performed, results of investigative procedures, and instructions regarding analgesia. It is common practice in our day surgery unit for medical staff to see patients in the postoperative period to explain their findings and not necessarily routinely follow patients up in out-patients. Our study aimed to simulate the provision of new verbal information to patients within this postoperative period and measure ability to retain and recall such information 30 min later.

We randomly allocated 200 postoperative patients to receive information: in the post-anaesthetic care unit when able to sustain a conversation ('early' 100); or 30 min after admission to the discharge ward ('late' 100). Patient demographics and anaesthetic details were recorded. A control group of 100 participants performed the same task without general anaesthesia or sedative medication. Participants were asked to remember five household objects and their recall tested 30 min later (household objects were chosen so as to avoid any potential confusion from 'false' medically related information). We analysed continuous variables with ANOVA or unpaired *t*-test, categorical variables with Fisher's exact test. Numbers in Table 4 are means (standard deviation) unless otherwise stated.

The late group was given the task 40 min after the early group: 99% of the late group remembered being given the task compared with 77% of the early group. The late group recalled more objects than the early group despite having longer anaesthetics and more opioid. Participants who had not received anaesthesia or sedation recalled more objects than the postoperative groups.

We conclude that day surgery patients should be told new information close to discharge home to maximize its retention, supported by written information.

Keywords: anaesthesia recovery period; memory; ambulatory surgical procedures

Kinetics of nitrous oxide onset and offset

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With low concentrations of inhaled anaesthetics, tests of psychomotor function show graded anaesthetic effects, and can thus indicate the 'effect site' action and concentration of the agent.[1] If the test gives a prompt result, we can follow the onset and offset of the anaesthetic, and estimate the kinetics of central nervous system uptake. Although the digit symbol substitution test (DSST) is sensitive to nitrous oxide effects, the standard version takes about 2 min to complete. We used a shortened version of the test to study volunteers

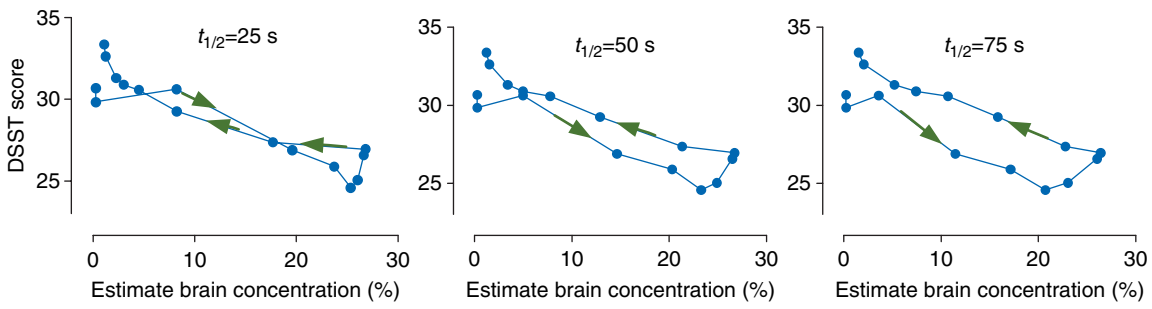

Fig 8 Onset and offset of nitrous oxide effect: mean values of DSST for 19 subjects, related to modelled brain concentrations using three different half-times. Arrow heads indicate the direction of change.

given 0, 5% or 30% nitrous oxide, in a double-blind study. They carried out a series of short DSSTs, before, during and after a step change into and out of the test gas, to assess mental function at ~60 s intervals during the onset and offset of the effects of nitrous oxide. We measured end-tidal nitrous oxide concentration and then modelled effect-site concentrations using half-times of 25, 50, and 75 s.

We present data from 19 subjects (13 male) age 21 (6) yr, weight 72 (12) kg, height 177 (12) cm (mean, SD). As expected, there was no discernible effect of 5% nitrous oxide on the DSST, and 30% nitrous oxide had clear effect. By using a $T_{1/2}$ k_{e0} of 25 s, we found minimal difference in the dose–response relationship for onset and offset. With longer half-times, the effect 'led' the modelled brain concentration, suggesting that these modelled concentrations changed too slowly (Fig. 8). Previous estimates of brain effect-site concentration during onset have used the processed EEG[2] and given values >2.3 min. Our estimate of the kinetics is very different. This could be because the measure we used is an exclusively cerebral effect, we obtained an instant measure of anaesthetic effect, and there could be limited neural 'inertia' in the measure. Our values are consistent with a brain blood flow at this site of more than 150 ml s^{-1} 100 g^{-1} tissue.

Keywords: pharmacokinetics; anesthetics, inhalation; psychometrics

Acknowledgement

Supported by bench fees from University of Edinburgh Department of Neuroscience.

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Functional analysis of the p.Gly3990Val *RYR1* variant using a human cDNA clone in HEK293 cells

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Malignant hyperthermia (MH) is a pharmacogenetic disorder triggered by exposure to potent inhalation anaesthetics and depolarizing neuromuscular blocking agents. In recent years, efforts have been made to expand the genetic diagnostic panel for MH to negate the necessity of invasive muscle biopsies for diagnosis of MH susceptibility. The main gene responsible for predisposition to MH is *RYR1* which codes for the Ryanodine Receptor, a skeletal muscle calcium release channel. The European Malignant Hyperthermia Group put forward a set of guidelines that must be fulfilled for novel *RYR1* variants to be included on the genetic diagnostic panel for MH. One of which is functional characterization in an *in vitro* expression system of standardized genetic background. Here, we report the first characterization of a p.Gly3990Val *RYR1* variant using a human cDNA clone. The p.Gly3990Val variant represents almost 10% of all UK cases of MH that possess an as yet, functionally uncharacterized *RYR1* mutation.

Full-length, wild-type human *RYR1* was subcloned into a shuttle vector followed by site-directed mutagenesis to create the mutant construct, before full-length re-assembly in a mammalian expression vector. Both wild-type and p.Gly3990Val *RYR1* were transfected into HEK293 cells. Forty-eight hours post transfection, cells were loaded with a fluorescent Ca^{2+} indicator. Cells were then exposed to incremental concentrations of caffeine using an eight-channel rapid perfusion system. Caffeine evokes intracellular Ca^{2+} release from the sarcoplasmic reticulum stores in the HEK293 cells that can be visualized using confocal microscopy as a temporary increase in fluorescence (Fig. 9).

p.Gly3990Val *RYR1* mutants were seen to respond with intracellular Ca^{2+} release at 1 mM caffeine whereas wild-type *RYR1* did not. The reactions to all subsequent concentrations of caffeine were exaggerated in the p.Gly3990Val transfected cells, reacting with a quicker and prolonged Ca^{2+} release. A statistically significant increase in Ca^{2+} release was observed in p.Gly3990Val mutants at each caffeine concentration that elicited a response (e.g. At 10 mM mean $\pm$ 95% CI for wild type=378.3 $\pm$ 212.6 and p.Gly3990Val=970.9 $\pm$ 403.8, P=0.0046). Based on this, it looks likely that the p.Gly3990Val *RYR1* mutation can be added to the genetic diagnostic panel for MH.

Keywords: malignant hyperthermia; ryanodine receptor 1; pharmacogenetics; skeletal muscle

Acknowledgement

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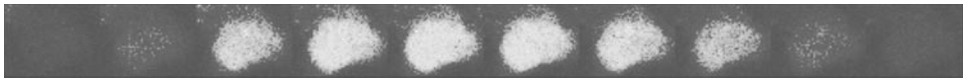

Fig 9 Time sequence showing a HEK293 cell transfected with wtRYR1 releasing calcium upon stimulation with 5 mM caffeine visualized by confocal microscopy.

Table 5 Median (range) plasma AEA, OEA, and PEA concentrations *$P<0.05$ (Friedman ANOVA with Dunn's post-test) compared with day 1

	Day 1 sepsis ($n=9$)	Day 2 sepsis ($n=9$)	Recovery ($n=9$)	Volunteer ($n=5$)
AEA (nM)	0.82 (0.35–1.99)	0.63 (0.33–1.49)*	0.64 (0.26–1.37)*	0.55 (0.47–0.72)
OEA (nM)	6.41 (3.20–10.42)	5.30 (2.51–9.84)	4.20 (3.27–8.27)	3.69 (3.17–4.89)
PEA (nM)	16.35 (2.99–46.35)	12.73 (0.49–46.05)	13.96 (2.23–30.26)	5.12 (3.54–10.46)

Plasma endocannabinoid concentrations in sepsis

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The endocannabinoids (EC) anandamide (AEA) and the 'entourage' lipids oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) are involved in many physiological and pathological conditions.[1] Our group has previously shown that simulated *in vitro* sepsis with lipopolysaccharide causes the release of EC from neutrophils and alteration in cannabinoid receptor expression.[2] This study aims to investigate plasma endocannabinoid concentrations in patients with sepsis.

With REC approval and informed consent, we have recruited patients in ICU with a diagnosis of sepsis. Blood was collected into 2.7 ml EDTA tubes (Sarstedt Monovette) from each patient on days 1, 2, and on clinical recovery from sepsis. Samples were transferred in ice, plasma retrieved by centrifuge at 4°C, endocannabinoids extracted,[3] and quantified by ultra high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS).[4]

Preliminary data from the first nine patients with recovery samples available and laboratory reference values (volunteers) are shown in Table 5. The patients ages ranged from 32 to 79 yr with an F:M of 4:5, their 24 h APACHE II scores ranged from 15 to 30.

These preliminary data suggest plasma AEA concentrations are elevated during sepsis. Further data are required to confirm these findings.

Keywords: endocannabinoids; chromatography, liquid; mass spectrometry

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Effects of mitochondria-targeted antioxidants on biochemical markers of organ function and interleukin-6 in an *in vivo* model of sepsis

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The mortality rate of patients with sepsis-induced organ failure remains high. The precise pathogenesis of such organ failure is unknown, but changes occur in mitochondria which result in altered oxidative phosphorylation and ATP production. Mitochondria are a major source of reactive oxygen species in a resting cell and oxidative stress and mitochondrial damage occur in patients with sepsis. Antioxidants which specifically protect mitochondria against oxidative stress have been developed. We assessed the effect of targeted forms of co-enzyme Q10 (MitoQ) and vitamin E (MitoVitE) on plasma creatinine concentration (renal function), alanine amino transferase (ALT, hepatic function) activity and interleukin-6 (IL-6) level after a septic insult in a rat model.

Male rats (~400 g) were anaesthetized with isoflurane and a tracheostomy was performed to permit ventilation. Rats then received i.v. lipopolysaccharide (LPS, 0.1 mg kg^{-1}) plus peptidoglycan (PepG, 1 mg kg^{-1}). Rats then randomly received either 20 mg kg^{-1} MitoQ or MitoVitE in saline as an i.v. infusion at 1.5 ml h^{-1}, or the same volume of saline, and were monitored and maintained at a constant body temperature. After 6 h, a laparotomy was performed and blood was obtained by cardiac puncture.

Creatinine, ALT and IL-6 were higher in animals which received LPS/PepG compared with saline controls ($P<0.05$, Fig. 10). In rats treated with LPS/PepG plus either MitoQ or MitoVitE, creatinine, ALT, and IL-6 were lower than without MitoQ/MitoVitE (Fig. 10).

We have confirmed that MitoQ or MitoVitE treatment results in lower biochemical markers of organ dysfunction and lower IL-6 levels after an inflammatory insult in this rat model of sepsis-induced organ dysfunction. Studies are ongoing to investigate the effect of other doses of these antioxidants.

Keywords: antioxidants; sepsis; ubiquinone; vitamin E; rats

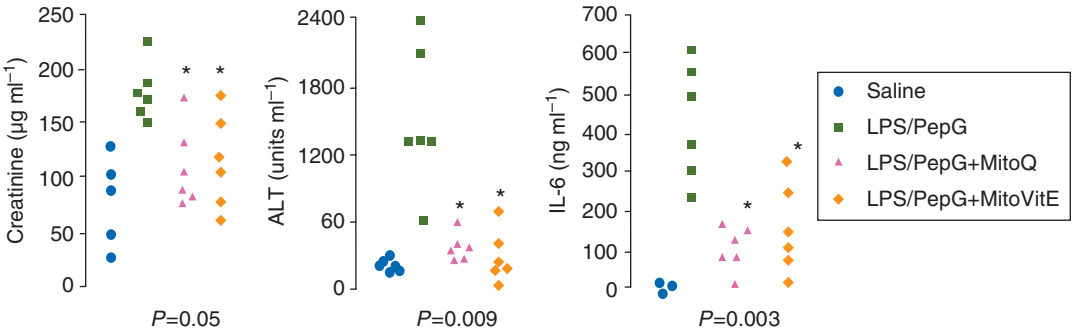

Fig 10 Creatinine, ALT, and IL-6 in rats treated as follows: Saline, LPS/PepG, LPS/PepG+MitoQ, LPS/PepG+MitoVitE. *P*-value is Kruskal–Wallis. *Lower than LPS/PepG only ($P<0.05$).

Acknowledgement

This work was funded by the Medical Research Council.

Modulation of toll-like receptor pathways and cytokine levels by mitochondria-targeted vitamin E in an endothelial model of sepsis

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Sepsis is characterized by increased oxidative stress and excessive production of inflammatory cytokines. MitoVitE (vitamin E attached to a lipophilic cation) allows selective accumulation and antioxidant protection within mitochondria. We hypothesized that MitoVitE modulates cytokine expression and underlying gene expression.

Human endothelial cells were treated with 0.2 μg ml^{-1} lipopolysaccharide (LPS, from *Escherichia coli* 0111:B4) plus 20 μg ml^{-1} peptidoglycan (PepG), in the presence and absence of 5 μM MitoVitE, for 24 h. Interleukin (IL)-6 and IL-8 were measured using enzyme immunoassay and quantitative polymerase chain reaction (qPCR) analysis was carried out on 50 target genes from the human toll-like receptor (TLR)-2 and -4 signalling pathways.

qPCR data were analysed using SABiosciences PCR array data analysis software. LPS/PepG+MitoVitE was calibrated against baseline LPS/PepG alone, with a cut-off of ±2-fold change. Hypoxanthine-guanine phosphoribosyltransferase (HPRT)-1 was used as a reference gene. Six genes were up-regulated, and 27 genes were down-regulated. The central inflammatory genes up-regulated were IRAK-4 (interleukin-1 receptor-associated kinase 4), AP-1 (activator protein-1), NFκB1, and NFκBIA (inhibitors of nuclear factor κB binding); and down-regulated were TRAF-6 (tumour necrosis factor receptor-activated factor 6 adaptor molecule), IFNB1 (interferon-β receptor) and IL-8. No change was found in IL-6 mRNA expression. These genes are known to be involved in regulating IL-6 and IL-8 production by modulating redox sensitive transcription factor activation. These mRNA changes may begin to explain the mechanism of the changes in IL-6 and IL-8, measured using enzyme immunoassay, which were significantly lower in cells treated with LPS/PepG+MitoVitE than with LPS/PepG alone ($P<0.05$, Fig. 11).

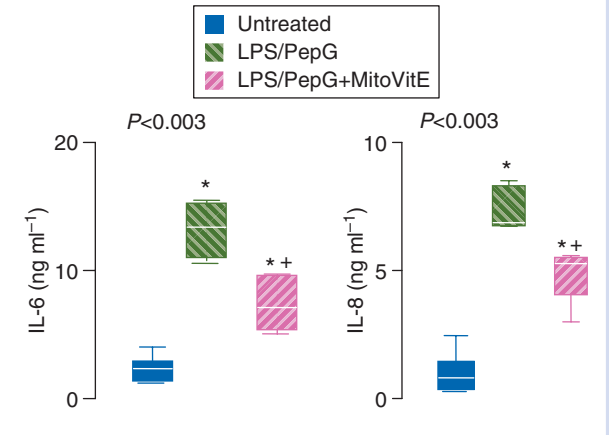

Fig 11 Effect of 5 μM MitoVitE on IL-6 and IL-8 cytokine levels after culture of endothelial cells treated with LPS plus PepG. (Median, IQR and range, n=6). P-values=Kruskal–Wallis. *Higher *vs* untreated ($P<0.003$); $^{+}$lower *vs* LPS/PepG ($P<0.02$) Mann–Whitney.

We have identified targets within TLR2 and TLR4 pathways which are modulated by MitoVitE during exposure to LPS/PepG which begin to explain the mechanisms of altered cytokine expression mediated by MitoVitE.

Keywords: antioxidants; vitamin E; endothelial cells; RNA, messenger

Acknowledgement

Funded by the *British Journal of Anaesthesia* and the Royal College of Anaesthetists.

Plasma nociceptin/orphanin FQ concentrations in patients undergoing cardiac surgery

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Nociceptin/orphanin FQ (N/OFQ) is an endogenous opioid peptide which in addition to effects on pain pathways has cardiovascular and inflammatory effects.[1] Carvalho and colleagues[2] demonstrated an increased mortality in septic rats exposed to N/OFQ and our group has previously reported increased plasma N/OFQ concentrations in patients with sepsis who subsequently died compared with survivors.[3] In this study, we used cardiopulmonary bypass (CPB) as a model of the systemic inflammatory response syndrome[4] to determine whether N/OFQ is acutely up-regulated.

With REC approval and informed consent, 40 patients undergoing cardiac surgery under standard general anaesthesia and CPB were recruited. Blood samples were obtained at induction of anaesthesia, 3 h post-CPB, and 18–24 h post-CPB. Plasma N/OFQ peptide concentrations were determined by radioimmunoassay after solid phase extraction.[3]

There was a significant increase (31% in median value) in plasma immunoreactive N/OFQ concentrations 3 h post-CPB, which returned to baseline levels 18–24 h post-CPB (Table 6).

In this CPB model of inflammation, there was an initial increase in plasma N/OFQ concentrations, likely to be from immune cells. The functional consequences of this increase and its potential block are worthy of further investigation.

Keywords: nociceptin-orphanin FQ (N-OFQ peptide); systemic inflammatory response syndrome; cardiopulmonary bypass

Table 6 Clinical and plasma N/OFQ data expressed as median (IQR) or number; $n=40$. AoXC, aortic cross-clamp; CABG, coronary artery bypass grafting. Data were analysed using Kruskal–Wallis ANOVA with Dunn's multiple comparison test. *$P<0.05$ compared with induction sample. 5, 4, and 3 samples were below the limit of detection of the assay in the induction, 3 h and 18–24 h post-CPB samples, respectively

Sex	28:12 (M:F)
Age (yr)	70.5 (61–76)
CABG/Valve replacement/ CABG+Valve/Aortic root	17/15/7/1
CPB time (min)	89 (76–123)
AoXC time (min)	54 (45–74)
Temperature during CPB (°C)	32 (29–32)
Plasma N/OFQ at induction of anaesthesia (pg ml^{-1})	9.3 (7.4–12.6)
Plasma N/OFQ 3 h post-CPB (pg ml^{-1})	12.2 (9.2–14.4)*
Plasma N/OFQ 18–24 h post-CPB (pg ml^{-1})	10.3 (7.5–13.1)

Acknowledgement

This work was supported by the AAGBI and *BJA*/RCoA.

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Individual bibliometrics in UK anaesthesia

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Bibliometric indices of the research contribution of researchers, research institutions, and journals are becoming widespread and may be used to inform funding and promotion decisions. Previous reports have suggested that the quantity of anaesthetic academic output from the UK is declining.[1] At present, there are no published data on the distribution of commonly used bibliometrics in the UK anaesthetic research community.

A contemporary list of active academic anaesthetists was compiled using the list of departments detailed in the Pandit report and searching departmental websites. Individual publication data were retrieved from ISI Web of Knowledge® (May 2010) and the following indices calculated: total number of publications (N); total number of citations; average citations per article; H-index (H is the number of publications with $\geq H$ citations); G-index (G is the number of publications where the sum of citations is $\geq G$);[2] and modified impact index[2] (MII$=H/(10^{\alpha}\times N^{\beta})$). A subset of data (2004–8) were also assessed for comparison with contemporary European data at individual and departmental levels.

Eighty-two academic anaesthetists were identified from 19 academic units across the UK. There was reasonable correlation between log H and log N for the complete data ($r^2=0.84$) and weaker correlations for the subset [$r^2=0.68$ (individual), 0.66 (departmental)] (Table 7).

There is no single, universally accepted metric of research quality. The β coefficient of the MII is in the range for European departments of anaesthesiology (0.55) and critical care (0.594), and for the UK medical sciences as a whole (0.433), suggesting that even if the number of papers published is declining, the impact of these papers is on a par with other countries and specialities. These data will allow individuals and departments to critique their research performance in a more objective fashion than before.

Keywords: bibliometrics; anesthesia; critical care

Table 7 Bibliometrics in UK anaesthesia

Index	Median [inter-quartile range]		
	All papers (individual)	2004–8 (individual)	2004–8 (departmental)
Total number of publications	65.5 (27–120)	10 (6–16)	44 (26–66)
Total number of citations	567 (183–1418)	—	280 (197–548)
Citations per article	10.5 (5.6–16.4)	—	6.8 (5.0–12.4)
H-index	13 (8–20.75)	5 (3–7)	9 (8–12)
G-index	22 (12–34)	—	—
Modified impact index	1.02 (0.82–1.18)	1.03 (0.83–1.3)	0.99 (0.83–1.21)
Modified impact index coefficients	α: −0.013, β: 0.624	α: −0.034, β: 0.677	α: 0.198, β: 0.495

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Incidence of preoperative hypoxaemia in patients undergoing surgical repair of a proximal femoral fracture

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Fractures of the femoral neck are associated with a significant mortality and morbidity in elderly patients. Hypoxia is a common postoperative complication, but the incidence of hypoxia before surgery has only been investigated in a single Australian study which showed that 34% of patients had Sp_{O_2} <95% while breathing room air.[1]

The study was conducted as part of an ethically approved randomized controlled trial, investigating goal-directed fluid therapy in elderly patients undergoing surgical repair of a proximal femoral fracture. As part of that study, patients had an arterial blood gas measured while in the anaesthetic room awaiting subarachnoid anaesthesia.

The data from 29 patients were analysed. The results are shown in Table 8. Ten patients (34%) had a Pa_{O_2} <8 kPa, of which only three were receiving supplemental oxygen. All 10 patients also had Sa_{O_2} of <95%. Only one patient had a Pa_{CO_2} that was greater than normal.

This study shows a high rate of hypoxia in patients presenting for hip fracture surgery which was generally unrecognized, untreated, or both. This is in contrast to the biochemical and cardiovascular parameters which were largely within normal limits. Oxygen therapy remains a key part of preoperative optimization in this high-risk surgical population.

Keywords: hypoxia; hip fractures

Acknowledgement

This study was funded by a grant from the National Institute of Health Research (NIHR).

Table 8 Patient characteristics and results of arterial blood gas analysis. Values shown are mean (range), mean (SD) or number (%)

Age (yr)	84 (64–94)
Male	8 (28)
Receiving supplemental oxygen	9 (31)
Sa_{O_2}	95 (4)
Ventilatory frequency (bpm)	18 (4)
Pa_{O_2} (kPa)	11.3 (7.2)
$Pa_{O_2}/F_{I_{O_2}}$ ratio	41 (12)
Pa_{CO_2} (kPa)	5.2 (1.3)
Bicarbonate (mmol litre^{-1})	25 (2)
Sodium (mmol litre^{-1})	136 (5)
Haemoglobin (g dl^{-1})	11.5 (1.1)
Systolic arterial pressure (mm Hg)	158 (30)

Reference

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Cardiovascular changes after subarachnoid anaesthesia for proximal femoral fracture repair

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Patients with proximal femoral fractures are often elderly with numerous co-morbidities. The cardiovascular effects of subarachnoid block (SAB) in this high-risk population have never been elucidated using arterial pulse contour analysis.

Ethical committee approval was gained. All participants gave informed consent, or assent was provided by their caring consultant as appropriate. Patients were eligible if aged ≥60 yr and listed for repair of proximal femoral fracture under SAB. A LiDCO^{TM} plus (LiDCO Ltd, Cambridge, UK) monitor was calibrated and cardiovascular data were recorded continuously before and for 10 min after SAB.

Results are given as mean (SD). Twenty-one patients were recruited [age 84 yr (6.2)]. Four subjects were male. Twelve

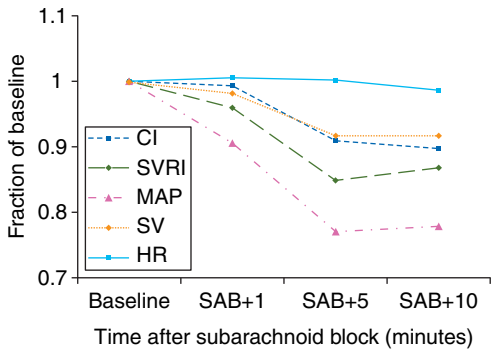

Fig 12 Cardiac index (CI), systemic vascular resistance (SVRI), mean arterial pressure (MAP), stroke volume (SV), and heart rate (HR) after SAB.

were established on vasoactive medication before operation. The dose of hyperbaric bupivacaine administered was 12.5 mg (1.8). Five patients received vasopressors. Cardiac index decreased by 9% (17) at 5 min post-SAB. Systemic vascular resistance decreased by 15% (21), whereas heart rate remained constant (Fig. 12).

The decrease demonstrated in CI has not been shown in elderly patients having SAB for elective orthopaedic procedures.[1] This may be due to inadequate resuscitation of acute haemorrhage or prolonged dehydration in emergency patients, or a reflection of the reduced physiological reserve in this patient population.

Keywords: measurement techniques, lithium dilution; anaesthetic techniques, subarachnoid; hip fractures

Acknowledgement

This study was funded by a grant from the National Institute of Health Research (NIHR).

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Thiel embalmed cadavers for ultrasound-based regional anaesthesia training and research

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Shorter working hours and shift systems are limiting trainee clinical experience. Essential technical skills are being developed in environments other than the operating theatre. The ideal model for regional anaesthesia training should simulate the passive and dynamic components of nerve block such as nerve anatomy, needle movement, fascial penetration, perineural fluid injection, and inadvertent intraneural and intravascular injection. A new development in regional anaesthesia simulation is the Thiel embalmed cadaver,[1] preserved using a novel technique which minimizes formaldehyde use, enables full flexibility of the limbs, and is compatible with ultrasound imaging, unlike cadavers preserved conventionally. As the University of Dundee is the first to introduce Thiel cadavers to the UK, an opportunity existed to evaluate the visibility of anatomical structures during cadaver regional anaesthesia.

The interscalene axillary, femoral, and popliteal nerves were scanned at 2, 3, 5, 8, 11, and 14 weeks after embalming. Scanning of all nerves was performed with a 10-5 MHz linear probe using a self-optimization facility. Once the best image site was identified, 1 ml of Thiel moistening solution was injected around each nerve, and a 30 s video recording made. Visibility of nerves, muscle, fascia, blood vessels, and needle passage was ranked using a seven-point ordinal scale. Rater agreement was assessed using the intraclass correlation. In addition, nerve visibility was assessed with the Vienna score, an ordinal scale from 1 to 4, the spread of solution measured as the log area under the curve of spread using ultrasound elastography (log AUC), and Zone Speed Index (ZSI). Distribution of data used the Shapiro–Wilk test, parametric data were analysed by the *t*-test (SD), non-parametric with Mann–Whitney, and paired comparisons with the Wilcoxon signed-rank test. Correlation of data used Pearson's and Spearman's test as appropriate.

Results are presented for the interscalene block. All blocks were performed on the left side of the body. Full rotation of the neck was possible. Mean (SD) distance from the skin was 1.2 (0.3) cm. With regard to ultrasound image quality, mean (SD) visibility score for scalenus anterior was 5 (0.9), scalenus medius 4.8 (1.2), sternocleidomastoid 5.3 (0.8), and nerve roots 5.2 (1.2). Median (IQR) Vienna score for nerve roots was 2.5 (2–3). With regard to nerve block, mean (SD) needle visibility was 2.8 (1.2), needle tip visibility 1.3 (0.5). There was a difference in median (IQR) visibility of spread for B-mode ultrasound 4.5 (3–5) and elastography 7 (6.25–7), $P=0.04$.

This pilot study of Thiel cadavers has shown good image quality of nerves, muscle, and vasculature over an initial 12 week period. Subjective visibility scores correlated well with elastography and Zone Speed Index. On the basis of these findings, the Thiel cadaver should be considered.

Keywords: ultrasound; cadaver

Reference

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Anaesthetists' workload in a simulated environment: impact of introducing new technology designed to reduce drug errors

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Management of anaesthetists' workload (physical effort, mental effort, and psychological stress) during anaesthesia is important for patient safety. The Borg workload scale[1] has been used to quantify anaesthetist's workload. This scale can be used by anaesthetists for self-reporting, or by observers for evaluating workload. As part of an international study, we are currently investigating the role of the SAFE-Rsleep® system (a system, which utilizes bar-code technology, automated visual and auditory verification of syringes, and automatic record keeping)[2] in preventing drug errors[3] in a simulated environment.

We aimed to see whether (i) the introduction of SAFE-Rsleep® altered the anaesthetist's workload, and (ii) whether self reported Borg workload scores by the anaesthetist differed from the observer's score.

We measured the workload scores of 10 anaesthetists as they completed 2 high-fidelity scenarios, one with and one without the SAFERsleep® system, lasting approximately 45 min each. During each scenario, anaesthetists reported the Borg workload scale score 4–6 times as prompted randomly using computer software; at the same time a trained observer also evaluated the anaesthetist's workload. The Borg scores range between 6 and 20. The anaesthetists were instructed that a score of 12 was equivalent to the workload of a routine uncomplicated tracheal intubation. The observer used a computer program which derives the score by integrating multiple workload constructs. A copy of the scale was attached to the anaesthetic machine throughout the scenarios as a visible prompt for the anaesthetist.

On comparison, we found that the highest, mean or lowest Borg workload scores, as reported by anaesthetists or evaluated by the observer, when using the SAFERsleep® system were no different from the corresponding scores when the conventional methods were used. There was, however, a tendency for the observer to underestimate workload at stressful times compared with the self-reported scores of the anaesthetist (Table 9).

Keywords: workload; observation; safety management

Acknowledgements

AAGBI for a project grant, David Merry for software development, Kylie-Ellen Edwards for assistance.

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A systematic study in Thiel cadavers of the visibility of echogenic needles for regional anaesthesia

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Regional anaesthesia provides many benefits, but there remain serious transient or long-lasting clinical side-effects. Ultrasound-guided regional anaesthesia has improved block efficacy, but has not been universally accepted because anaesthetists have difficulty visualizing needles.[1]

Two echogenic needles from Braun (denoted BE) and Pajunk (PE), aiming to provide high reflection at steep and flat puncture angles, have been introduced. The primary aim of our study was to compare the visibility of these needles with a standard Braun needle (denoted BS) using the Thiel cadaver as our anatomical model. These retain full flexibility of the limbs, and have demonstrated high-quality ultrasound images, ready tracing of peripheral nerves and spread of solution, and recognizable intraneural injection. Neck rotation for interscalene block, external shoulder rotation for axillary block, and hip and knee flexion for sciatic block are all possible.

We first conducted a pilot study of 48 i.m. needle injections inserted in-plane and out of plane at four angles (30°, 45°, 60°, and 75°), using an engineered block. The visibility

Table 9 Borg workload scores. Data are presented as median (IQR). *P=0.005

Borg workload scores	Using SAFERsleep® system		Using conventional methods	
	Anaesthetist self-reported	Observers evaluation	Anaesthetist self-reported	Observers evaluation
Highest	16 (15,17)	15* (14,16)	15 (14,16)	14.5 (13,15)
Mean	13 (12,15)	13 (12,14)	12 (12,14)	12 (12,13)
Lowest	12 (11,13)	12 (11,12)	12 (10,12)	12 (11,12)

of the needle was assessed by two independent observers with a five-point Likert scale.

The pilot study showed a non-parametric distribution of data using the Shapiro–Wilk test. Median visibility scores were higher for the PE needle inserted at 75° out of plane and 30° in plane. With these data, we calculated an effect size of 0.47 for 'needle' and an effect size of 0.43 for 'angle', $\alpha=0.5$, $\beta=0.2$, and using a randomized block ANOVA power analysis (PASS, UT, USA), we required a total of six blocks, that is, 72 injections in plane and out of plane.

For the formal study, a total of 144 observations were made. Intraclass correlation between observers was 0.91. In plane, the median visibility scores were 1, 1, and 3 for the BS, BE, and PE needles, respectively, Friedman's *Q* 6.50, $P=0.04$. *Post hoc* tests showed a difference between BS and PE needles. Out of plane, the median visibility scores were 1, 1, and 3 for the BS, BE, and PE needles, respectively, Friedman's Q 7.50, $P=0.02$. *Post hoc* tests showed differences between the PE and both Braun needles.

In conclusion the PE needle was found to be more visible than the BS needle in-plane, and more visible than both the BS and BE needles out of plane.

Keywords: ultrasound; needle; cadaver

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Use of the continual reassessment method to estimate the ED_{95} dose of 0.5% bupivacaine for ultrasound-guided supraclavicular brachial plexus block

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Local anaesthetic toxicity from brachial plexus blocks is a major concern for anaesthetists. There have been several recently published case reports of toxicity from bupivacaine even in recommended 'safe' clinical doses.[1 2] Although the ED_{50} of 0.5% bupivacaine for supraclavicular brachial plexus block has been reported (using up-and-down methodology),[3] no credible trials have specifically sought to determine the more clinically useful ED_{95} dose of bupivacaine or indeed any local anaesthetic for these blocks. We propose to use the Continual Reassessment Methodology (CRM), which is a sequential Bayesian method based on a one-parameter model (originally designed for Phase I and II oncology drug trials)[4] to determine the ED_{95} dose of 0.5% bupivacaine for supraclavicular brachial plexus block.

This double-blind, prospective dose finding trial was scheduled for 40 ASA I–III patients presenting for elective upper limb surgery and supraclavicular block. On the basis of our previous experience, including previous dose-finding studies,[3] we anticipated that the ED_{95} of 0.5% bupivacaine for this block to be between 15 and 27 ml. We arbitrarily divided this range into six dose levels (12, 15, 18, 21, 24, and 27 ml) to be available within the study and assigned *a priori* probabilities of successful block of 0.5, 0.75, 0.90, 0.95, 0.98, and 0.99, respectively, to the six dose levels. Using the CRM program, this created an initial dose–response curve that subsequently shifted direction dependent on the success or failure of the block on each cohort of patients (two patients per cohort). Our starting dose was 21 ml. The allocated dose to the next cohort of patients was re-estimated by the study statistician using the CRM program to be the dose level with the updated (posterior) response probability closest to 0.95.

Table 10 Results of block outcome in the first phase of recruitment

Cohort	Volume 0.5% bupivacaine (ml)	Result of supraclavicular block
1	21	Success, success
2	18	Success, fail
3	27	Fail, success
4	27	Success, fail

Analysis after inclusion of the first eight patients (Table 10) gave posterior probability values of 0.19, 0.35, 0.51, 0.60, 0.70, and 0.76 for our six dose levels, respectively, and indicated that the ED_{95} value was likely to be greater than our maximum dose level. This has required us to define new dose levels before further recruitment.

Although the ED_{95} dose of bupivacaine is yet to be determined, this first phase of our trial suggests it to be >27 ml.

Keywords: brachial plexus; bupivacaine; dose–response relationship, drug; ultrasonography

Acknowledgements

This study was funded by a grant from the Association of Anaesthetists of Great Britain and Ireland through the National Institute for Academic Anaesthesia.

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Accuracy of nomogram-based calibration of cardiac output monitoring in patients aged 80 or over

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Minimally invasive cardiac output (CO) measurement devices are increasingly used to guide goal-directed fluid therapy in

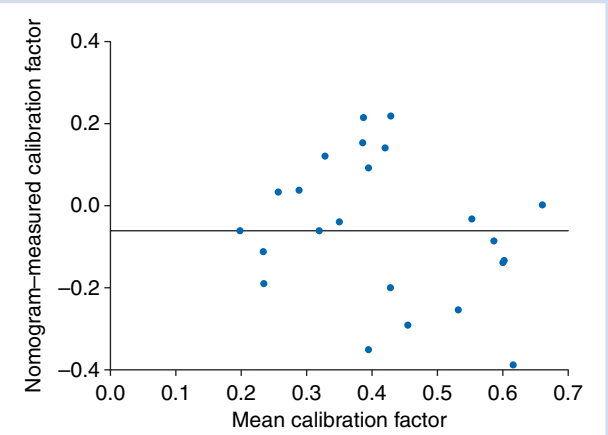

Fig 13 Difference between nomogram and measured calibration factors plotted against mean calibration factor. The solid line shows mean with SD of 0.17.

both elective and emergency settings. Newer devices are now available for use without indicator dilution generated calibration. A nomogram which compliments the PulseCO pressure waveform algorithm is used to produce a calibration factor for use with the LiDCOrapid haemodynamic monitor (LiDCO Ltd, Cambridge, UK). This device applies the calibration factor to the nominal stroke volume and CO calculated by arterial pressure waveform analysis. The LiDCO nomogram is based on a data set of patients with a maximum age of 82 yr (personal communication), and has not been formally validated for use in individuals above this age.

As part of an ethically approved randomized controlled trial using lithium indicator dilution calibrated LiDCO™ plus monitors, calibration factors for 23 participants aged 80 yr and over were recorded. Measured calibration factors were compared with those produced by the manufacturer's nomogram.

The mean age of the patients was 85 (range 80–94) yr. The mean calibration factor after lithium indicator dilution calibration was 0.449 (SD 0.179) compared with that produced by the PulseCO pressure waveform nomogram of 0.391 (SD 0.141). A Bland–Altman plot was used to compare the two methods (Fig. 13).

Calibration factors calculated by the manufacturer's algorithm may vary in individuals aged over 80 yr by up to 0.39. This suggests that estimates of absolute cardiac indices using non-indicator dilution generated calibration factors may be unreliable in this group.

Keywords: measurement techniques, lithium dilution

Acknowledgement

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Sugammadex allows the use of rocuronium in place of succinylcholine during rapid sequence induction of anaesthesia

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The use of rocuronium 1 mg kg^{-1} has been suggested as an alternative to the use of succinylcholine during rapid sequence induction (RSI) of anaesthesia.[1] The main disadvantage of its use has been the inability to antagonize its effect rapidly in case of failure to intubate or ventilate. Sugammadex (Sug) has been shown to reverse even a profound rocuronium block rapidly.[2 3] The present study examines the safety of using rocuronium followed by sugammadex in place of succinylcholine during a simulated cannot intubate–cannot ventilate scenario during RSI.

Ninety adult patients undergoing elective surgery were included in the study. They were preoxygenated for 3 min after which anaesthesia was induced with propofol 2–2.5 mg kg^{-1} and fentanyl 1 μg kg^{-1} followed by application of cricoid pressure and 1 mg kg^{-1} of succinylcholine (Sux; n=30) or 1 mg kg^{-1} of rocuronium (Roc; n=60). Three minutes after the neuromuscular blocking agent, 30 patients each in the Roc group received Sug 10 mg kg^{-1} (Sug 10) or 16 mg kg^{-1} (Sug 16) and those in the Sux group 7–10 ml of normal saline. The main endpoints recorded were the time to resumption of spontaneous ventilation as indicated by the return of diaphragmatic movement, movement of the reservoir bag, and recordable end-tidal CO_2. Any decrease in Sp_{O_2} of 90% or less before the resumption of spontaneous ventilation was noted. All the observations were made by a blinded observer and the study was terminated when the patients started to breathe. Any decrease in Sp_{O_2} to <90% before the resumption of spontaneous ventilation was noted and gentle manual ventilation commenced. At this point, patients were manually ventilated and anaesthetized appropriately. The data were subjected to analysis of variance.

The times to all clinical indices of recovery were similar among the groups (Table 11). The number of patients in

Table 11 Times to first return of clinical indices of recovery from the time of Sux or Roc administration (median and range; *n=29)

	Diaphragmatic movement (s)	Reservoir bag movement (s)	Recordable E'_{CO_2} (s)	Lowest Sp_{O_2} (%)
Roc+Sug 16	220 (207–374)	217 (203–313)	228 (212–395)	100 (88–100)
Roc+Sug 10*	222 (193–279)	225 (194–285)	238 (203–359)	100 (84–100)
Sux	237 (61–477)	234 (61–477)	270 (65–531)	99 (73–100)

whom Sp_{O_2} decreased to <90% before the start of breathing was 1, 3, and 4 in Roc+Sug 16, Roc+Sug 10, and Sux groups, respectively. The lowest Sp_{O_2} values were not significantly different among the groups. Our results indicate that rocuronium can safely be used in place of succinylcholine as sugammadex 16 mg kg^{-1} can restore spontaneous respiration in case of failure to intubate or ventilate with a lower incidence of desaturation than with Sux. The group receiving Sug 10 mg kg^{-1} had a higher incidence of desaturation than the group receiving Sug 16 mg kg^{-1}.

Keywords: nueromuscular blocker; rapid sequence induction; sugammadex

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Comparison of aortic and aorto-femoral pulse wave velocity measured using continuous wave Doppler ultrasound

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Decreased compliance of the conduit arteries is now recognized as an independent risk factor for developing cardiovascular pathology.[1] Aortic pulse wave velocity (aPWV) is regarded as the gold standard method for the non-invasive measurement of arterial compliance. Currently, there is no consensus about which sites should be used for optimal estimation of aPWV. True aPWV is a variable of great importance as the compliance of the aorta determines cardiac afterload. The most commonly used technique for measuring aPWV is tonometry, but measurement sites are limited to superficial vessels.

The purpose of this study was to estimate the difference in pulse wave velocity measured between the ascending aorta and common femoral artery with values measured between the ascending aorta and abdominal aorta.

Ethics Committee approval was obtained to study patients undergoing elective surgery requiring general anaesthesia. Doppler signals were recorded for 2 min with the proximal probe held on the supraclavicular fossa (to insonate the ascending aorta) and the distal probe held at the abdominal aorta at the umbilical level. Doppler signals were recorded again with the proximal probe in the same position and the distal probe moved to the inguinal ligament to insonate the femoral artery. Pulse transit times between the two

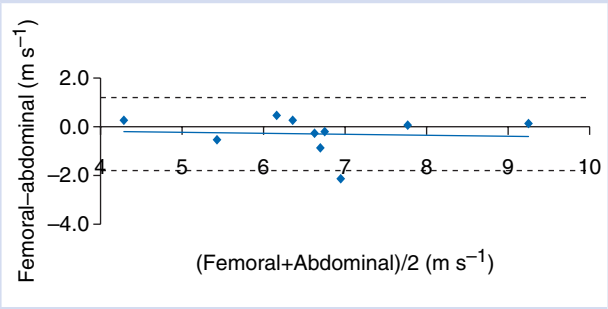

Fig 14 Bland–Altman plot comparing femoral and abdominal sites. Dotted lines show limits of agreement.

Doppler signals were measured by cross-correlating the signals and the aPWV was calculated, knowing the distance between the probes (measured to the nearest millimetre with a flexible tape).

There was good correlation between the pulse wave velocity measured at the abdominal and femoral sites (r=0.87, P<0.005, n=10). The Bland–Altman analysis showed that the mean difference between the two approaches was −0.28 ms^{-1}. A paired t-test revealed that there was no significant difference in PWV between the two measurement sites [PWV_{abd}=6.77 ms^{-1} (1.47) (SD); PWV_{fem}=6.49 (1.42)]. There was one outlier (Fig. 14).

The femoral measurement site provides a good estimate of true aPWV values.

Keywords: diagnostic techniques, cardiovascular; pulse wave velocity; aortic compliance; Doppler ultrasound

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Communication between propofol and γ-aminobutyric acid binding sites on γ-aminobutyric acid type A receptors

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The γ-aminobutyric acid type A ($GABA_A$) receptor is a member of the pentameric ligand-gated ion channel (pLGIC) family. Nineteen genes encode α1–6, β1–3, γ1–3, ρ1–3, δ, ε, θ, and π $GABA_A$ subunits. Each subunit has a large extracellular amino (N)-terminus and four membrane spanning (M1–M4) domains. GABA binds to the N-termini of adjacent α and β subunits initiating a conformational wave that opens the channel gate within M2.[1] Normal activity of the receptor is critical for maintaining a balance between neuronal excitation and inhibition. An epilepsy

mutation in the γ2 gene reduces the efficacy of GABA by replacing a conserved lysine in the extracellular loop connecting M2 and M3 with methionine (K289M).[2] The i.v. anaesthetic propofol induces a reversible loss of consciousness by potentiating the actions of GABA and directly activating the $GABA_A$ receptor[3] through an interaction with M2 amino acids.[4] Important progress has been made identifying anaesthetic modulatory sites on the $GABA_A$ receptor. However, little is known about the modes of communication between these sites, the GABA binding site and the channel gate. We used the epilepsy mutant γ2(K289M) subunit and the homologous synthetic α1(K278M) mutation to investigate how propofol increases the efficacy of GABA as an agonist of α1β2γ2 receptors.

HEK cells were transfected with wild-type (WT) and mutant α1, β2 and γ2 cDNAs. Whole cells were voltage clamped at −60 mV and recombinant $GABA_A$ receptors were functionally characterized with equimolar NaCl- and CsCl-based internal and external solutions. GABA was applied rapidly either alone or with propofol. The rate of current deactivation (i.e. the time taken for channels to close after removal of GABA) was established by stepping out of GABA into saline in the absence or presence of the $GABA_A$ receptor antagonist bicuculline. We modelled mutant and wild-type receptors using high-resolution structures of the evolutionarily related acetylcholine binding protein (from *Aplysia californica*) and pLGICs (from *Gleobacter violaceus* and *Erwinia chrysanthami*) as templates.

Mutant subunits reduced the efficacy of GABA as an agonist of α1β2γ2 receptors. The deactivation of WT currents was resistant to bicuculline, suggesting that GABA does not unbind before the channel closes. In contrast, bicuculline accelerated deactivation of mutant receptors suggesting that GABA unbinds before channel closure a mechanism that could contribute to reduced efficacy. Propofol restored the efficacy of GABA and conferred bicuculline resistance to the deactivation of currents mediated by mutant receptors. $GABA_A$ receptor structural models suggest that the conserved lysine residue in the M2–M3 loop is involved in communication between the channel gate and the GABA binding site.

The epilepsy mutation affects a key residue in the $GABA_A$ receptor by reducing the efficacy of GABAergic inhibition. The change in structure and function induced by this mutation may provide some insight into the mechanisms governing agonist efficacy and the actions of general anaesthetics.

Keywords: pharmacology, receptors; GABA

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Characterization of the bifunctional opioid UFP505

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Morphine is a gold standard analgesic acting at μ-opioid receptors (MOP) with analgesia accompanied by side-effects, for example, tolerance. If δ-opioid receptors (DOP) are blocked at the same time that MOP is activated, then analgesia with reduced tolerance results.[1] As part of an ongoing programme to design mixed MOP agonist/DOP antagonist drugs (bifunctional) we have characterized the prototype pseudopeptide H-Dmt-Tic-Gly-NH-CH_2-Ph (UFP505).[2] We have measured ability to interact with MOP and DOP receptors with differential agonism/antagonism and the effects of 1 h pretreatment on cell surface MOP receptor numbers.

We have used Chinese Hamster Ovary cells expressing human recombinant MOP, DOP KOP (κ), and NOP (nociceptin/orphanin FQ) receptors ($CHO_{hMOP/hDOP/hKOP/hNOP}$).[3] Receptor binding was measured using the radioligand [^{3}H]diprenorphine ([^{3}H]DPN) in saturation format to determine receptor density (B_{max}) and affinity (pK_D) or displacement format to determine the affinity (pK_i) of UFP505. Functional activity at MOP and DOP was assessed by measuring agonist stimulated GTPγ[^{35}S] binding. Loss of cell surface receptors was measured using [^{3}H]DPN in saturation format after 1 h treatment of CHO_{hMOP} with 10 μM UFP505.

UFP505 displaced [^{3}H]DPN binding to MOP and DOP receptor with pK_i 7.79 (0.18) and 9.82 (0.06) [mean (SEM), n=5], respectively. Affinity at KOP and NOP was negligible. At MOP in a GTPγ[^{35}S] binding assay, UFP505 behaved as a full agonist (compared with MOP agonist endomorphin-1) with a pEC_{50} (potency) and E_{max} (efficacy:stimulation factor) of 6.23 (0.15) and 2.24 (0.15) (n=3), respectively. At DOP, UFP505 (10 nM) reversed the effects of the DOP agonist DPDPE in the GTPγ[^{35}S] assay with potency (pK_B) of 9.81 (0.18) (n=3), in agreement with pK_i determined in [^{3}H]DPN binding assays. Pretreatment of CHO_{hMOP} cells with 10 μM UFP505 for 1 h produced substantial loss of cell surface receptors with no change in DPN pK_D. B_{max} and pK_D values for control and 1 h UFP505 treated cells were 332 (53) fmol mg^{-1} protein and 9.20 (0.11) and 155 (12) fmol mg^{-1} protein and 9.15 (0.10), respectively (n=5).

Here we show that UFP505 is a bifunctional MOP agonist/DOP antagonist capable of producing tolerance like actions in a single MOP expression system. The next stage is to examine the effects of this ligand in a double (MOP and DOP) expression system.

Keywords: opioid receptors; opioid side effects; bifunctional opioids; radioligand binding

Acknowledgement

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Fibreoptic intubation rates in a UK teaching hospital

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Airway management is the foundation upon which anaesthesia is built and fibreoptic intubation (FOI) is a key facet of this skill. Despite this, many trainee anaesthetists in the UK have been unable to perform sufficient FOIs to gain competence. The situation is likely to be compounded by the time constraints presented the European Working Time Directive. The incidence of FOI varies greatly between countries. In Canada, FOIs make up 1.4% of all tracheal intubations,[1] while in Switzerland, the rate is in excess of 12%.[2] To our knowledge, the incidence of FOI within the UK has never been determined. We aimed to establish the incidence of FOI in adult patients, in a UK teaching hospital, in order to determine what FOI training opportunities actually exist.

Guidance from the National Research Ethics Service (NRES) classified the project as service evaluation, meaning that formal ethical approval was unnecessary. Local approval was gained from our institution's audit committee. We prospectively documented the details of every adult (≥16 yr of age) FOI undertaken in our institution over a 12 month period into a departmental database. We also collected data on all episodes of failed intubation over the same period of time. The total number of tracheal intubations that occurred during the study period was estimated using local data submitted to the Royal College of Anaesthetists National Audit Project 4 (NAP4).

A total of 11 712 episodes of tracheal intubation were estimated to have occurred during the data collection period. One hundred and forty-one FOIs were performed giving an incidence of FOI of 1.2% or 1:83 (95% confidence interval 1–1.4%). Of these, 86 (61%) were in awake and 55 (39%) in anaesthetized patients. Only 16 (11%) FOI were done solely for the purposes of FOI training. There were 19 episodes of failed tracheal intubation, giving an incidence of 0.16% or 1:616 (95% confidence intervals 0.09–0.25% or 1:404 to 1:1004).

The FOI rate of 1.2% in our institution is comparable with that of North America[1] and that seen in Australia (where FOI make up only 0.76% of all tracheal intubations undertaken by trainees)[3] but is low in comparison with other European countries.[2] Only a small number of FOIs are undertaken for training purposes which is in contrast to other institutions where teaching is the primary indication for up to 45% of FOIs.[2] The rate of failed intubation in our institution of 1:616 is comparable with that seen in other studies.[1 4 5] We suggest that a greater number of FOIs should be undertaken to allow trainees to gain, and consultants maintain, the FOI expertise necessary for the provision of safe anaesthesia.

Keywords: airway, intubation, fibre optic

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A pragmatic approach to effect-site target-controlled infusion: the concept of an apparent k_{e0}

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A new method proposed by the author to determine a suitable blood–brain equilibration rate constant for the Marsh pharmacokinetic (PK) model was based on the hypothesis that during target-controlled infusion (TCI), if the target concentration is set to the calculated effect-site concentration (Ce_{CALC}) once

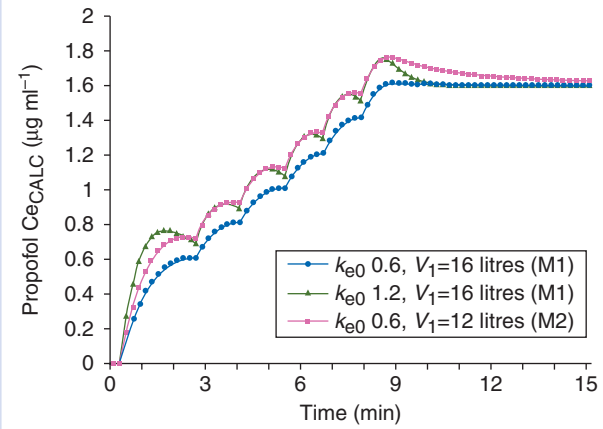

Fig 15 Propofol (Ce_{CALC}) with input doses derived from effect-site targeting.

a desired level of sedation is reached, sedation level should remain constant if the correct blood–brain equilibration rate constant (k_{e0}) is used. As this method has been criticized on the basis of possible inaccuracy in the PK model, further simulation studies have been done to examine the influence of changes in volume of distribution (V_1) and k_{e0} on Ce_{CALC}.

The program PK-SIM was used with the Marsh model (V_1 16 litre, Cl 1.9 litre min^{-1}, M1) and a modified Marsh model with V_1 12 litre, Cl 1.9 litre min^{-1} (M2). With M1 and a k_{e0} of 0.6 min^{-1}, an initial propofol effect-site target (Ce_T) of 0.6 μg ml^{-1} was increased in increments of 0.2 μg ml^{-1}, as each target was predicted to be reached, to a maximum of 1.6 μg ml^{-1}. The doses delivered with this simulation were then used as inputs in simulations with M1 with k_{e0}s of 0.6 and 1.2 min^{-1} and M2 with a k_{e0} of 0.6 min^{-1} (Fig. 15).

With M1, k_{e0} 0.6, Ce_{CALC} followed the concentrations obtained in the effect control simulation. With M2 (V_1 12 litre), the same doses led to higher values for Ce_{CALC} reaching 1.8 μg ml^{-1}, a similar value to that seen in M1 with a k_{e0} of 1.2 min^{-1}.

With any group of patients, V_1 is likely to vary widely from the average value used in a PK model. This work shows that changes in V_1 can mimic changes in k_{e0} such that a wide range of apparent k_{e0} values would be required to achieve a stable effect in all patients. However, by examining a range of k_{e0} values in different groups of patients, the apparent k_{e0} value providing a stable effect in the greatest number of patients will acknowledge the degree of PK variation in the population studied. This apparent k_{e0} which best follows the increase in actual effect-site concentration may differ from values determined in integrated PK/PD studies but may be more clinically useful.

Keywords: pharmacology, propofol; kinetics, drug; models, computer