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ABSTRACTS

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*(The name of the person 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.)*

ORAL PRESENTATIONS

Classical opioid receptor mRNA is not present in whole human blood

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Opioids are immunomodulators and two sites of action have been proposed; direct on the immunocyte or indirect on the hypothalamic–pituitary–adrenal (HPA) axis.[1] There are historical data in support of the former target, but we have refuted this in several polymerase chain reaction (PCR)-based studies, indicating that a range of individual immune cell types do not produce MOP (μ), DOP (δ), or KOP (κ) receptor transcripts.[2] The aim of this study was to measure MOP, DOP, and KOP receptor mRNA extracted from whole blood (containing the full complement of circulating immunocytes), treated with a range of common opioids and also an *in vitro* septic stimulus.

Whole blood from five healthy volunteers was collected into S-monovette EDTA tubes. One millilitre samples were incubated for 24 h (37°C and 5.3 kPa CO_2) as (i) control—no addition, (ii) morphine 10 μM, (iii) fentanyl 10 μM, (iv) LPS 5 μg ml^{-1}, (v) lipopolysaccharide (LPS) and morphine, and (vi) LPS and fentanyl. These concentrations were supramaximal and in the case of opioids exceed clinical plasma concentrations. Whole blood RNA was extracted using the RiboPure™-blood kit according to the manufacturer's guidelines. RNA was further processed with a DNase enzyme to remove gDNA and converted to cDNA using reverse transcriptase. Samples were assessed for opioid receptor gene expression using TaqMan probes on a StepOne real-time PCR machine.[3] GAPDH was used as a housekeeper gene.

mRNA transcripts could not be detected for any of the classical opioid receptor genes in peripheral whole blood in all incubation conditions. Data for MOP and KOP are shown in Table 1. Two different TaqMan probes for DOP receptors were used and showed amplification in non-template controls (no reverse transcription). Melt curve analysis of these PCR products showed a pattern consistent with amplification of genomic DNA and as such DOP mRNA is not present. Consistent with our previous work, NOP mRNA was present.

These data further demonstrate the absence of classical opioid receptor mRNA (and by inference receptor protein) on circulating immune cells. We would suggest that any effects of opioids on immunomodulation are via effects on the HPA axis.

Acknowledgement

StepOne PCR machine was purchased using a grant from *BJA*/RCoA.

Table 1 PCR data for MOP and KOP. Data are cycle threshold (C_t) $mean_{(range)}$. ND, not detected; GOI, gene of interest. Concentrations: morphine and fentanyl 10 μM, LPS 5 μg ml^{-1}

Treatment	MOP-C_t		KOP-C_t	
	GAPDH	GOI	GAPDH	GOI
Control	$24.21_{(23.90–24.87)}$	ND	$24.18_{(23.76–24.57)}$	ND
Morphine	$24.17_{(23.63–24.92)}$	ND	$24.19_{(23.51–24.98)}$	ND
Fentanyl	$24.27_{(23.65–24.79)}$	ND	$24.41_{(23.87–24.67)}$	ND
LPS	$25.57_{(25.08–26.00)}$	ND	$25.67_{(25.00–26.07)}$	ND
LPS+morphine	$25.74_{(24.72–27.04)}$	ND	$25.76_{(25.02–26.95)}$	ND
LPS+fentanyl	$26.20_{(25.16–27.55)}$	ND	$26.13_{(25.41–27.69)}$	ND

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How valid is patient-reported height and weight using an interactive, computerized preoperative assessment questionnaire (ePAQ-PO)?

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Anaesthetic preoperative assessment is a requirement for all patients before surgery. ePAQ-PO (electronic Personal Assessment Questionnaire Pre-Operative) is a web-based instrument designed for use in routine clinical practice.[1] Also proving a comprehensive assessment of a patient's medical and anaesthetic history, ePAQ-PO also calculates BMI from patient-reported height and weight. Similar systems have been used safely and effectively in other specialities.[2]

Ethical approval was obtained from the national research ethics service, and written informed consent obtained from 300 patients who completed the ePAQ-PO in a study designed to evaluate its psychometric properties. As part of this online questionnaire, patients were asked to estimate their height and weight. All patients subsequently attended their routine face-to-face preoperative assessment appointment where they were weighed and measured. One hundred and fifty patients completed ePAQ-PO a second time for test–retest validation.

The resulting mean (SD) differences between patient (self) reported and measured data for weight, height, and BMI were −1.4 (8.1) kg, 2.1 (3) cm, and −1.0 (2.6) kg m^{-2}, respectively.

World Health Organization (WHO) BMI classification was correctly self-estimated in 78% of patients and was within one WHO category in a further 21%.

Test–retest ePAQ-PO data were available for 138 patients. One patient, who recorded their height as 2 cm, was removed from this data set. The test–retest mean (SD) score differences for weight, height, and BMI were −0.34 (2.47) kg, −0.22 (2) cm, and 0.16 (1.2) kg m^{-2}, respectively.

Patients tended to under-report their weights and over-report their heights, but the resulting BMI error was rarely significant. Our web-based questionnaire gives similar results to patients' self-reported height and weight obtained using a telephone survey.[3] Web-based self-reporting appears to give accurate estimates of patients' height and weight which could be useful for preoperative screening and triage of patients.

Funding

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Characterization of novel fentanyl-based bivalent opioids

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Opioids produce analgesia along with several major side-effects, including the development of tolerance, particularly with chronic use. Tolerance at the MOP (μ) receptor is reduced by antagonizing DOP (δ) receptors and this can be achieved with bivalent pharmacophores.[1] In this study, we have synthesized a number of fentanyl (MOP agonist) derivatives to which we have added the DOP antagonist pharmacophore Dmt-Tic. The two pharmacophores are joined by linker molecules with different length and chemical structure (C2; C3 and O).

Membrane fragments prepared from Chinese hamster ovary cells expressing MOP, DOP, KOP (κ), and NOP (nociceptin/orphanin FQ) receptors ($CHO_{hMOP/DOP/KOP/NOP}$) were used to assess binding affinity and functional activity. Affinity at MOP, DOP, and KOP was assessed using [^{3}H]diprenorphine and at NOP using [^{3}H]UFP-101.[2 3] Functional potency (pEC_{50}) and efficacy (E_{max}) was assessed using GTPγ[^{35}S] binding assays.[3]

O, C2, and C3 bound to MOP/DOP/KOP/NOP receptors with higher affinity for the DOP receptor, as shown in Table 2. In functional screens at MOP, O and C3 behaved as partial agonists, while C2 displayed negligible efficacy. Indeed at the MOP receptor, C2, C3, and O were able to shift the concentration–response curve of fentanyl to the right to yield affinity (pK_B) values consistent with pEC_{50} values (characteristic of a partial agonist). All bivalents did not stimulate GTPγ[^{35}S] binding alone at DOP but shifted the concentration response to [DPen^{2,5}]enkephalin parallel to the right with pK_B values

Table 2 Affinity and functional activity [mean (SEM) $n \geq 5$]. Reference for MOP was fentanyl [pK_i: 7.71 (0.09), pEC_{50}: 7.07 (0.20), E_{max}: 3.88 (0.29)]. Reference for DOP was naltrindole in binding [pK_i: 9.51 (0.12)] and [DPen^{2,5}]enkephalin in GTPγ[^{35}S] assays [pEC_{50}: 7.70 (0.02), E_{max}: 2.77 (0.06)]. αE_{max} is the efficacy relative to fentanyl

	MOP			DOP		
	O	C2	C3	O	C2	C3
pK_i	7.91 (0.23)	7.31 (0.06)	7.58 (0.10)	8.17 (0.22)	8.03 (0.28)	8.16 (0.17)
pEC_{50}	7.52 (0.27)	6.74 (1.02)	7.13 (0.29)	Inactive	Inactive	Inactive
E_{max}	1.98 (0.31)	1.18 (0.06)	2.19 (0.46)	Inactive	Inactive	Inactive
αE_{max}	0.35	0.06	0.42	Inactive	Inactive	Inactive

~8. The binding affinity and functional potency of fentanyl alone at MOP was similar to that of the bivalent ligands (Table 2). There was no agonist activity detected at the KOP or NOP receptors (not shown).

Adding Dmt-Tic (DOP) spaced by ≤3 carbon atoms interferes with the ability of the fentanyl (MOP) pharmacophore to activate MOP receptor. We are examining a further series of fentanyl-based backbones with increased (C3–C6) to hopefully restore MOP agonist activity.

Acknowledgement

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Mortality predictors in patients with haematological malignancies admitted to critical care

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Critical care admission of patients with haematological malignancies has traditionally been viewed as likely to result in a poor outcome, but recent studies have reported more encouraging results. We therefore aimed to examine outcome predictors in these patients.

A retrospective cohort of consecutive haematological patient admissions was gathered using a predefined case report form. Outcome was evaluated using intensive care unit (ICU) and hospital discharge times and at 1 and 2 yr follow-up. The primary outcome measure was ICU mortality. Univariate logistic regression analyses, adjusted by age, gender, and haematological diagnosis, were performed to identify factors predicting outcome. Multivariate analyses were performed to identify independent predictors of outcome.

Between September 12, 2002, and March 22, 2008, 134 haematology patients were admitted to critical care, of whom 83 (61.9%) were male. The median age was 59.5 [inter-quartile range (IQR) 47–65] yr. The most common haematological diagnoses on admission were multiple myeloma in 31 (23.1%) cases, acute myeloid leukaemia in 31 (23.1%) patients, and non-Hodgkin lymphoma in 23 (17.2%) cases. The median APACHE II score on admission was 18 (IQR 13–23); 41 (30.6%) patients had previously undergone bone marrow transplant. One hundred and six (79.1%) had at least one organ failing or being supported, and 67 (50%) had two or more organ failures.

Twenty-two (16.4%) patients received continuous veno-venous haemofiltration (CVVH), 63 (47%) inotropes or vasopressors, 51 (38.1%) ventilatory support. Unit and hospital mortality rates were 35.8% (48 patients) and 47.8% (64 patients), respectively. At 1 and 2 yr follow-up, mortality had further increased to 69.4% (93 patients) and 77.3% (102 patients), respectively.

At univariate analysis, age (P=0.41), gender (P=0.64), haematological diagnosis (P=0.24), previous BMT (P=0.72), need for CVVH (P=0.71), white cell count (P=0.29), neutrophils (P=0.63), creatinine (P=0.92), and bilirubin (P=0.57) on admission did not influence critical care survival. However, admission APACHE II score [odds ratio (OR)=0.94, 95% confidence interval (CI)=0.88–0.99, P=0.02], number of organs supported (OR=0.26, 95% CI=0.15–0.44, P<0.001), number of organ failure or supported (OR=0.39, 95% CI=0.25–0.58, P<0.001), $Pa_{O_2}/F_{I_{O_2}}$ (P/F) ratio (OR=1.1, 95% CI=1.04–1.15, P<0.001), inotropic requirement (OR=0.22, 95% CI=0.1–0.5, P<0.001), ventilatory support status (OR=0.41, 95% CI=0.27–0.64, P<0.001) influenced survival. At multivariate analysis, the P/F ratio (OR=1.13, 95% CI=1.1–1.21, P<0.001) remained an independent factor influencing survival.

In this cohort of haematological patients admitted to critical care, organ failures and need for organ support were related to outcome. The P/F ratio was the only independent

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predictor of mortality. The critical care mortality rate was 35.8%, although at 2 yr follow-up, mortality had reached 77.3%.

Effect of prone positioning on cardiac output and liver blood flow in the awake healthy volunteer

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Recent occurrence of severe postoperative liver failure at our institution has prompted investigation into whether anaesthesia for surgery in the prone position can influence perioperative liver function. Cardiovascular instability is a well-recognized complication of the prone position.[1] As part of a series of studies, we wished to investigate the effect of prone positioning on cardiac output and liver blood flow simultaneously in healthy, awake volunteers.

Participants were placed in the supine position. Cardiovascular monitoring was established using the Finometer (Finapres Medical Systems BV, The Netherlands). After achieving baseline cardiovascular stability, blood samples were obtained for routine hepatic enzyme levels and arginase (a sensitive marker of reperfusion induced hepatocellular necrosis). Indocyanine green (ICG) plasma disappearance rate (ICG-PDR) was recorded using the LiMON (Pulsion Medical Inc., TX, USA). The participants were then turned to the prone position using thoracic and pelvic bolsters for support. After 1 h, blood sampling and ICG-PDR measurements were repeated and the participant returned to the supine position. After a further hour, blood and ICG-PDR was obtained for a third and final time. Cardiovascular parameters were recorded at 10 min intervals throughout the duration of the study. Cardiovascular parameters, liver enzyme levels, and ICG-PDR were tested for change using serial paired *t*-tests with the Bonferroni correction.

There were a total of 10 volunteers (four male). Group characteristics were: age 20.4 (0.966), height 174 (12.2) cm, weight 64.8 (11.6) kg [mean (standard deviation)]. Cardiac output and ICG-PDR were significantly reduced in the prone position compared with supine positions (Table 3). Heart rate, mean arterial pressure, and hepatic enzyme levels were not significantly associated with change in position.

We have demonstrated a significant and reversible reduction in cardiac output and ICG-PDR caused by prone positioning in young healthy volunteers in the absence of general anaesthesia, surgical fluid loss, or vasoactive agents. The effect is acute in onset occurring within 1 h, is reversible on returning to the supine position, and is not associated with laboratory biochemical evidence of hepatocellular dysfunction.

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Proportion of patients undergoing emergency surgery at risk of postoperative pulmonary and cardiac complications

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The ARISCAT is a weighted scoring system comprising seven clinical variables.[1] An ARISCAT score 26–45 identifies patients at intermediate risk and >45 at high risk of postoperative pulmonary complications (PPCs). A revised cardiac risk index (RCRI) >1 identifies patients at risk of major adverse cardiac events (MACE).[2] To quantify the proportion of emergency surgery patients at risk, we undertook a multicentre prospective audit in a UK patient cohort.

The audit was conducted in six South West hospitals simultaneously over 2 weeks in July 2012. We aimed to record ARISCAT, RCRI, and postoperative ward for every patient having an operation in the designated emergency theatre. Data were anonymized and centralized for analysis using Internet-based software (SurveyMonkey™).

Audit data were collected for 437 of the 513 patients (85%) (Table 4). Information on the remainder was retrieved from hospital systems. The median ARISCAT and RCRI scores of audited patients were 8 (IQR 8–26) and 0 (IQR 0–0), respectively.

Sixty-five audited patients (15%) underwent laparotomy, of whom 35 had an ARISCAT>45. Nine were admitted to the surgical ward, 11 to extended recovery or HDU, and 15 to ICU.

According to ARISCAT and RCRI scores, 11% of emergency surgery patients are at high risk for developing PPCs and 7%

Table 3 Effect of position on cardiac output, ICG-PDR, and plasma arginase level. All data are mean (standard deviation)

Variable	Supine baseline	Prone	Supine post-prone	*P*-value
Cardiac output (litre min^{-1})	4.69 (0.991)	3.54 (1.08)	3.73 (0.999)	0.003
ICG-PDR (% min^{-1})	31.1 (9.70)	19.6 (4.37)	24.6 (5.54)	0.001
Arginase (ng ml^{-1}) (normal range 1.8–30 ng ml^{-1})	10.1 (5.70)	9.60 (5.10)	9.70 (5.80)	0.570

Table 4 ARISCAT and RCRI risk scores *vs* postoperative destination

	Total audited, *n* (%)	Postoperative ward		
		Surgical ward, *n* (%)	HDU/extended recovery	ICU
ARISCAT				
0–25	325 (74)	308 (95)	7 (2)	10 (3)
26–45	66 (15)	47 (71)	7 (11)	12 (18)
>45	46 (11)	13 (28)	15 (33)	18 (39)
RCRI				
0	350 (80)	314 (90)	18 (5)	18 (5)
1	58 (13)	41 (70)	5 (9)	12 (21)
>1	29 (7)	13 (45)	6 (21)	10 (34)
ARISCAT>25 and RCRI>1	20 (5)	6 (30)	6 (30)	8 (40)
ARISCAT>45 and RCRI>1	13 (3)	2 (15)	5 (39)	6 (46)

at high risk for MACE. A proportion of at these risk patients do not receive planned critical care after operation.

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Detection of airway obstruction during opioid analgesia after surgery

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We have developed a device (RESpeck) that can provide a reliable measure of respiratory rate at frequent intervals in patients receiving patient-controlled morphine analgesia after surgery. Since it senses chest wall movement, it may continue to indicate respiration during airway obstruction. Airway obstruction and respiratory disturbance are frequent during opioid analgesia after surgery. The chest wall can move with a different pattern during obstruction, with paradoxical ribcage movement. By sensing movement at two positions, automatic detection of obstructive events may be possible.

We studied 25 patients in a surgical ward receiving opioids for analgesia after major gynaecological surgery. Respiratory movement was detected with two encapsulated tri-axial accelerometers: one placed below the costal margin in the midclavicular line, and the other was placed first at the umbilicus (~30 min recording) and then below the middle of the clavicle (~30 min recording). Nasal flow was sensed with a nasal cannula and pressure transducer. Data were transmitted wirelessly to a computer. The breathing patterns of the patients were classified using the nasal flow signal. Six patients had repeated cycles of airway obstruction. In each cycle, progressive flattening of the airway flow profile was followed by a sudden recovery. Five episodes were measured in each 30 min period of recording. The root mean square of the signal amplitude was used to quantify movement. Movements in the time periods before, during, and after recovery from obstruction were compared by analysis of variance.

Nasal flow signals decreased during obstruction ($P<0.0001$), and subcostal movement increased ($P<0.03$). There were no significant changes in umbilical movement, but clavicle movements decreased ($P<0.012$) (Fig. 1).

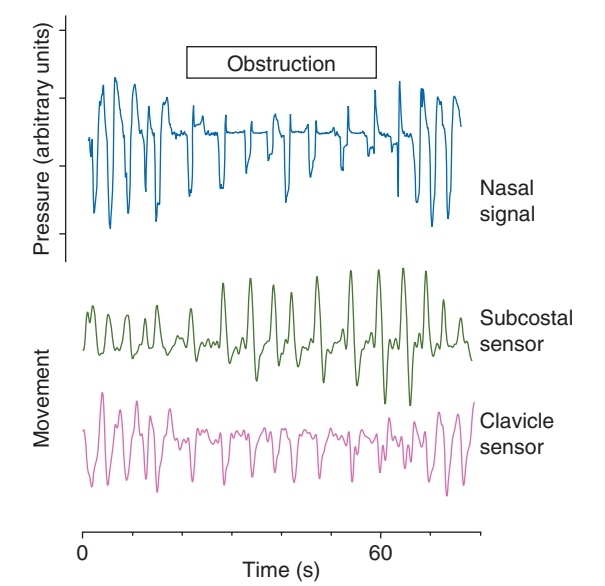

Fig 1 Reciprocal changes in signal size from subcostal and clavicle positions during an episode of partial airway obstruction.

We conclude that with suitable sensor positions, automatic detection of cyclical airway obstruction may be possible. However, another four patients in our sample had persistent, non-cyclic obstruction which would not be detected by differential changes in the movement signals.

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Pharmacogenomics of anaphylaxis to neuromuscular blocking agents

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Anaphylaxis to neuromuscular blocking agents (NMBAs) has an estimated incidence of 300 cases per year in the UK, with as many as 5% resulting in fatality.[1] The mechanisms that lead to acquisition of anaphylaxis remain poorly characterized and to date, there is no method for predicting these adverse events. Recent advances in the field of pharmacogenomics, and the new genotyping technologies, have highlighted the role HLA polymorphisms play in determining susceptibility to immune-mediated drug hypersensitivity reactions. We propose to investigate the genetic associations behind this phenomenon. It is our hypothesis that predisposition of anaphylaxis to NMBAs is genetically determined, and that genome-wide approaches will identify both HLA and non-HLA genes predisposing to these reactions.

Consenting adult patients, with an allergy clinic determined diagnosis of NMBA anaphylaxis will be recruited to this case/control study. To date, we have identified a sample size ~2000 patients. Two ethnically matched controls will be recruited to each index patient. Patient information will be sampled with a case reporting form and a 9 ml sample of EDTA blood will be obtained for the purpose of genome-wide association study.

It will be our intention to undertake genome-wide association studies (GWAS) in 50% of the case group (randomly identified), and use the other 50% of case samples, together with anaesthetic-exposed controls, for the replication.

The field of pharmacogenomics is rapidly evolving and so far has identified several HLA alleles that predispose to drug-induced hypersensitivity reactions. The most notable is the association of Abacavir hypersensitivity in the Caucasian population and the HLA-B*5701 allele.[2] These reactions are largely T-cell-driven and are thus dependent upon initial recognition of the drug by MHC class I or II proteins. Anaphylaxis to NMBAs differs in that it is IgE mediated, and to date no good genetic predictors have been identified, largely because this phenotype has not been subjected to genome-wide approaches. However, the process of sensitization has been shown to rely upon initial drug recognition and binding by antigen-presenting cells, via MHC class II.[3] A genome-wide approach also provides us with the opportunity to look at non-HLA genes, such as cytokines and chemokines, which may also play a role in predisposition. Identification of predisposing genes may allow the development of preventing strategies, for example, through prospective genotyping, and will also provide mechanistic insights, which will help in the development of anaesthetic agents of the future and in intervention strategies.

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Impact of preoperative chemoradiotherapy on functional capacity and health-related quality of life in rectal cancer patients

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Preoperative chemoradiotherapy (CRT) improves outcomes in patients with rectal cancer.[1] However, CRT may reduce the quality of life (QoL) and cardiopulmonary reserve. It has been proposed that exercise training may mitigate these effects.[2] The objectives of this study were to determine the impact of CRT before surgery for rectal cancer on exercise capacity and QoL and to examine the association between these changes.

Patients undergoing CRT before surgery for colorectal cancer were studied. Patients underwent cardiopulmonary exercise testing with measurement of anaerobic threshold (AT) and VO_2peak before and after CRT. QoL was assessed at the time of both exercise tests using the EORTC QLQ-C30. Data are expressed as median (range).

Twenty-four patients (18 male) aged 61.0 (23.7–80.8) yr were studied. The results of assessments performed before and after CRT are shown in Table 5.

There were no significant associations between the changes in AT and VO_2peak and the changes in the various QoL domains.

This study demonstrated a modest decrease in functional capacity with CRT but a dramatic effect on all aspects of QoL. It suggests that the effects of preoperative CRT may not be mitigated by a single intervention such as exercise training. Studies in this area need to take account of other interventions given to mitigate the systemic effects of CRT.

Acknowledgement

Yorkshire Cancer Research.

Table 5 Assessments before and after preoperative CRT

	Pre-CRT	Post-CRT	Change	*P*-value
AT (ml kg^{-1} min^{-1})	13.5 (8.7–19.9)	12.3 (7.3–26.9)	−0.9 (−5.2 to 7.0)	0.065
VO_2peak (ml kg^{-1} min^{-1})	19.4 (12.6–40.9)	17.1 (11.5–43.4)	−0.9 (−7.2 to 2.5)	0.005
Global QoL	94 (87–100)	25 (8–38)	−69 (−92 to −56)	<0.001
Physical function	97 (87–100)	50 (16–77)	−47 (−75 to −10)	<0.001
Role function	87 (94–100)	54 (16–77)	−40 (−78 to −17)	<0.001
Emotional physical	94 (87–100)	50 (16–77)	−43 (−84 to −10)	<0.001
Social function	94 (87–100)	50 (16–77)	−44 (−78 to −10)	<0.001
Cognitive function	94 (87–100)	54 (16–77)	−42 (−84 to −17)	<0.001
Nausea and Vomiting	11 (0–33)	50 (16–77)	42 (−17 to 66)	<0.001
Pain	6 (0–33)	50 (16–77)	44 (−17 to 77)	<0.001
Fatigue	94 (87–100)	50 (16–77)	−50 (−78 to −17)	<0.001

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Effects of glucocorticoids in macrophages

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Glucocorticoids (GC) act through the intracellular glucocorticoid receptor (GR). They have a crucial role in the response to stress in part due to their effects on the innate immune system: patients admitted to intensive care with severe systemic inflammation and a dysregulated GC response have been reported to have increased mortality.[1] Supplementation remains in use clinically,[2] but despite multiple clinical trials, any mortality benefit from this intervention is the subject of ongoing uncertainty.[3] It may be argued this is because the therapy cannot be adequately targeted. This lack of targeting reflects our incomplete knowledge of the molecular mechanism of action of GC. While there is a role for conventional transcriptional regulation via local GR response elements and NFκβ, knowledge of this pathway has yet to lead to therapies or patient selection strategies that enable clinicians to consistently improve outcomes in the intensive care unit setting.

We are taking a new approach to identifying key molecular mechanisms in the response of the innate immune system to GC, focusing on the macrophage as a key cellular target. Macrophages are the central player in innate immunity and being critical in normal development and homeostasis.[4] Our core aim is to determine if chromatin remodelling is part of the macrophage response to GC and if this involves action at a distance from the transcription start site.

Table 6 Total number of gene transcripts with a log fold change of ≥1.5 in response to dexamethasone 100 nM at any time during a 24 h timecourse

Species	Transcripts up	Transcripts down
Mus musculus	82	15
Homo sapiens	188	94

We measured the transcriptional response by microarray over a 6 point 24 h timecourse for both mouse bone marrow-derived and human monocyte-derived macrophages (MDM). This demonstrates that transcriptional activation dominates in both systems, with human MDM appearing more sensitive (Table 6). From this, we can identify target chromosomal loci in both these systems that are disproportionately differentially regulated when compared with the genome as a whole.[5]

It is known that most GR binding is distant from transcriptional start sites[6] and that alteration of chromatin architecture is a feature of the response to GC in cell lines.[7] Further study of our target loci will begin with characterization of changes to higher order chromatin structure using fluorescent *in situ* hybridization using paired probes spanning these regions.

Funding

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Effects of a 6 week prehabilitation programme in operable rectal cancer patients after long-course neoadjuvant chemoradiotherapy

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It is estimated that 70% of cancer patients experience side-effects such as fatigue and decreased physical fitness as a result of cancer treatments. Exercise may be an effective intervention which may help attenuate the deleterious effects of treatment. We aim to examine the heart rate (HR) response of these patients to a 6 week structured, responsive, exercise, training programme (SRETP) as measured by cardiopulmonary exercise testing (CPET) and Ergoline Opticare Trainingskatre chip cards.

We prospectively studied 15 consecutive patients (eight males and seven females) with locally advanced rectal cancer staged at T3-4/N+. The median age was 63 years. The mean BMI was 26.4. All patients completed 5 weeks of NACRT. All patients underwent a CPET immediately after NACRT (week 0), week 3, and at week 6. Each patient undertook 6 weeks of interval exercise training on an ergoline ergometer training bike, 30–40 min sessions, three times a week with 95% adherence. The training intensities were derived from each individual CPET and were of a moderate-to-high intensity. HR data from each session were stored to the trainingskatre chip card.

The median age was 63 yr. The mean body mass index was 26.4 kg m^{-2}. Data derived from the first and last exercise session are presented in Table 7.

Table 7 HR response of the 6 week SRETP

Variables measured	Week 0	Week 6	Significance
Resting HR (beats min^{-1})	82.9 (15.2)	77.3 (11.9)	0.013
Maximum HR (beats min^{-1})	138.5 (22.9)	132.3 (14.2)	0.345
Moderate load (W)	39.6 (18)	49.4 (20.6)	<0.001
Severe load (W)	70.7 (27.9)	79.6 (29.7)	<0.001

SREPT was well tolerated by the patients with a very good adherence. There was a significant reduction in resting HR and a significant increase in load (moderate and maximum) between week 1 and week 6. An exercise programme, such as SREPT, should be considered as part of standard care for all cancer patients after neoadjuvant cancer therapies.

Intrathecal ropivacaine ± opioid *vs* bupivacaine ± opioid perioperatively: a meta-analysis

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Intrathecal ropivacaine has been associated with a shorter duration of motor block than intrathecal bupivacaine,[1] but a recent meta-analysis[2] suggested a delayed onset of sensory block with ropivacaine for knee arthroscopy. This meta-analysis examines the onset and recovery characteristics of the two local anaesthetics in prospective randomized controlled trials (RCTs).

The keywords, ropivacaine, bupivacaine, intrathecal, spinal, and Caesarean section, were used to search Medline, EMBASE (1980–2011) and Google Scholar to identify RCTs and published abstracts, without language restrictions. The Jadad scale[3] was used to assess the quality of the RCTs. RevMan statistical software® utilized inverse variance and a random effect model to calculate weighted mean difference (WMD), with 95% confidence intervals for continuous variables and odds ratio and the Mantel–Haenszel (M–H) method for dichotomous variables. The primary outcome was time to onset of sensory block. Secondary outcomes were: time to complete motor block, duration of motor block, duration of sensory block, time to first request for analgesic, time to mobilization, and incidence of hypotension.

Seventeen RCTs comprising 1014 patients published from 2001 to 2011 were included. Fentanyl, morphine, and sufentanil were the most common opioids used. Caesarean sections, abdominal, urological, and orthopaedic procedures with or without intrathecal opioids were studied. The Jadad score ranged from 2 to 5. There was no difference in time to onset of sensory block (P=0.3). Time to complete motor block was quicker and duration of motor block was significantly longer with bupivacaine. Duration of sensory block was prolonged, as was the time to first request for analgesic in the bupivacaine group. Time to mobilization was significantly longer for bupivacaine with an increased incidence of hypotension (Table 8).

Intrathecal ropivacaine has advantages over bupivacaine with a shorter duration of motor block and time to

Table 8 Comparison between intrathecal ropivacaine and bupivacaine

Outcomes	No. of studies/patients	WMD, i.v., random, OR, MH, 95% CI	*P*-value
Primary outcome			
Time to onset of sensory block (min)	10/565	−0.16 (−0.51, 0.19)	0.3
Secondary outcomes			
Time to complete motor block (min)	6/316	−2.4 (−3.97, −0.88)	0.002
Duration of motor block (min)	14/842	48.9 (35.53, 62.25)	<0.00001
Duration of sensory block (min)	8/484	40.25 (24.43, 56.08)	<0.0001
Time to first request for analgesic (min)	4/222	14.6 (0.95, 28.34)	0.04
Time to mobilization (min)	4/182	73.95 (49.53, 98.37)	<0.001
Incidence of hypotension	13/810	1.6 (1.04, 2.35)	0.03

mobilization, and a reduced incidence of hypotension. The onset of sensory block is similar with both drugs.

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Prolonged postoperative morbidity is an independent risk factor for reduced long-term survival

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Surgical mortality is a significant public health issue and there is wide variation in immediate postoperative mortality between institutions and countries.[1 2] Even for patients who survive to hospital discharge, previous data have indicated that there may be long-term consequences of postoperative complications.[3] Therefore, we have evaluated the relationship between postoperative morbidity and long-term survival, and adjusting for perioperative risk, in order to test the hypothesis that short-term postoperative morbidity is an independent determinant of long-term survival after surgery and that the level of this risk varies over time.

A total of 1362 patients were recruited into two observational studies at the Middlesex Hospital, UK, between 2001 and 2005.[4] Ethics approval was granted for both the original and follow-up studies. The following data were prospectively collected on all patients: patient characteristics, risk adjustment data (ASA and POSSUM score), operation name, postoperative length of stay, and outcome data (PostOperative Morbidity Survey on days 3, 5, 8, and 15). The Medical Research Information Service tracked each patient and notified us of the date of death or exit from the NHS.

Univariate analyses of long-term survival were conducted using the Kaplan–Meier plots. Variables identified on univariate analysis to be predictive of long-term survival with $P<0.05$ were selected for inclusion in a Cox regression multivariable analysis. Stepwise modelling, dropping variables based on significance testing, initially at $P>0.10$ and subsequently $P>0.05$, narrowed our initial model of 49 variables down to a final model of nine variables.

Our results show that, independent of pre- and intraoperative risk factors (gender, surgical speciality, and POSSUM score), the occurrence of neurological morbidity (prevalence 2.94%) after surgery is associated with a relative hazard for long-term mortality of 2.08 ($P<0.002$; 95% CI 1.37–2.61). Furthermore, if a patient has a prolonged length of stay with any type of morbidity (prevalence 15.57%), the relative hazard for death in the first 12 months post-surgery is 2.87 ($P<0.002$; 95% CI 1.85–4.43) and for the next 2 yr is 1.91 ($P<0.002$; 95% CI 1.27–2.88).

We believe that these are the first data to precisely demonstrate the trajectory over which postoperative morbidity continues to affect survival after surgery. Our findings have biological plausibility and strengthen the case for investment in research and infrastructure aimed at reducing the risk of perioperative morbidity.

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Systematic review and meta-analysis of the influence of anaemia on mortality in hip fracture

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Hip fractures are very common and with the increasing age of the population will continue to be responsible for a significant healthcare burden. Anaemia is common in these patients.[1] Studies of the association between anaemia and outcome have produced varied results. We undertook a systematic review of the literature. The population of interest was elderly patients sustaining a fragility hip fracture; the exposure anaemia [haemoglobin (Hb) <12 g dl^{-1}] and outcome mortality.

A systematic search was conducted of MEDLINE, EMBASE, Cinahl, and Amed databases. Titles and abstracts were screened to identify papers containing data on anaemia in hip fracture patients rejecting: duplicates; comparisons of surgical procedures; letters; review articles; and editorials. Full-text papers were assessed using The Newcastle-Ottawa quality assessment tool by two separate reviewers and agreement reached by consensus.

A total of 17 747 papers were identified on initial search, of which 17 relevant papers were identified; two of these were excluded for quality issues. Ten papers contained data on the relationship between admission haemoglobin and mortality and were included in the meta-analysis (Fig. 2). There was disparity in the definition of anaemia with five studies using

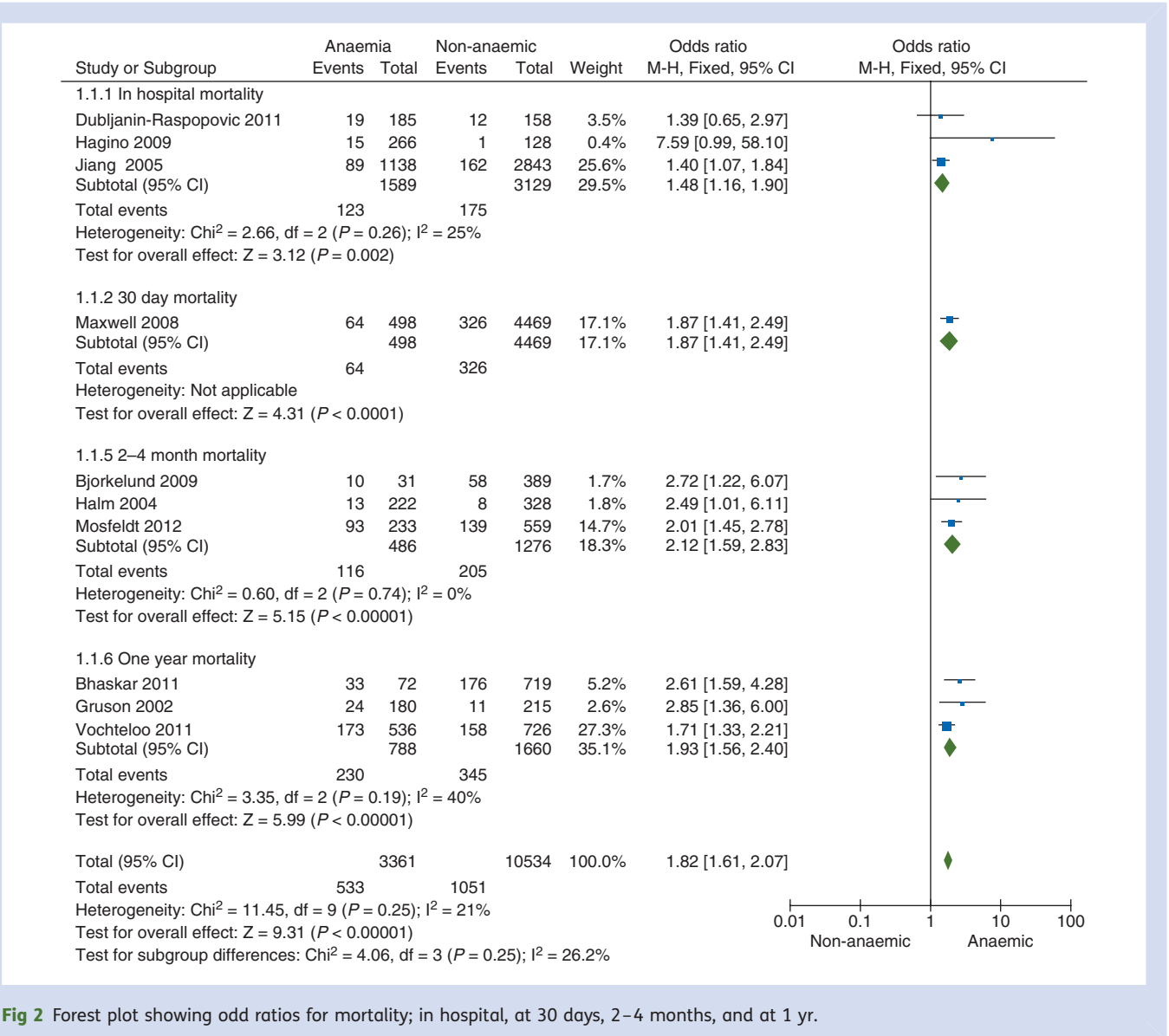

Fig 2 Forest plot showing odd ratios for mortality; in hospital, at 30 days, 2–4 months, and at 1 yr.

Hb <12 g dl^{-1} (women) and <13 g dl^{-1} (men), and four an Hb <10 g dl^{-1} and it was unspecified in one. The cohorts are from comparable populations of community-dwelling subjects, with only one study excluding patients with cognitive impairment and pre-fracture immobility.

Despite moderate differences in patients studied, there is a consistent association between admission anaemia and mortality, though these studies cannot address causation.

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Functional EIT with evoked response images reveal areas of changing conductivity in the brain during the Valsalva manoeuvre

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Functional EIT with evoked response (fEITER) is a functional neuroimaging device which has been used to monitor the brain of 15 volunteers performing the Valsalva manoeuvre (VM). Preliminary analysis of fEITER waveforms revealed conductivity changes in response to the VM.[1 2] Slower changes were attributed to haemodynamic changes in the brain, whereas sub-second changes were attributed to neuronal activity, resulting in autonomic outflow.[1] Reconstructed images have demonstrated sub-second conductivity changes in areas of the brain associated with autonomic responses to the VM. Voxel data relating to the insular and pre-frontal cortex were extracted and analysed.

Thirty-two Zipprep™ (Covidien, UK) electrodes were placed on the scalp of each volunteer according to the international 10–20 system of EEG electrode placement. Monitoring with fEITER was undertaken for 60 s; the VM was initiated at 10 s and released at 25 s. Voxel data relating to the insular and pre-frontal cortex were extracted from the images using MatLab and MayaVi software. Voxel data across all volunteers were pooled, normalized, and statistically analysed using the Wilcoxon signed-rank test.

Before VM onset, pooled voxel data for the insular and pre-frontal cortex were statistically compared with pooled voxel data for the same areas of the brain after onset of the VM using a sub-second epoch of 500 ms. Results demonstrated significant differences in conductivity at the insular and pre-frontal cortex after initiation of the VM (Wilcoxon signed-rank test, $P<0.0005$. See Fig. 3). The insular and pre-frontal cortex have previously been identified as neural components of initiating autonomic outflow in response to the VM using functional MRI.[3]

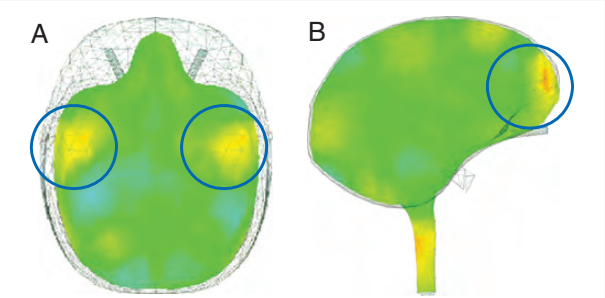

Fig 3 Single subject images of the brain during the VM. Conductivity changes are visible in circled areas relating to the insular (A) and pre-frontal cortex (B) after onset of the VM.

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Alterations of stimulus-induced gamma oscillatory activity during propofol sedation

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Stimulus-induced gamma oscillations in the 30–80 Hz range have been implicated in a variety of functions, including visual processing, memory, and attention.[1] Investigating the effect of sedation on these oscillations may provide an insight into sedative mechanisms. Therefore, we investigated the modulation of stimulus-induced gamma band activity during mild sedation using magnetoencephalography (MEG).

Fifteen right-handed, healthy male volunteers (mean age 26 yr; range 20–41 yr) participated in an MEG session which included a baseline recording (*awake state*) followed by a *sedated state* recording. Visual task: subjects were presented with a visual stimulus consisting of a vertical, stationary, maximum contrast, three cycles per degree, square-wave grating presented on a grey background. The duration of each stimulus was 1.5–2 s followed by 2 s of fixation cross only. Each recording session took ~8 min. MEG recording and analysis: whole-head MEG recordings were made using a CTF 275-channel radial gradiometer system sampled at 1200 Hz (0–300 Hz bandpass). Offline, data were first epoched from −1.5 to 1.5 s around stimulus onset and

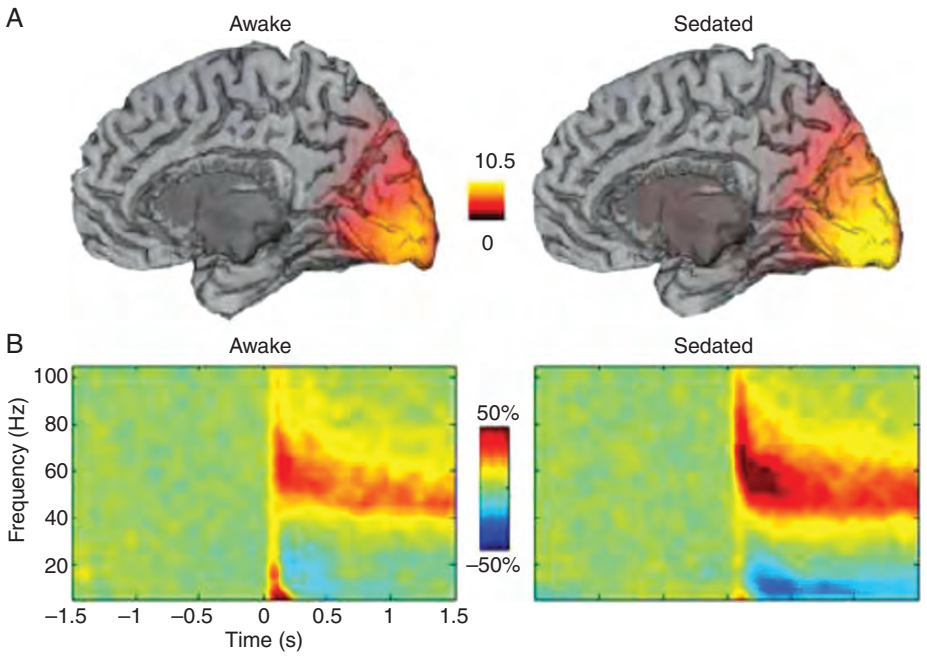

Fig 4 (A) Grand-averaged source localization of gamma oscillations (40–80 Hz) (*t* statistics). (B) Grand-averaged time-frequency spectrograms showing source-level oscillatory amplitude changes.

source localizations were performed using synthetic aperture magnetometry one for induced responses, and one for evoked responses. Time–frequency responses of the peak location voxel (MR scan) were generated to produce the amplitude envelope and percentage changes computed for each frequency band. The evoked field was also computed and the peak amplitude and latency of the M100 and M170 responses quantified. Sedation protocol: sedation was induced with propofol (TCI—Marsh protocol)[2] until a mild sedation (OAA/S level 4) was achieved.

The mean (SD) effect-site concentration of propofol required for mild sedation was 1.07 (0.2) μg ml^{-1}. During sedation, there was a significant increase in induced gamma band activity (60%; $P=0.01$), reduction in alpha amplitude (94%; $P<0.01$) while the evoked response showed a significant reduction in the amplitude of the first wave (M100; $P=0.008$) and the second wave (M150; $P<0.001$) and increased latency of M100 ($P=0.002$) (Fig. 4).

This is the first report of *in vivo* modifiability of stimulus-induced gamma oscillations. Since gamma oscillations are generated by GABAergic mechanisms, these findings suggest either a hypersynchronous cortical mechanism or alteration of long-range thalamo-cortical gamma oscillations, induced by propofol sedation.[3]

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Ventilator delivery systems for asthma inhalers

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Bronchodilators and steroid may be delivered to ventilated patients by inserting the aluminium part of a metered dose inhaler (MDI) into a port on a variety of devices manufactured expressly for that purpose.[1] MDIs delivering drugs to treat asthma use two different propellants, HFA 227ea (apaflurane) for sodium cromoglicate (Intal™, SanofiAventis, Guildford, Surrey, UK), budesonide/eformoterol (Vannair™; AstraZeneca, Auckland, New Zealand) and HFA 134a (norflurane) for Duolin™, salbutamol 100 μg and ipratropium 20 μg (Rex Medical Ltd, Auckland, New Zealand), and Respigen™, salbutamol (Mylan, Auckland, New Zealand); norflurane is an inhalation anaesthetic agent which has been studied in dogs.[2] Polyvidone 3 and polyethyleneglycol 600 help dissolve the powder of Intal, the inhaler contains 112 full doses of drug and each actuation produces 16 ml of drug and propellant. Vannair produces 9 ml of propellant and drugs, has a dose counter on the base of a small aluminium container, and contains 120 inhalations.

The method of measuring the propellant volume of norflurane MDIs has been described.[3] Four in-line devices for

Table 9 Oxygen percentages for each inhaler and device

	5×Duolin™ (9 ml per puff)	5×Respigen™ (11 ml per puff)	5×Vannair™ (9 ml per puff)	5×Intal™ (16 ml per puff)
L-Trace	88%	87%	89%	81%
Spirale	86%	87%	89%	82%
Intersurgical	87%	86%	87%	79%
RT 200	90%	91%	93%	91%

MDI delivery of drugs to intubated and ventilated patients were studied *in vitro*. An anaesthetic ventilator and tubing delivered 100% oxygen with a tidal volume of 500 ml at a rate of 12 bpm through each device attached to a size 7 mm i.d. 28 cm length cuffed tracheal tube inserted and sealed by cuff inflation in the opening of a 1 litre anaesthetic reservoir bag. From the distal end of the bag, gas contents were sampled by a Philips MP70 G5-O_2 analyser. When 100% oxygen content of the reservoir bag was seen, shaken inhalers of norflurane and apaflurane propelled drugs were separately actuated five times during a period between ventilations into the devices. The DDS Spirale® (Armstrong Medical, Coleraine, Northern Ireland, UK) system was used in the 'open' position and has no leak from the inhaler port when in the 'closed' position. The other three devices have caps to seal the inhaler port when not being used, an MDI delivery connector (1964001, Intersurgical, Berkshire, UK), and a single swivel tube inhaler, L-Trace (60-60-009, Jackson Allison, Auckland, New Zealand). The 'Three in one respiratory care system' RT 200 (Fisher&Paykel Healthcare, Auckland, New Zealand) has a port as part of the distal 'Y' of the tubing. Decreases in oxygen percentages were recorded for each inhaler and device.

Using the RT 200, five puffs of duolin *before* a respiratory filter/humidifer gave a 91% oxygen level. Decreases in oxygen levels are a result of the exertion of a propellant partial pressure and detrimental clinical effects are unlikely after five puffs (Table 9). Salbutamol and salbutamol/ipratropium are more useful bronchodilator drugs in acute asthma. Beneficial smooth neuromuscular blocking agent effects of norflurane and apaflurane need investigation.

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Adjustment of extravascular lung water calculation for volume of resected lung does not improve construct validity in thoracic surgical patients

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Acute lung injury complicates the postoperative course of 5–10% of patients undergoing lung resection and carries a high mortality. Transpulmonary thermodilution (TPTD) may be a useful monitoring modality during the postoperative period, allowing determination of extravascular lung water index (ELWI).[1] TPTD assumes the ratio between intrathoracic blood volume and global end-diastolic volume is constant (ITBV/GEDV=1.25). This assumption has been questioned in the context of lung resection where pulmonary blood volume (PBV) might be expected to decrease; potentially resulting in underestimation of ELWI.[1 2] We compare unadjusted ELWI (ELWIn) with values adjusted for the volume of resected lung tissue according to a novel proprietary algorithm (Edwards Lifesciences—ELWIe) and with a value derived by an anatomical segment counting approach (ELWIa) in patients undergoing lung resection to test the hypothesis that adjusted values of ELWI will improve the construct validity of ELWI measurement in this context.

The need for ethical approval was waived by the West of Scotland Research Ethics Committee. We performed TPTD monitoring using the EV1000 platform (Edwards Lifesciences) during the postoperative period in eight patients undergoing lung resection. TPTD was performed in triplicate at 6 h intervals up to 42 h after operation. Construct validity was determined by assessing Spearman's correlation between ELWI values, oxygenation indices and chest X-ray (CXR) scores. Analysis was performed using SPSS v19.

The mean age of the study group was 64.6 yr (range 52–73). Patients underwent pneumonectomy (n=1), bi-lobectomy (n=2), lobectomy (n=4), and sub-lobar resection (n=1). Sixty-four TPTD results were available for paired comparison with 62 $Pa_{O_2}/F_{I_{O_2}}$ (mm Hg), 61 $Sa_{O_2}/F_{I_{O_2}}$ (%), and 19 CXR scores, respectively.

Adjustment of extravascular lung water calculation for volume of resected lung does not improve construct validity. Association between ELWI and oxygenation indices is weakened or lost after adjustment for the volume of resected lung tissue (Table 10). We hypothesize that after resection, PBV does not decrease to the extent predicted by the ELWIe and ELWIa algorithms due to recruitment of previously non-perfused

Table 10 Association between ELWI values, oxygenation indices, and CXR scores. Spearman's correlation, $^{**}P<0.01$; $^{*}P<0.05$

	ELWIn	ELWIe	ELWIa
$Pa_{O_2}/F_{I_{O_2}}$	−0.52**	−0.06	−0.37**
$Sa_{O_2}/F_{I_{O_2}}$	−0.33**	−0.09	−0.19
CXR score	0.51*	0.31	0.59**

pulmonary vasculature; resulting in relative maintenance of ITBV/GEDV. The explanation for the relative underperformance of ELWIe is unclear, but may reflect the inability of the ELWIe algorithm to accommodate bi-lobectomy.

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Comparison of three advanced haemodynamic monitors to measure circulating volume status during major rectal surgery

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UK guidelines support the intraoperative use of advanced haemodynamic monitors to guide fluid therapy during major surgery.[1] Several of the minimally invasive technologies currently available are unvalidated in this setting. We simultaneously compared uncalibrated pulse power analysis with a pulse wave transit time method to measure cardiac index (CI) and with a plethysmography variability index method to characterize circulating volume.

We studied 24 patients during rectal resection under general anaesthesia (age range 24–84, open 18, lap-assisted 6). Continuous non-invasive monitoring of CI (EsCCO, Nihon Kodhen, Japan) was initiated before the induction of anaesthesia. After induction, a radial arterial cannula was placed and continuous arterial pulse power analysis commenced (LiDCOrapid, Cambridge, UK). Paired CI readings by EsCCO and LiDCO, and indices of intravascular filling: stroke volume variability, SVV (LiDCO), and plethysmography variability index PVI (Rainbow 7 oximeter, Masimo, CA, USA) were recorded immediately before and after surgical incision and then at 15 min intervals until the conclusion of surgery.

A total of 356 paired readings were available for comparison of CI between monitors (Fig. 5).

Three hundred and seventy-eight paired readings were available for comparison of SVV and PVI. Within-patient correlation between PVI and SSV was 0.19; 95% CI 0.09–0.29.

There are wide limits of agreement between LiDCO and EsCCO for the measurement of CI in this population. Correlation between LiDCO SVV and Masimo PVI for the characterization of circulating volume was weak.

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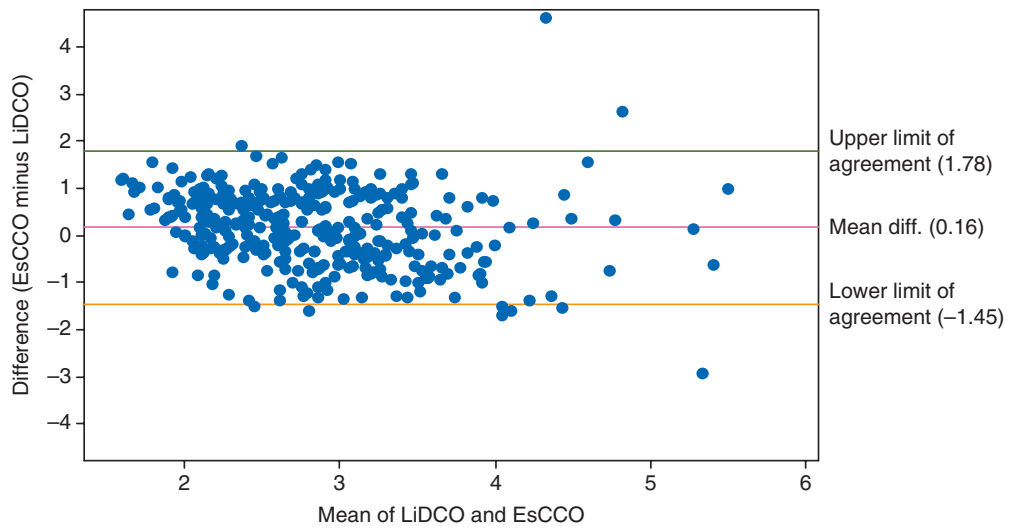

Fig 5 Bland–Altman plot LiDCO *vs* EsCCo determination of CI. Average difference between methods 0.16 litre min^{-1} m^{-2}; 95% confidence interval 0.08–0.25. Limits of agreement −1.45 to + 1.78 litre min^{-1} m^{-2}. The plot indicates increased variability at CI>4 litre min^{-1} m^{-2}.

Calibrating functional magnetic resonance imaging using hypercapnia and hyperoxia to provide $CMRO_2$ maps of the brain

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The rate at which the brain metabolizes oxygen is referred to as the cerebral metabolic rate of O_2 ($CMRO_2$) and is a direct indicator of cerebral health. By mapping the regional and spatial extent of O_2 metabolism in the brain, essential insights can be made into the underlying metabolic changes that occur during the treatment and progression of numerous brain diseases while also providing an important diagnostic tool.[1 2] $CMRO_2$ is intrinsically linked with the fMRI (functional magnetic resonance imaging), BOLD (blood oxygen level dependent) signal, and CBF (cerebral blood flow), which can both be measured using MRI. By performing hypercapnic and hyperoxic respiratory manipulations and concurrently acquiring BOLD and CBF time series, we prove this relationship can be exploited to produce whole brain absolute $CMRO_2$ maps.

Using a 3T GE HDx MRI 7 healthy participants [aged 27–39; mean age 34.7 (3.8); 1 female] were scanned and simultaneous BOLD and CBF time series data were collected. At the same time, an interleaved respiratory manipulation was delivered using a system for dynamic end-tidal forcing,[3] allowing independent control of end-tidal partial pressures of oxygen ($P_{E'_{O_2}}$) and carbon dioxide ($P_{E'_{CO_2}}$). The respiratory manipulation consisted of five 1 min periods of hyperoxia (+200 mm Hg above normoxia) that were bookended by two 2.5 min periods of hypercapnia (+8 mm Hg above normocapnia). One minute intervals of normocapnia and normoxia (rest) began and ended the session and all following challenges were followed by 1 min of rest throughout the session. The total duration of the session was 18 min. BOLD, CBF, $P_{E'_{O_2}}$, and $P_{E'_{CO_2}}$ time series were then plugged into a BOLD signal model[4] in order to calculate cerebral venous oxygen saturation (Sv_{O_2}) and in turn absolute $CMRO_2$.

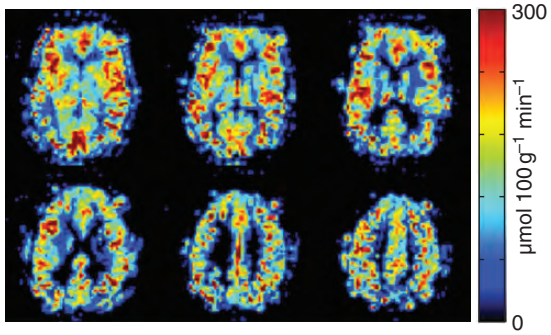

Fig 6 Example of whole brain absolute $CMRO_2$ map from a single subject.

Analysis was done on a voxel-wise basis and whole brain absolute $CMRO_2$ maps were successfully produced in all seven subjects. Images show the expected contrast between grey and white matter of the brain with grey matter exhibiting higher oxygen metabolism as expected (Fig. 6). Average grey matter values across all subjects were as follows: CBF=50 (6) ml 100 g^{-1} min^{-1}, Sv_{O_2}=0.58 (0.06), and $CMRO_2$=167 (38) μmol 100 g^{-1} min^{-1}. These values agree well with positron emission tomography (PET), currently the gold standard for ascertaining $CMRO_2$, values from the literature.[5]

Initial results in a healthy cohort indicate promise for this technique with clinical and pharmacological applications in diseases where $CMRO_2$ becomes altered.

Acknowledgement

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Changes in objectively measured physical fitness after long-course neoadjuvant chemoradiotherapy and a 6 week prehabilitation programme in locally advanced rectal cancer patients: a blinded interventional study

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In the UK, it is standard practice for locally advanced rectal cancer patients to receive 5 weeks of long-course neoadjuvant chemoradiotherapy (NACRT). However, the effects of NACRT on physical fitness are largely unknown. We aim to investigate the effect of NACRT and the effects of a 6 week structured, responsive, exercise, training programme

(SRETP) on objectively measured physical fitness in resectable rectal cancer patients.

We prospectively studied 18 consecutive patients (11 male and 7 female) with T3-4/N+ rectal cancer who completed a standardized 5 weeks of long-course NACRT. All patients underwent a cardiopulmonary exercise test (CPET) immediately before and after NACRT (Week 0), Week 3, and Week 6 of the exercise programme. All patients undertook a 6 week structured exercise programme on a training bike (30–40 min per session, three sessions per week). The training intensities were responsive to each CPET and were of a moderate-to-severe intensity.

The median age was 66 yr. The mean BMI was 26.1 kg m^{-2}. Post-NACRT illustrated significant reductions in VO_2 at lactate threshold (LT) (12.0–10.4 ml kg^{-1} min^{-1}; $P<0.01$), VO_2 at peak (18.5–16.3 ml kg^{-1} min^{-1}; $P<0.0001$), and O_2 pulse at LT (8.3–7.5 ml kg^{-1} min^{-1}; $P<0.001$). After 6 weeks of SRETP, there was a significant increase in VO_2 at LT (10.4–12.7 ml kg^{-1} min^{-1}; $P<0.001$) and peak (16.3–19.3 ml kg^{-1} min^{-1}; $P<0.001$), O_2 pulse at LT (7.5–8.9 ml $beat^{-1}$; $P<0.001$). Work rate at LT and work rate at peak also improved significantly.

NACRT before major rectal cancer surgery significantly reduces objectively measured physical fitness as assessed by CPET. This may increase perioperative risk and thereby alter postoperative outcome. After SRETP, we observed an increase in VO_2 at LT and peak, O_2 pulse, and work rate at LT and peak, illustrating the improvement of objectively measured physical fitness before major rectal cancer surgery. This study illustrates the proof of principle that rectal cancer patients can be trained in the available time before major surgery and that this candidate intervention can be used to improve surgical outcome.

Cardiopulmonary exercise variables predict postoperative in-hospital morbidity after major rectal cancer surgery: a blinded observational study

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Patients with reduced cardiopulmonary fitness are more likely to encounter postoperative complications. Cardiopulmonary exercise testing (CPET) has never been used to risk assess rectal cancer patients. We aim to investigate the use of CPET variables as predictors for postoperative complications in patients undergoing major elective rectal cancer resection.

We prospectively recruited 95 consecutive patients who underwent CPET to assess their cardiopulmonary fitness before major surgery. All surgeons and anaesthetists were blinded to CPET results. CPETs were reported in a blinded fashion. All outcome data were collected prospectively.

Ninety-six patients (72 males) were included. Forty-six (48.4%) encountered an in-hospital complication. Seventy-two per cent underwent neoadjuvant cancer treatment. CPET variables included: oxygen uptake (VO_2) at anaerobic threshold (LT) 11.2 ml kg^{-1} min^{-1} (IQR 9.4–13.4) and VO_2 peak 18.9 ml kg^{-1} min^{-1} (SD 5.81). ROC curve analysis of VO_2 at LT (cut-off value 10.6 ml kg^{-1} min^{-1}) and VO_2 peak (cut-off value 18.6 ml kg^{-1} min^{-1}) gave AUC values of 0.87 (95% CI 0.78–0.95, $P<0.001$) and 0.85 (95% CI 0.77–0.93, $P<0.001$), respectively. Multivariable logistic regression was calculated using gender, age, and operation type alongside VO_2 at LT (dichotomized around the median 11.2 ml kg^{-1} min^{-1}): OR 0.07 (95% CI: 0.03–0.19), $P<0.001$ and VO_2 at peak (one-point change above the median): OR 0.75 (95% CI 0.66–0.85), $P<0.001$. We found no differences in complications between patients having neoadjuvant treatments and those going straight to surgery (Fisher's exact test $P>0.05$).

Both VO_2 at LT and peak are able to effectively predict postoperative complications after elective rectal cancer resection. An increase in VO_2 at peak of 1 ml kg^{-1} min^{-1} reduces the odds of complications by 25%, while VO_2 at AT of $\geq$11.2 ml kg^{-1} min^{-1} reduces the odds of complications by 93%. Appropriately identifying high-risk patients can allow for tailored perioperative management along with the introduction of a preoperative exercise training programme that might improve surgical outcome.

Study to investigate the correlation between non-invasive cardiac output monitoring and oxygen consumption during exercise testing

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Cardiac failure is the most important risk factor for postoperative mortality. Cardiopulmonary exercise testing (CPET) is utilized before operation to identify heart failure. Although a reduced peak VO_2 and anaerobic threshold are markers of cardiac failure, their values are also influenced by other factors, for example, anaemia. We hypothesized that a more objective measure of cardiac output response to exercise may offer utility over CPET in identifying cardiac failure. The NICOM (Cheetah Medical) provides an indirect measure of cardiac output using bioreactance technology. The peak cardiac power measured during exercise using

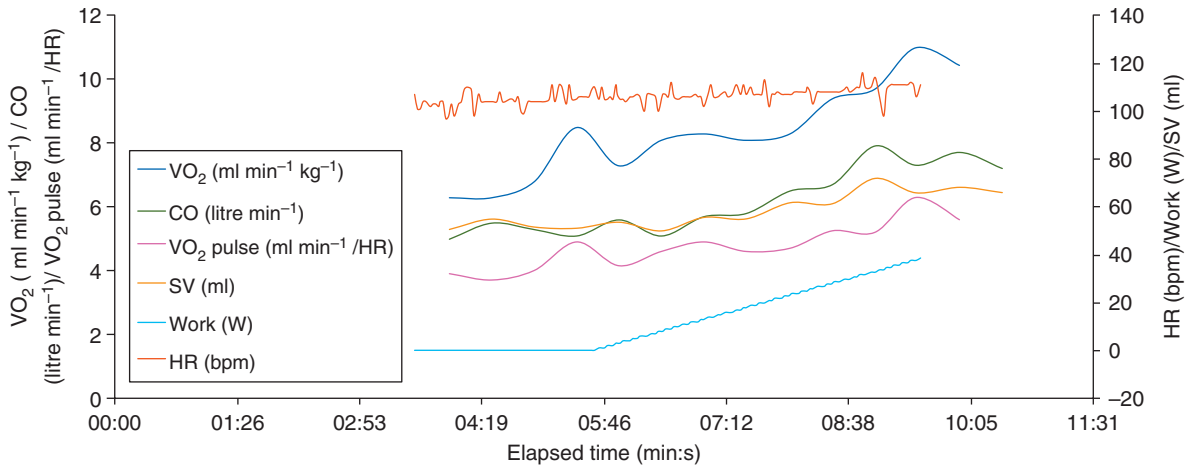

Fig 7 Graph to show NICOM and gas exchange (CPET) with increasing load.

NICOM has been shown to be a better prognostic indicator in heart failure than peak VO_2. There are no published data examining the potential role of exercise NICOM in the preoperative population.[1 2]

Twenty-three consecutive patients referred for preoperative CPET were additionally monitored during exercise using NICOM. A bicycle ergometer (Lode) was used with a variable ramp load of 10–20 W min^{-1} applied. Breath-by-breath analysis was performed using a Medgraphics Ultima $CardiO_2$ measurement system. Patients exercised to a symptom-limited maximal effort with oxygen consumption (CPET) and stroke volume and cardiac output (NICOM) measured throughout the test (Fig. 7).

Data were analysed calculating correlation coefficients with repeated observations between subjects using Bland and Altman's methods (there were 9 exclusions). Significant correlation between patients was seen when comparing VO_2 pulse (ml min^{-1}/HR) and stroke volume (ml) ($r=0.7$, $P<0.0001$) and VO_2 (ml min^{-1}) and cardiac output (litre min^{-1}) ($r=0.82$, $P<0.001$).

Further research is required to assess whether exercise NICOM offers utility in identifying the high-risk surgical patient.

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Human γδ T cells in severe bacterial sepsis

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Severe sepsis kills more people than breast cancer and traffic accidents combined.[1] Many of these deaths will occur on an intensive care unit after prolonged and costly hospital stays. Despite advances in patient management and the introduction of new treatments, the mortality associated with severe infection remains unacceptably high and largely unexplained. [2] With the overwhelming failure of drugs designed to modulate the early pro-inflammatory phases of sepsis,[3] focus has now moved to the immunosuppression seen in the later stages of the disease.[4] Coupled with high levels of late mortality, this stage of sepsis has great potential for exploitation. γδ T cells are unique to humans and primates and represent only a minor population in the peripheral circulation; yet they expand dramatically in many infections and may exceed all other lymphocyte populations within days.[5] These cells differ fundamentally from other human T cells. They occupy a unique niche in microbial recognition as they are directly activated by (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP), an essential metabolite in some Gram-positive and most Gram-negative bacteria. The innate-like capacity of γδ T cells to recognize HMB-PP offers a simple means to respond to numerous pathogens, by targeting a vital metabolic route shared by these organisms.

By sampling whole blood at Day 1 and 5 from 60 patients with severe sepsis requiring intensive care admission, we have used multi-colour flow cytometry to identify all major leucocyte populations together with their expression of activation and differentiation markers *ex vivo*. Cytokine analysis was performed using the Meso Scale Discovery system.

We show that severe sepsis with HMB-PP-positive infections carry rates of mortality double that caused by HMB-PP negative infections (Fig. 8). We show that these infections are linked with excessive levels of pro-inflammatory cytokines and activation of γδ T cells. We show clear evidence of Day 1 monocyte down-regulation of surface CD86 and HLA-DR expression that may represent early immunosuppression. We show early evidence that by activating γδ T

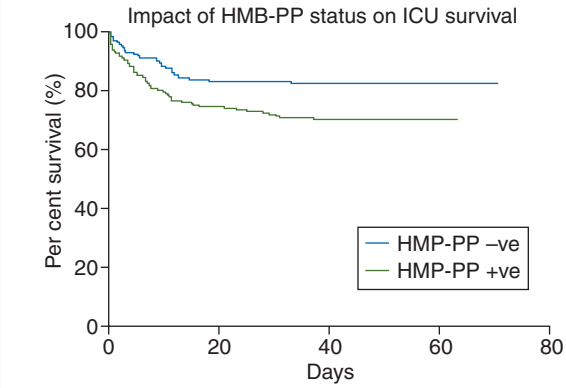

Fig 8 Kaplan–Meir analysis showing an elevated mortality rate of 35% in HMB-PP+ infection *vs* 17% in HMB-PP-infections.

cells in the later stages of sepsis, we may reverse these monocyte changes indicative of immunosuppression.

These two conflicting roles of γδ T cells highlight a new emerging picture of sepsis as a disease process where immune timing, balance, and individualized targeted therapies are key concepts that should to be explored and embraced.

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POSTER PRESENTATIONS

Argon combined with hypothermia protects against hypoxia–ischaemia-induced brain damage in rat neonates

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Hypoxic-ischaemic encephalopathy in newborns is a major cause of mortality and disability. Currently, there is no effective treatment apart from therapeutic hypothermia, which provides moderate neuroprotection.[1–3] Argon, an abundant and inexpensive noble gas, has recently been demonstrated to be neuroprotective.[4] In this study, the effects of argon in combination with hypothermia on neuronal cell death and neuroinflammation induced by hypoxic-ischaemic insult were investigated in a neonatal asphyxia model in rats.

Seven-day-old rats were subjected to unilateral common carotid artery ligation under 1–2% isoflurane anaesthesia (the total anaesthesia time <10 min) followed by hypoxic (8% oxygen balanced with nitrogen) insult for 90 min in a purpose-built chamber equipped with a water bath at 37°C. After 1 h recovery with dame, they were exposed to 70% argon or nitrogen balanced with oxygen at 35°C, or nitrogen balanced with oxygen at 37°C for 2 h. Their brains were removed 24 h or 4 weeks after gas exposure for immunofluorescence staining and histological analysis, respectively.

Argon in combination with hypothermia decreased the fluorescence intensity of cleaved caspase-3 (an apoptotic marker) staining to 1.11 (0.06) arbitrary unit from 1.72 (0.09) of the injurious controls ($P<0.01$) in the cortex and to 1.10 (0.04) from 1.72 (0.07) of controls ($P<0.01$) in the hippocampus. NF-κB, an inflammatory marker, was also reduced in the cortex [1.16 (0.06) *vs* 1.76 (0.09) of injury controls, $P<0.001$] and hippocampus [1.04 (0.06) *vs* 1.92 (0.31) of injury controls, $P<0.05$] with the treatment. Another neuroflammatory sign astrogliosis induced by hypoxia-ischaemia in the hippocampus was significantly decreased in the treated group. Argon combined with hypothermia reduced infarction size by 54% ($P<0.001$) when compared with that of injurious controls. Hypothermia alone also conferred a protection but to much less extent when compared with the combined treatment.

Argon combined with moderate hypothermia provides substantial neuroprotections against cerebral hypoxia–ischaemia damage in newborns by reducing neuroapoptosis and neuroinflammation.

Acknowledgement

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Non-invasive optical estimation of local venous oxygen saturations

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Breathing causes variations in blood volume in the peripheral vascular bed, which are evident as respiratory-induced intensity variations on recorded photoplethysmography (PPG) signals during spontaneous and mechanical ventilation.[1] It has been suggested that suitable signal analysis of PPG signals in the respiratory frequency range can produce estimations of local venous oxygen saturation (Sxv_{O_2}).[2] Although

saturations lower than those of arterial blood have been obtained from PPG analysis of oesophageal[2] and peripheral measurements, these have not been validated by comparison with co-oximetry of venous blood. The aim of this study was to record PPG waveform effects and derived venous saturations during exaggerated inspiratory and expiratory airway pressures in volunteers.

Twelve healthy volunteers performed unforced breathing for 1 min, followed by 2 min of forced breathing through a narrow tube. Airway pressure monitored from the mouthpiece was displayed in real time on a computer screen so that the volunteers could aim for recommended rate, rhythm, and airway pressure values. At the end of the recording period, venous blood, sampled from the dorsum of the hand, was analysed in a co-oximeter (Radiometer ABL80). PPG-derived venous saturations were estimated using the Fourier analysis of PPG signals in the respiratory frequency range.

The preliminary data (Fig. 9) showed good correlation between PPG-derived Sxv_{O_2} and blood co-oximetry values (r=0.805, mean difference=+2.3, n=12). These results justify further studies in volunteers and mechanically ventilated patients.

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Use of a photographic overlay technique to revisit mechanisms and limitations of Macintosh laryngoscopy

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A mathematical ('JISTX') model for Macintosh use based on X-ray laryngoscopy images was revisited using a novel photographic overlay technique.[1 2] The previous model described an index to predict difficult Macintosh laryngoscopy (F value) and a causative 'Peardrop' effect. The aim of this clinical study was to revisit the mechanisms and limitations of the device.

Thirty-six patients undergoing elective tracheal intubation as part of their clinical care were recruited. Standardized lateral photographs taken at the moment of maximal laryngeal exposure were overlaid with equivalent images of the Macintosh laryngoscope blade. After processing at life size, the images were marked up for analysis with a modification of the JISTX lines and for new measure of 'inevitable residual volume' (IRV) of the tongue using AnalyzingDigitalImages software.[3] The POGO (percentage of glottic opening) view obtained was analysed by regression modelling relative to preoperative measures, basic overlay measures, and new area measures of tongue distribution.

Worsening of POGO view was related to increasing blade eyeline deviation (P=0.000). Equally the POGO view was negatively correlated with area representing the IRV of the tongue (P=0.000), while, as expected, the F value was positively correlated (P=0.008) (Fig. 10).

The new method confirmed and enlarged on the original idea that the partial peradrop effect is an everyday aspect of Macintosh use and suggested a mismatch between IRV (residual tongue) and F (space available to accommodate it) as the basis for most causes of difficulty and that each might be predicted from preoperative measures.

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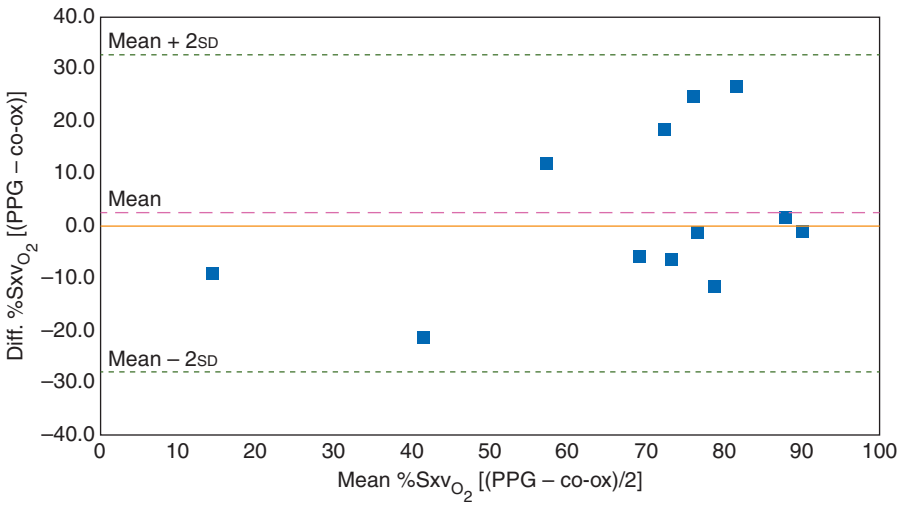

Fig 9 Bland–Altman plot comparing PPG-derived and co-oximetry (co-ox) results.

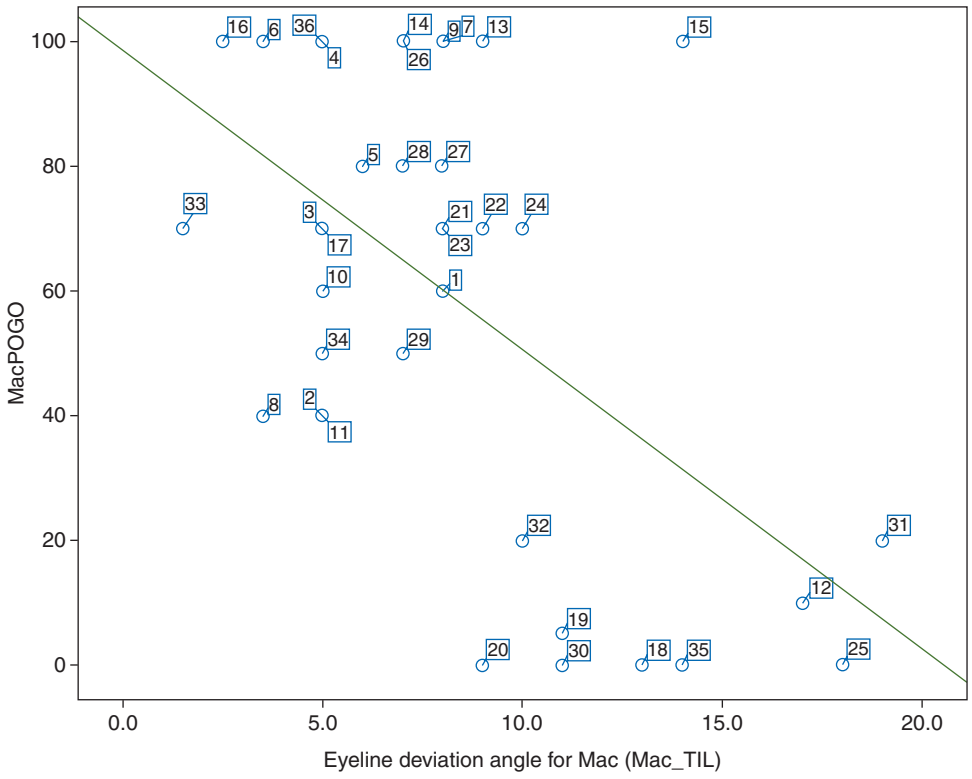

Fig 10 Scatter plot showing correlations between Macintosh POGO score and Eyeline deviation angle, Mac_IL (individual cases are labelled).

3 Digital Earth Watch software by Global Systems Science website. Available from http://www.globalsystemsscience.org/software/download

Altered phosphotidylcholine synthetic pathways in patients with acute respiratory distress syndrome

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Phosphatidylcholines are an integral part of pulmonary surfactant and cellular membranes and are synthesized *de novo* by two clinically distinct pathways. The molecular specificity of PC output varies between these pathways, where mono and di-unsaturated PC species are predominantly generated by the cytidine diphosphate choline (CDP-choline) pathway and polyunsaturated fatty acids (PUFA) by phosphatidylethanolamine-*N*-methyltransferase (PEMT) pathway. PUFA are capable of generating eicosanoids and have been long recognized as mediators of inflammation in various acute and chronic inflammatory conditions. ARDS is characterized by acute overwhelming inflammatory process and alterations in the eicosanoid profile is a recognized feature. Consequently, this study was aimed to assess the molecular specificity of PEMT pathway in patients with severe ARDS.

We recruited 10 patients with severe ARDS ($Pa_{O_2}/F_{I_{O_2}}$ $<$100 mm Hg) and 10 healthy controls. Both groups were infused with a natural isotope of choline (methyl-$_{D9}$-choline chloride). Blood samples were obtained at serial time points until day 4 of recruitment. Samples were centrifuged and the supernatant was lipid extracted. This was analysed by electro-spray ionization mass spectrometry where the phosphocholine head group was identified by *m/z*+184 and subsequent *m/z*+187 for one and *m/z*+190 for two deuteriated methyl group incorporations. From this, we estimated quantitative flux through PEMT pathway for all patients.

At maximal synthesis, there was a significant reduction in total PC synthesis in patients via PEMT pathway (44% absolute reduction). This was coupled with reductions in the rate of total PC synthesis and absolute concentrations of PUFA-based PC species in plasma. The molecular specificity of PC synthesis was similar for both groups, where PUFA species (e.g. 20:4 and 22:6) were highly selective through this pathway.

In conclusion, there are significant alterations in PC synthetic pathways in patients with ARDS. Therapeutic modulation of PUFA may moderate inflammatory process in ARDS.

Acknowledgement

This study was supported by Southampton NIHR Respiratory Biomedical Research Unit and The National Institute of Academic Anaesthesia (NIAA), UK.

Does levobupivacaine rectus sheath block improve postoperative analgesia after open gastric bypass surgery?

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There are very few data as to the best approach to postoperative analgesia after midline laparotomy for open gastric bypass surgery. Epidural analgesia remains the 'gold standard' for patients undergoing upper abdominal surgery, but is technically challenging and frequently impractical in the morbidly obese. Consequently, i.v. morphine via patient-controlled analgesia (PCA) is the mainstay of postoperative analgesia in this patient population. I.V. morphine is associated with variable analgesia, drowsiness, respiratory depression, and centrally disordered respiratory control. We have therefore performed a randomized controlled trial pilot study to examine whether rectus sheath block before wound closure improves postoperative pain scores and reduces PCA morphine consumption.

We performed a prospective, randomized, double/single-blind controlled pilot study in 60 female patients undergoing open gastric bypass using standardized anaesthetic and surgical techniques. The study group Levobupivacaine (chirocaine, LA, 20 patients) received local infiltration 0.5% levobupivacaine 40 ml into the rectus abdominis muscle by the surgeon before wound closure; the positive control group (placebo, C+, 20 patients) received an equivalent volume of 0.9% saline infiltration; and the negative control group (control, C−, 20 patients) no infiltration. All received a postoperative loading dose of morphine sulphate of up to 0.1 mg kg^{-1}, morphine PCA, and an induction dose of diclofenac 100 mg. Anthropometric data, morphine usage, and visual analogue pain scores were collected at 0, 1, 4, 12, and 24 h.

Visual analogue pain scores (VAS) and morphine use (Fig. 11) were lower in the LA group when compared with the combined control group at multiple (but not all) time points in the postoperative period, the differences disappearing with time. The greatest differences were seen between the LA and C+ groups, with the LA and C− groups behaving similarly to one another.

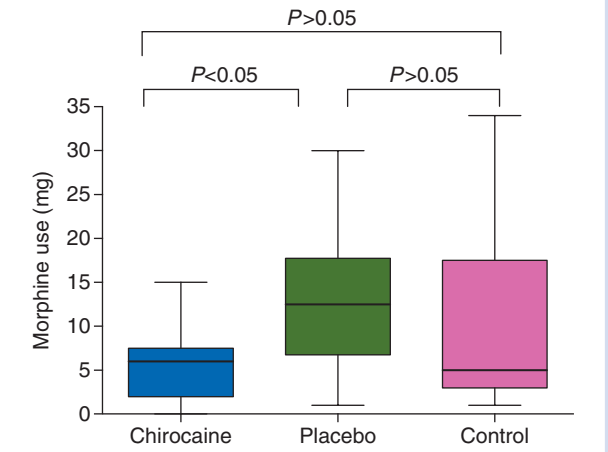

Fig 11 Morphine use at 1 h.

This study demonstrated an analgesic effect of rectus sheath block against a pooled positive/negative control group, but heterogeneity in the control calls into question whether this was solely due to analgesic benefit of the block or related to increased pain in those receiving saline placebo.

Eudract number 2005-000803-32

Establishment of a trainee-led multicentre anaesthetic research and audit network

South West Anaesthetic Research Matrix ('SWARM')

Southwest Peninsula Deanery, Plymouth, UK

For full contributor list, see http://www.ukswarm.com

The relatively short duration of rotational training posts presents a barrier to trainee-led audit and research. We established a network linking all six centres in the South West School of Anaesthesia and carried out a collaborative multicentre audit as a proof of concept.

Thirty-eight of 63 respondents to an e-mail survey of anaesthetic and intensive care trainees in the school (n=167) declared that they not been involved in research and only nine had been involved in a multicentre trial. A senior trainee, mentored by a consultant, addressed this unmet need by setting up a collaborative network to initiate and carry out a large clinical project. With the support of the Professor of Anaesthesia, Regional Advisor and Specialist Training Committee, we invited expressions of interest then nominated a central board and trainee representatives at each site. Consultant mentors at all sites were nominated by informal means with the endorsement of clinical governance and research leads and college tutors.

A multicentre audit, 'SWARM AP 1', was conducted in all sites simultaneously over 2 weeks in July 2012. We aimed

to collect audit data for every operation carried out in the designated emergency theatre. Emergency theatre caseload and supervision was benchmarked against RCoA targets (Table 11).[1] Data were anonymized and centralized using Internet-based software (SurveyMonkey™).

Eighty-two anaesthetists collected detailed audit data from 437 of 513 cases with summary information on the others retrieved from hospital systems. Two hundred and sixty of the 437 (59.5%) audited cases commenced 08:00–18:00 (target 60%), 139 (31.8%) commenced 18:00–00:00. Thirty-eight (8.7%) commenced 00:00–08:00 (target 5%): 21 (55%) of these met the NCEPOD definition of 'emergency' (target 100%).[1] Fifty-five of 437 (12.6%) audited cases were ASA IV or V.

All participating centres produced acceptable data collection rates. This collaboration demonstrates the potential of a trainee-led network to generate and deliver a useful project.

Funding

Supported by a Peninsula Deanery Education Innovation Grant.

Reference

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Xenon or nitrous oxide reduce but isoflurane enhances amyloid β-induced neuronal death *in vitro*

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Alzheimer's disease (AD), a progressive neurodegenerative disease and the most common form of dementia in older people, may be associated with exposure to anaesthesia and surgery.[1] AD-affected brains have raised levels of amyloid beta (Aβ), a naturally occurring peptide with unclear physiological and pathological roles. We have examined how co-exposure to Aβ and inhalation anaesthetic agents affect cortical neuronal viability in primary cultures.

Primary mouse cortical neurones were derived from prenatal mouse pups and cultured in Neurobasal media supplemented with B27 for 7 days. At the start of anaesthetic, exposure media was changed to one containing 0.8 μM Aβ1-42 and cells were incubated in an atmosphere containing isoflurane (0.5%, 1.5%, and 2%), nitrous oxide (25%, 50%, and 74%) and xenon (25%, 50%, and 74%), in 21% O_2 with 5% CO_2, balanced with nitrogen at 37°C for 24 h. Cell viability was then immediately determined using MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide] assay and compared with naïve control cells exposed only to air with 5% CO_2, at 37°C.

Cell viability was reduced by exposure to 0.8 μM Aβ1-42 alone for 24 h by more than 50%. Viability was further reduced by increasing concentrations of isoflurane, but preserved by increasing concentrations of xenon and nitrous oxide ($P<0.05$) (Fig. 12).

These data may suggest that in the AD-affected brain, clinically used isoflurane concentration may show greater neurotoxicity when compared with clinically used concentrations of other inhalation anaesthetic agents.

Funding

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Table 11 Recruitment to multicentre audit, and selected results stratified by centre

Centre	Caseload, audited/total, *n* (%)	Audited operation commenced, 00:00–08: 00, NCEPOD 'Emergency'/ total audited, *n*	Audited patient ASA IV or V, with consultant in theatre/total audited, *n*
A	45/65 (69)	1/1	8/9
B	33/44 (75)	3/3	3/3
C	56/73 (77)	1/4	7/7
D	104/119 (87)	10/17	14/25
E	94/107 (88)	2/4	4/4
F	105/105 (100)	4/9	7/7
Total	437/513 (85)	21/38	43/55

Multicentre observational audit of arterial catheter thrombosis in the North-Western region of England

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Arterial catheters are commonly used in anaesthesia and in critical care for pressure monitoring and blood sampling. The transducer is attached to a pressurized flushing solution in order to reduce the incidence of catheter thrombosis. A National Patient Safety Agency (NPSA) alert in 2008[1] highlighted the potential dangers of different flush solutions,[2 3] recommending that only 0.9% saline flush be used. This represented a change in practice for many hospitals that were using heparinized saline flush ('Hepsal' 10 IU ml^{-1}). Our aim was to survey current practice and observe associated catheter occlusion rates in the Association of North-Western Intensive Care Units (ANWICU) in England.

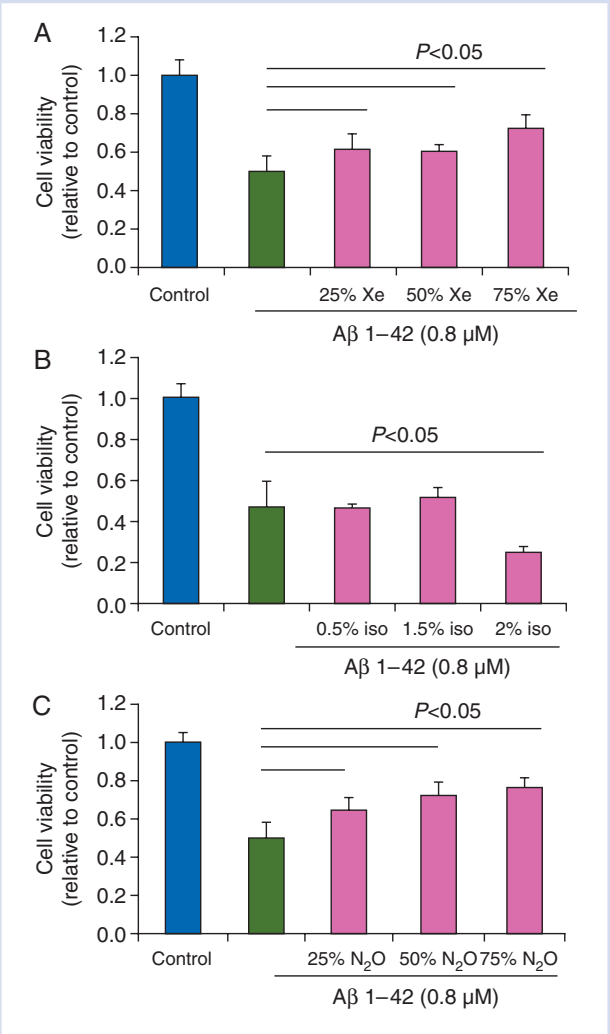

Fig 12 MTT assay data from primary neuronal culture. Exposure to Aβ1–42 at 0.8 μM reduced cell viability (green bar), when compared with control conditions. Isoflurane 2% exposure increased Aβ1-42 toxicity, whereas N_2O and xenon increased cell viability at all concentrations tested. n=10–12 per group. Mean (SD).

A prospective survey was performed over the period of one calendar month at eight member hospitals of the North-Western Learning and Development Group of ANWICU (kNOWLEDGe). A data collection form was completed on insertion and removal of arterial catheters. Information was collected on the flush solution and system used, type and site of catheter, number of hours the catheter was *in situ*, and the reason for removal. Data were pooled and analysed using SPSS 19.0 (IBM systems).

Of the eight participating hospitals (four teaching, four district general), five exclusively used saline as flush solution, two used heparinized saline, and one used both. Complete data for 445 catheters demonstrated the mean lifespan of an arterial catheter was 111 h (95% CI 101–121 h). Catheters with heparinized flush solution (n=151, 34%) had an increased mean lifespan of 136 (117–155) *vs* 98 (87–109) h for saline-flushed catheters (n=294, 66%) (P<0.01, Mann–Whitney U-test)

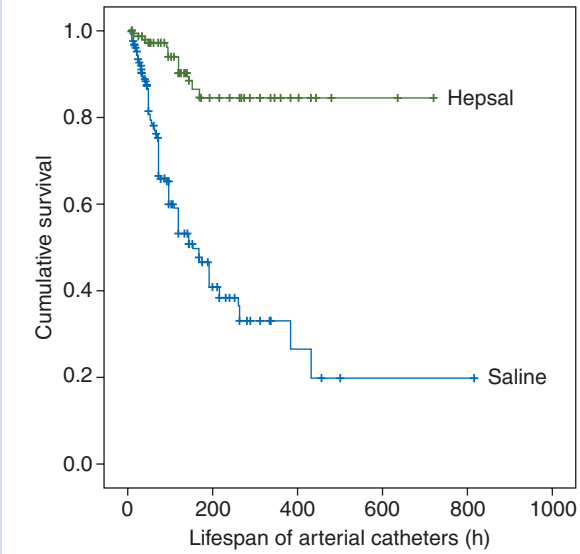

Fig 13 Kaplan–Meier survival curve for Hepsal flush *vs* Saline flush.

(Fig. 13). Blockage was increased with saline flush (n=121, 41.2%) *vs* heparinized flush (n=12, 7.9%) (P<0.0001, χ^2 test). Using multiple logistic regression, an odds ratio of 19.9 (6.62–59.8) for the likelihood of blockage using saline was found. Hospital (ICU) was also significant. No difference was detected between types of catheter.

Our results suggest that using heparinized saline flush solution is associated with increased survival of arterial catheters. This is at odds with current national guidance. We suggest that a randomized controlled trial should be performed to establish whether there is indeed an increased thrombosis rate with saline flush solutions. Guidance may then need to be reviewed considering the patient harm and morbidity caused by repeated placement of blocked arterial catheters.

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Audit on patient satisfaction with epidural analgesia

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The aim of this audit was to evaluate patient satisfaction with epidural analgesia (EA) in non-obstetric patients and

determine what influences patient satisfaction. Retrospective data were collected from the computer-based epidural database (APIS) for all patients from Leeds Teaching Hospitals between January 1, 2010, and May 31, 2012. Data collected comprised the following variables: patient's age, sex, BMI, surgical speciality, epidural interspace, depth of epidural space, infusion regimen, whether the patient was asleep or awake during catheter insertion, whether a consultant or trainee was performing the procedure, pain score at the time of first visit and over last day (0–3), Bromage score (0–3), pain nurse's assessment of overall epidural efficacy (0–3), the number of days the epidural was active, whether the patient's expectations of epidural were satisfied, and morbidity report. Statistical tests were used to compare satisfied and unsatisfied patients. Student's *t*-testing was used for normally distributed data, the Mann–Whitney for non-normally distributed data, and Fisher's exact test for categorical data. A *P*-value of <0.05 was considered statistically significant.

A total of 2304 EA patients were on the APIS database. After excluding 361 patients with no satisfaction data recorded, 1943 (84.3%) patients were analysed, of which 1755 (90.4 %) were satisfied and 188 (9.6%) were unsatisfied with EA. Unsatisfied patients were significantly younger [58.3 (16.3) *vs* 63.4 (14.6) yr, respectively, $P<0.0005$]. BMI was not significantly different between the two groups. Unsatisfied patients showed significantly higher pain scores (median 1 *vs* 0, respectively, $P<0.0001$), lower efficacy scores (median 1 *vs* 3, respectively, $P<0.0001$), and shorter duration of epidural analgesia [1 day (range 0–5) *vs* 3 days (range 0–7), respectively, $P=0.01$]. There was no statistical difference in terms of whether the patient was asleep or awake when the epidural catheter or whether a consultant or trainee inserted it. Bromage scores were not significantly different between the two patient groups; neither was there a difference regarding infusion type. Complication rates (49.5% *vs* 4.1%, respectively) and catheter disconnection (12% *vs* 6.2%) were higher in unsatisfied patients.

Our study shows a similar percentage of unsatisfied patients with epidural analgesia with other studies. The increase in pain threshold with age may explain the fact that unsatisfied patients were significantly younger than satisfied patients. It became obvious that technical problems during epidural catheter insertion, and catheter complications after operation were associated with higher pain scores and consequent dissatisfaction. Higher pain intensity, and shorter duration of epidural analgesia were the main factors that were associated with patient dissatisfaction. Bromage scores, BMI, the anaesthetist's experience, type of infusion solution, or whether the patient was asleep or awake when the epidural catheter was inserted was not associated with satisfaction to a significant extent. Pain nurses' assessments of efficacy were an accurate measure in this study and correlated well with rates of patient satisfaction.

Determining the best introducer for intubating with the C-MAC® D-blade videolaryngoscope

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The C-MAC® D-Blade is a new highly angulated videolaryngoscope blade designed specifically for patients with difficult airways and is used with the current C-MAC modular system.[1] However, a good view of the laryngeal inlet directing the tube into the trachea can be difficult. The use of an introducer can overcome this. The aim of this study was to determine which introducing device is most useful with the C-MAC D-blade videolaryngoscope.

Twenty-four anaesthetists were allowed two intubation attempts, in one easy and one difficult laryngoscopy scenario in a SimMan® 3G manikin with six tracheal tube introducer strategies. These included: tracheal tube with no introducer; tracheal tube with hockey-stick-shaped stylet; tracheal tube with Gliderite® stylet; bougie introducer loaded with tracheal tube distally (at the tip of the bougie); bougie introducer loaded with the tracheal tube proximally (at the top of the bougie); bougie introducer loaded with the tracheal tube after insertion into the trachea. The primary outcome was time to intubate and statistical analysis was based on a latin square design. A *P*-value of <0.025 was considered significant.

In the easy scenario, overall all intubations were successful. In the difficult scenario, intubation failed in the tube alone (13/24) and the tube with hockey-stick-shaped stylet (1/24). Insertion times are shown in Table 12. Differences between pairs were significant in the easy setting for:

Table 12 Insertion time data

Easy scenario	Insertion times (median, IQR)	Difficult scenario	Insertion times (median, IQR)
Hockey stick stylet	8.5 (7, 11)	Gliderite stylet	11.5 (10, 17.5)
Gliderite stylet	10 (8, 11.5)	Hockey stick stylet	14 (12, 22)
Bougie loaded distal	11 (10, 12.5)	Bougie loaded distal	15.5 (12, 23.5)
Tube alone	11 (7, 31.5)	Bougie not loaded	16.5 (14, 21)
Bougie loaded proximal	12 (11, 13.5)	Bougie loaded proximal	16.5 (15.5, 20.5)
Bougie not loaded	13 (11, 14.5)	Tube alone	60 (26.5, 60)

hockey stick stylet *vs* bougie not loaded, Gliderite stylet *vs* bougie not loaded, and hockey stick stylet *vs* bougie loaded proximal. In the difficult setting, difference between pairs was significant for: all introducers *vs* tube alone, Gliderite stylet *vs* bougie not loaded, and Gliderite stylet *vs* bougie loaded proximal.

Stylets appeared to offer faster intubation times in both easy and difficult airways. However, any differences could be considered small in terms of clinical difference. The use of a tube without an introducer in the difficult setting led to failures and should probably be avoided.

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Intubation difficulty and cervical spine fusion: a retrospective review

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Laryngoscopy and intubation require flexion and extension of some or all elements of the cervical spine. Fusion of the cervical spine will impair neck mobility and may impair visualization of the vocal cords during laryngoscopy. The objective of this retrospective review was to observe the change in Cormack and Lehane grade after cervical fusion of some elements of the cervical spine.[1]

The Sheffield operative database was interrogated. The database was formed of patients who had cervical spine fusion at more than one level, or where the fusion involved C0–C2. Where a second operation was recorded, where intubation was required patients formed the basis for our database and their records were retrieved. Patients having a single level fusion were not included as this was not expected to compromise subsequent intubation. The laryngoscope views in the primary and secondary procedures were recorded. Statistical analysis compared the demographics using Student's *t*-test. The χ^2 test of independence measured the differences between the intubation grades.

The database included 84 subjects having 91 pairs of procedures over a 6 yr period 2006–2012, where cervical spine surgery was part of the original procedure. The average age of the patients in the primary and secondary surgery group was 55 (11) and 57 (11) yr, respectively. The majority of primary procedures were two level fusions not involving the first or second cervical vertebrae. Six procedures involved a stabilization of the first or second cervical vertebra. The incidence of difficult intubation (Cormack and Lehane grade III and IV) was higher in the primary and secondary procedure than the value estimated from published literature ($P<0.001$) (Table 13). There was a low use of the Macintosh laryngoscope ($n=27$) and a preference for using aids to difficult intubation.

Although the numbers of cases in this audit were small, patients having cervical spine surgery appear to predispose to a higher incidence of difficult intubation. The use of intubation aids as a first choice of intubation aid may reflect a presumption of difficulty, or reflect the attempted acquisition of skills with intubation aids by trainees and consultants.

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Pilot investigation of deep inferior epigastric perforator free flap perfusion utilizing a multi-wavelength non-invasive optical sensor

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Deep inferior epigastric perforator (DIEP) free flaps are widely used as a reconstruction option after mastectomy for breast cancer.[1] During such cases, partial tissue necrosis can occur due to the insufficient blood supply to the transplanted tissue site. Therefore, monitoring of flap perfusion and early detection of flap failure is a prerequisite to flap survival.[2] There is a need to develop a non-invasive, easy to use, reproducible, and inexpensive monitoring device to assess flap perfusion after operation. A multiwavelength photoplethysmographic (PPG) sensor and battery-powered

Table 13 Number (%) of Cormack and Lehane views performed in the first or second surgical procedure. The expected numbers of the four Cormack and Lehane views were calculated from published values for the normal population[2]

	Cormack and Lehane Grade of intubation. Number of cases (%)			
	I	II	III	IV
Expected number of each intubation grade (%)	20 (73.9)	7 (24.3)	0 (1.6)	0 (0.2)
Primary procedure (%)	10 (37)	10 (37)	3 (11)	4 (15)
Secondary procedure (%)	12 (44)	6 (22)	9 (33)	0 (0)

processing system have been developed to investigate PPG signals and estimate free flap blood oxygen saturation continuously and non-invasively before operation, intraoperatively, and after operation.[3]

The developed reflectance PPG sensor consisted of two infrared, two red, and two green ceramic chip surface-mount LEDs and a surface-mount photodiode, as shown in Figure 14.

To evaluate the functionality of the PPG processing system, preliminary clinical investigations were carried out in 10 patients undergoing elective breast reconstruction with DIEP Flap. Local research ethics committee approval and patient consent was acquired before the study. The sensor was secured onto the exposed skin of the flap using surgical tape. Free flap PPG signals acquisition was conducted in the postoperative period at 15 min intervals in the first 2 h, every 30 min for the following 4 h and hourly for the next 12 h.

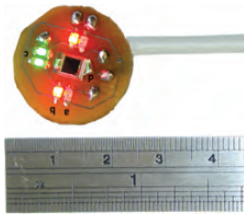

Fig 14 Reflectance photoplethysmographic flap sensor.

An initial observation shows that the amplitude of the PPGs recorded in the postoperative period experience a reduction in amplitude after ~7 h (Fig. 15). Such observations need further investigation in order to identify the underlying reasons which cause such change. The utilization of the green wavelength, with its strong absorption in melanin and haemoglobin and its short depth of penetration, may also provide some blood volumetric and flow activity of the free flap microcirculation.[4 5]

Funding

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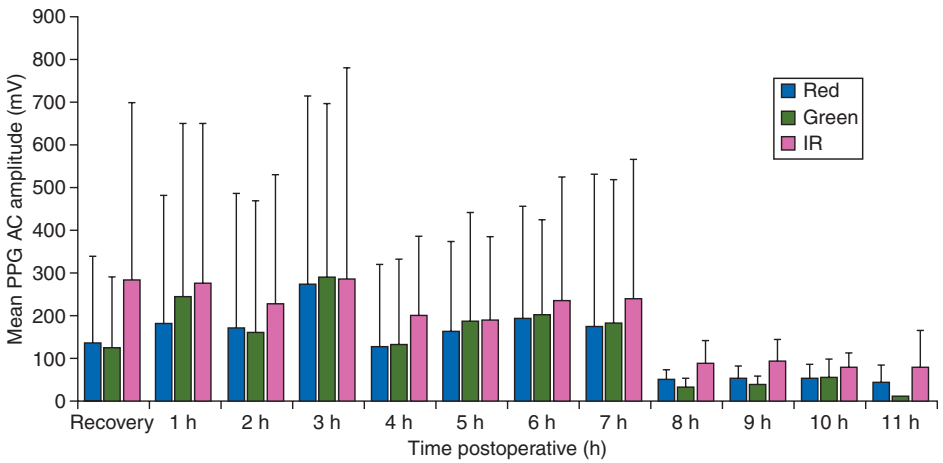

Fig 15 The mean amplitude of AC PPGs.