Abstracts of the Spring Anaesthetic Research Society Meeting (ARS)

The Royal College of Anaesthetists, London, UK, April 21–22, 2015

(The name of the person presenting the paper is shown in bold type. 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.)

Limitations of pulse oximetry in neonates: a double-blinded study; Protocol presentation

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Continuous SaO2 is a standard monitoring technology that detects hypoxic hypoxia during anaesthesia.1281 0 Pulse oximeters measure the proportion of oxygenated to total haemoglobin (SaO2) in pulsatile arterial blood. Averaging of pulse oximeter readings over 2–16 s or 4–32 beats decreases variability of the signal resulting from interference, thus increasing speciﬁcity (reducing the false-positive alarms).51 0 However, this reduces the sensitivity (increases false negatives) and therefore the risk of missing episodes of desaturation.10 Technology to improve signal integrity does not improve the accuracy.3467 Studies have shown that without preoxygenation and with an obstructed airway the time to desaturation in a 1-month-old patient is 6.6 s and in an 8-yr-old 33.6 s.68 The variable physiology of children means that a standard averaging time in pulse oximeters for all age groups reduces the ability of the monitor to warn of impending desaturation in the age groups that may be most sensitive to reductions in saturation.36 The rate of desaturation is faster in children because of higher metabolic rate and a lower functional residual capacity, and the recovery from a hypoxic insult may be slower.69

We suggest that the accelerated desaturation with critical events under anaesthesia puts these neonates at greater risk of hypoxic insult. Monitoring of neonates undergoing anaesthesia with pulse oximetry may require speciﬁcity to be sacriﬁced for greater sensitivity. The high heart rate may necessitate the averaging time to be different. Raising the threshold lower SpO2 alarm limit may reduce hypoxic events.

We propose that there is an optimal averaging time for neonatal pulse oximeters dependent on their rate of desaturation and that we use shorter averaging times to obtain a better reliability on SpO2 in these patients.6 To use this technology optimally, the best receiver operating characteristic curve for pulse oximetry (i.e. the graph between sensitivity and speciﬁcity) can be obtained by a double-blinded study to give better clinical outcomes for neonates undergoing anaesthesia.

We propose to undertake a double-blinded study on neonates undergoing anaesthesia with two pulse oximeters with averaging times of 5 and 10 s to calculate the optimal receiver operating characteristic curve with the smallest burden of hypoxia and the least hypoxaemia.

Two Masimo pulse oximeters with different averaging times of 5 and 10 s will be applied on the big toes during surgery in 20 patients. The burden of hypoxia and the receiver operating characteristic curve for each of the settings will be plotted. Measured outcomes include number and duration of signiﬁcant desaturation events and time spent within diﬀerent saturation ranges.

References

6. Hardman JD, Wills JS. Br J Anaesth 2006; 97: 564–70
Evaluating the effect of operator experience and bronchoscope type in performance of simulated bronchial wash

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Broncho-alveolar lavage (BAL) and bronchial wash (BW) are commonly used diagnostic and therapeutic techniques in the intensive care unit. The ability to perform BW or BAL safely is dependent on operator, equipment, and patient factors.1 Intuitively, prolonged procedures may be associated with more significant complications. There are no widely available metrics to evaluate the performance of one particular bronchoscope over another, other than user preference data.2 3 Our aim was to evaluate the effect of operator experience and bronchoscope type in performance of simulated bronchial wash.

Thirty consenting participants were divided into three groups (‘novice’<10 bronchoscopies, ‘experienced’10–19, or ‘expert’≥20) and performed timed BW on a pre-intubated AirSimTM Bronchi manikin (TruCorp Ltd, Belfast, UK) using each of three fibrescopes in random order: single-use Ambu aScopeTM 3 (Ballerup, Denmark) and Olympus BF-260 and Olympus BF-P40 re-usable fibrescopes (Olympus Corporation, Tokyo, Japan). The manikin could reliably hold 20 ml of fluid in each lung segment, hence participants were instructed to perform BW on the right followed by left lower lobes of the simulated lung, injecting 20 ml into each. Data were collected on time to complete components of the BW (navigation and actual BW), total volume of aspirated BW fluid, and user preference metrics for each bronchoscope. Results were analysed using a two-way repeated-measures ANOVA and Friedman tests.

There was a significant difference between experience (P<0.001) but not bronchoscope type (P=0.85) on the total time taken for the procedure. Novices were slower overall, with a mean difference of 37 s (95% confidence interval (CI) 7–68, P=0.13) between novices and experienced participants, and of 50 s (95% CI 20–81, P<0.001) between novices and experts. There were non-significant mean differences of 2–7 s between the three different bronchoscopes (for total time taken to complete the procedure). Time spent performing the BW accounted for much of the variation: the ‘expert’ group were a mean difference of 33 s faster than novices (95% CI 7–58, P=0.009). There was no significant difference between experience (P=0.41) or bronchoscope type (P=0.60) on the total BW volumes retrieved. There was a significant difference between the pooled Likert scores for the three bronchoscopes (P<0.001), with the Ambu aScope 3 pooled mean scores falling between those of the two Olympus bronchoscopes.

Our study demonstrates that operator experience causes significant differences in the time taken to complete BW. However, there were no differences between the three different bronchoscopes for either total time or total volume retrieved after BW. This may have implications for BW training in bronchoscopy, BW procedures, and bronchoscope choice in this setting.

References


Targeted training using a paediatric tracheostomy emergency algorithm improves performance in simulated scenarios

C. Doherty1, D. Atkinson2, I. Bruce1, R. Perkins1, R. Neal3, N. Bateman1, J. Russell4, J. Cooke5, M. Wyatt5, L. Bowes3, B. McGrath6

1Royal Manchester Children’s Hospital, 2Manchester Royal Infirmary, 3Birmingham Children’s Hospital, 4Our Lady’s Children’s Hospital, Crumlin, Dublin, 5Great Ormond Street Hospital, and 6University Hospitals South Manchester Teaching Hospital NHS Trust

We report the results of a paediatric patient safety initiative on behalf of the Paediatric Working Group of The National Tracheostomy Safety Project (NTSP).1 Local review of 54 tracheostomy clinical incidents in 2012 at a tertiary paediatric hospital demonstrated moderate patient harm in 25%, with major harm (including death) in 16%. Contributing factors included lack of access to information or emergency algorithms, loss of situational awareness, inadequate training, and poor communication, all of which are suitable for simulation-based quality improvement initiatives. National guidelines advocate standardization of resuscitation algorithms and equipment, use of bedhead signs, training, and care competencies.2 3 We developed and adapted these for the paediatric population.

A multidisciplinary team designed a paediatric tracheostomy emergency algorithm with paired bedhead sign and developed a training package, partly delivered using high-fidelity simulation. In-depth debriefing principles also highlighted the non-technical skills required to manage the emergency situation. Pre- and post-training scenarios were used in more than 450 volunteer healthcare professional encounters at local and national meetings. Scenarios were subtly different but had identical clinical courses and learning objectives.

Detailed complete performance data were collected from 141 consenting candidates: 37 anaesthetic trainees, 32 nurses, 52 ENT consultants, and 19 ENT trainees. There were significant improvements in performance metrics after training, as detailed in Table 1. There was a significant increase in the numbers of

<table>
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<th>Table 1 Time (in seconds) measured during candidate performance of scenarios. Paired sample t-tests were used to calculate differences between groups</th>
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<tr>
<td><strong>Pretraining Mean (sd)</strong></td>
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<tr>
<td><strong>Total scenario time</strong></td>
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<td><strong>Time SpO2 &lt;88%</strong></td>
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<td><strong>Time to call help</strong></td>
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candidates who called for help after training, from 122/141 (86.5%) to 134/141 (95.0%), \( \chi^2 (1)=6.10, \) Fisher’s exact \( P=0.01. \)

The results demonstrate that high-fidelity simulation improves surrogate metrics of performance after targeted teaching of new resources to manage paediatric tracheostomy emergencies. The improvements in measured metrics were likely to be clinically significant, overcoming bias associated with the repeated measures associated with the observational nature of our study. Further work should examine which professional groups could benefit most from targeted training. The educational package is currently under peer review. Our study supports adoption of this proposed national guidance, with future clinical evaluation.

References
1. www.tracheostomy.org.uk

Does fusion elastography improve the diagnosis of intraneural and extraneural median nerve injection when assessed by anaesthesia trainees?

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Nerve injection during regional anaesthesia still occurs. Neuropraxia secondary to regional anaesthesia is attributed to accidental intrafascicular injection. A recent editorial recommended that local anaesthetic be injected without direct needle-to-nerve contact.\(^1\) However, in practice, anaesthetists are poor at detecting intraneural injection. In studies examining postprocedure regional anaesthesia videos,\(^2\) one in six nerve blocks performed by trainee anaesthetists and thought to be extraneural were later diagnosed as intraneural by experts. This equates to a false-negative rate of 17\% for diagnosis of extraneural/intraneural injection and sensitivity of 83\%.

We wished to determine whether fusing elastography to a B-mode image improved the diagnostic ability of anaesthesia trainees to diagnose intraneural median nerve injection when viewing postprocedure videos within the soft embalmed Thiel human cadaver. Intraneural injection was defined by consensus of two experts who were also aware of nerve area and brightness measured using ImageJ (NLM, Washington, DC, USA). Trainees viewed 40 videos each 12 s in duration, without repeat, using three ultrasound modalities: (i) B-mode; (ii) the combination of B-mode and elastography; and (iii) repeated B-mode videos. Each trainee decided if each block was intraneural or extraneural and rated each decision with low, moderate, or high degree of confidence. Our primary end point was the area under the curve (AUC) of the multiple reader, multiple case, receiver operator characteristic (MRMC-ROC) curve (http:perception.radiology. uiowa.edu).

Area and brightness measurements from 160 videos showed that intraneural injection diagnosed by experts was associated with: (i) an increase in the cross-sectional nerve area of the median nerve on B-mode images [intraneural 23.8 [95% confidence interval (CI) 20.7–27.4], extraneural 17.5 (95% CI 15.0–20.3), difference 6.3, \( P=0.018 \); (ii) a decrease in the cross-sectional area of the elastogram [intraneural 42.1 (95% CI 36.6–48.4); extraneural 68.0 (95% CI 58.6–78.3), difference 25.9, \( P<0.001 \); and (iii) an increase in the brightness of the nerve on the fusion image [intraneural 120.3 (95% CI 108.9–133.0); extraneural 82.3 (95% CI 73.7–90.9), difference 38.0, \( P<0.001 \).
saline flush and swab samples were obtained at time zero (immediately after social clean) and at 24 and 48 h.

Complete microbiological results from 20 aScope3 bronchoscopes were obtained. Interestingly, three swabs and 10 flushes were ‘positive’ for microbiological growth at time zero, which did not always lead to further positive bronchoscope samples, nor represent the microbiology of the sputum samples obtained from the patient (via the bronchoscope). At 48 h, seven swabs and eight flushes were positive with a mixture of normal respiratory tract flora, significant pathogens, and fungi. Nine patients had contemporaneous respiratory samples that were positive, including five organisms that matched those grown from the bronchoscope used to collect the sample.

With pathogens cultured in 11 of 20 used bronchoscopes immediately after social cleaning and in 10 of 20 bronchoscopes at 48 h, our findings suggest that the sScope3 should not be re-used. Cross-contamination has been reported with re-useable bronchoscopes, and our results indicate that prolonged bedside storage may encourage microbiological growth. Culture of bronchoscopes themselves may be a potentially useful diagnostic tool, and further work should examine the clinical significance of pathogens isolated from bronchoscopes, but not patients, at different posture time frames.

Reference


Pretreatment with hydrogen-enriched saline attenuates morphine tolerance

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Neuroinflammation may involve development of morphine tolerance. It has been considered that peroxynitrite (PN) plays an important role in these processes.1,2–4 Hydrogen was reported to reduce PN; however, its role in morphine tolerance remains unknown. The aim of the present study is to investigate the preventive effects of hydrogen on morphine tolerance and the underlying mechanisms in rats.

Rats were treated with morphine (10 µg per dose, twice a day for 5 days) intrathecally via a catheter inserted through atlanto-occipital membrane and advanced to the lumbar enlargement of the spinal cord. Hydrogen-enriched saline (HS) or saline was given intraperitoneally (i.p.) at 1, 3, or 10 ml kg−1 10 min before each dose of morphine was administered. The PN-decomposition catalyst FeTM-4-PyPS5 (PN-DC) was given 1.5, 5, or 15 mg kg−1, i.p. The mechanical paw withdrawal threshold and thermal latency were assessed 1 day (baseline) before and on a daily basis up to 5 days during morphine injection. Astrogliosis, microgliosis, and pro-inflammatory cytokines (tumour necrosis factor-α, interleukin-1β, and interleukin-6) in the spinal dorsal horn were determined with immunostaining and western blot, respectively.

Morphine-tolerant animals showed a high sensitivity to mechanical and thermal stimuli together with increases of astrocyte and microglia activation and of tumour necrosis factor-α, interleukin-1β, and interleukin-6 expression. Pretreatment with PN-DC inhibited morphine tolerance in a dose-dependent manner. Treatment with HS attenuated morphine tolerance in a dose-dependent manner and significantly inhibited activation of astrocytes and microglia and release of cytokines at the highest dose studied. At the lowest dose, PN-DC or HS alone was not effective, but in combination they synergistically attenuated morphine tolerance and neuroinflammation.

Pretreatment with hydrogen-enriched saline prevents development of morphine tolerance by inhibiting PN-mediated neuroinflammation at the spinal cord level. Further study is needed to assess the therapeutic value of this strategy.

Acknowledgements

This study was supported by research grants from the National Natural Science Foundation of China (30972847, 81071533, 81101409, 81071059, and 81100984).

C.W. receives a fellowship from China Scholarship Committee, Beijing, UK.

References


Molecular mechanisms underlying regulation of myocardial nitric oxide synthase activity during cardiac surgery on cardiopulmonary bypass

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The mechanism responsible for myocardial stunning after cardiac surgery on cardiopulmonary bypass (CPB) is only partly understood. In isolated rat hearts subjected to an ischaemia-reperfusion (I/R) protocol,1 left ventricular dysfunction was associated with uncoupling of endothelial nitric oxide synthase (NOS) activity secondary to oxidation of the NOS cofactor, tetrahydrobiopterin (BH4). Currently, there are no evidence-based interventions to prevent functional consequences of I/R and myocardial dysfunction during on-pump cardiac surgery.2

Given that a synthetic formulation of the active 6R-isomer of BH4 is approved for the treatment of phenylketonuria, NOS uncoupling secondary to BH4 deficiency could be a promising therapeutic target. To test this hypothesis, we investigated regulation of myocardial NOS activity in patients undergoing on-pump cardiac surgery.

From 116 patients who underwent elective cardiac surgery on CPB, paired samples of the right atrial appendages were obtained before venous cannulation of the right atrium (PRE) and after myocardial reperfusion (POST). Superoxide production from atrial samples was measured by lucigenin (5 µmol litre−1) enhanced chemiluminescence and 2-hydroxyethidium (2-OHE) detection by high-performance liquid chromatography (HPLC).
Tetrahydrobiopterin, oxidized biopterins, GTP-cyclohydrolase 1 (GTPCH-1, the rate-limiting enzyme in BH4 synthesis), and NOS activity (14C L-arginine to L-citrulline conversion) were measured by HPLC.

Atrial superoxide production increased significantly after reperfusion [from 37.83 (SEM 3.71) RLU s⁻¹ mg⁻¹ before cannulation to 65.02 (6.01) RLU s⁻¹ mg⁻¹ after reperfusion, P<0.001; n=46 samples from 23 patients] because of uncoupling of NOS activity and increased mitochondrial and NOX2 oxidative activity (by 309 and 149%, respectively; P<0.001). Atrial content of BH4 was reduced (by 32%, P<0.001), as was GTPCH1 activity (by 50%, P<0.001) after reperfusion, while oxidized biopterins (BH2 and bioprotein) remained unchanged. Investigations of mechanisms of downregulation of GTPCH1 activity revealed an increase in protein expression of GFRP (GTPCH feedback regulatory protein) after reperfusion. Atrial NOS activity decreased significantly after reperfusion (by 60%, P<0.001) in the absence of changes in protein expression of eNOS or nNOS and the PRE-to-POST difference was not affected by BH4 supplementation (10 µM) or NOX2 inhibition. Instead, we identified increased endothelial NOS S-glutathionylation as the main mechanism for NOS uncoupling after reperfusion. Reversing NOS-S-glutathionylation with dithiorthreitol (100 µmol litre⁻¹) completely restored NOS activity after reperfusion (P=0.34).

Our findings suggest that NOS S-glutathionylation, rather than BH4 depletion, accounts for NOS dysfunction in patients after cardiac surgery on CPB and imply that in this patient cohort, BH4 supplementation is not effective in restoring atrial bioavailability of nitric oxide. Whether redressing atrial oxidative stress by deglutathionylation of eNOS will preserve NO redox balance and prevent perioperative myocardial dysfunction remains to be established.

References

Exploration of the NOP receptor in rat spleen, functional coupling of splenocytes to MAP kinase, and expression in a rat model of sepsis

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The nociceptin system consists of the peptide N/OFQ and its receptor, NOP. The N/OFQ–NOP system may be involved in sepsis,1 and previous work in a murine model has demonstrated that NOP antagonism reduced mortality, whilst exogenous N/OFQ increased mortality.2 This study examines splenic expression of NOP receptor mRNA in an animal model of sepsis. We further aimed to establish whether functional NOP activity could be assayed in isolated rat splenocytes through analysis of two downstream signalling systems, p38 and ERK1/2, mitogen-activated protein kinase (MAPK) pathways.

Fifteen male Wistar rats were assigned to three groups (n=5) and injected i.p. with either lipopolysaccharide (LPS) 25 mg kg⁻¹, LPS 25 mg kg⁻¹+UFP-101 (NOP antagonist) 0.03 mg kg⁻¹, or phosphate-buffered saline (PBS; control). Responses to LPS were assessed using behavioural changes such as piloerection and lethargy over 24 h. Animals were then culled by cervical dislocation after cardiac puncture under terminal anaesthesia, and spleens were harvested. Messenger RNA was extracted using the phenol–chloroform method, processed with a DNAase, and reverse transcribed to yield cDNA. qPCR using TaqMan® gene expression probes and SYBR® Green-based quantification analysis were used to determine expression of NOP transcripts. The MAPK activity was determined in splenocytes (from two healthy Wistar rats) in response to 1 µM N/OFQ, and activation was assayed using western blot analysis of phosphorylated ERK1/2 and p38. Responses were analysed via band densitometry.

The difference in cycle threshold (ΔCt) values, measured with Taqman® probes, for the treatment groups were significantly increased compared with the control (Table 3), but these findings were not confirmed using SYBR® Green. The ΔCt values from Taqman® probes and SYBR® Green were significantly different for each group (Student’s unpaired t-test, P<0.05). There was no phosphorylation of ERK1/2 in the splenocytes despite presence of the protein. The phosphorylation of p38 relative to basal changed depending on the length of stimulation with N/OFQ; highest phosphorylation occurred at 10 min (0.90-fold) and lowest at 20 min (0.51-fold), but with only two experiments undertaken it is unwise to draw conclusions from this.

Funding
BJA (John Snow award) via NIAA and Pathological Society.

References

Table 3 qPCR data for spleen cDNA from rats treated with LPS, LPS+UFP-101, or control (PBS), using E74-like factor 1 (ELF1) as the reference gene. TaqMan (ΔCt) values are shown as cycle threshold (Ct) or difference in cycle threshold (ΔCt) relative to ELF1 [mean (SEM)]. TaqMan (ΔCt) values differ significantly from the control (one-way ANOVA and Tukey’s range test, P<0.05).

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<tr>
<th>Treatment</th>
<th>TaqMan® Probes</th>
<th>SYBR® Green</th>
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<td></td>
<td>Ct</td>
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<tr>
<td>Control</td>
<td>24.20 (0.15)</td>
<td>38.82 (0.37)</td>
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<tr>
<td>LPS</td>
<td>23.92 (0.22)</td>
<td>40.54 (0.32)</td>
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<td>LPS+UFP-101</td>
<td>23.50 (0.33)</td>
<td>39.98 (0.30)</td>
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The effect of serratus plane block performed under direct vision on postoperative pain in breast surgery

M. Hards, A. Harada, I. Neville, S. Harwell, M. Babar, A. Ravalia, G. Davies

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Breast cancer is the most common cancer in the UK, and a woman’s lifetime risk of developing breast cancer is one in eight.1 Despite advances in surgery and the increasing use of chemotherapy and endocrine therapy before surgery, mastectomy remains a common operation for breast cancer. Postoperative pain is a common sequela of this type of surgery, and significant acute pain will progress to chronic pain in 25–60% patients.2 Recent studies have suggested that a serratus plane block is a viable alternative to regional anaesthetic techniques without the side-effect profile.3 Their results suggested that injection of local anaesthetic into serratus anterior provided predictable and long-lasting anaesthesia to the chest wall. The serratus muscles are superficial and easily identified during surgery, and serratus blocks target the thoracic nerves more selectively than pectoral blocks. Local blocks can reduce the use of opiates after surgery, thereby lessening opiate-related side-effects. Adequate postoperative pain management reduces postoperative complications, reduces patient anxiety, aids early discharge, and increases patient satisfaction.

We performed a retrospective study of elective breast surgery patients undergoing mastectomy over 6 months. Our sample included 16 patients who had received a serratus block and 11 patients who had wound infiltration with local anaesthetic only and who had a mastectomy in the 6 months preceding the study. A numerical rating score (0–10) was used to score pain subjectively. We collected data on the outcomes for the pain score and use of analgesia in recovery, the use of analgesia and antiemetics overnight, and the pain score and mobilization status of the patient 1 day after the operation.

Our results demonstrated excellent pain control in mastectomy patients compared with national audit data, with most patients requiring no analgesia or paracetamol only after surgery. There was also excellent control of nausea, and all patients were mobilizing after surgery. Our conclusions were that serratus block given under direct vision provides long-lasting regional anaesthesia, suitable for mastectomies, and currently appears to be more effective than wound infiltration only. It can be used for breast surgery as described and is likely to be of benefit for any surgery that involves the chest wall. However, further data will need to be collected to support this finding. We plan to perform a 12 month randomized control trial to investigate further the usefulness of the serratus plane block performed under direct vision as an anaesthetic technique.

References

Impact of NICE guidance and CQUINS on uptake of cardiac output monitors across the NHS: a trainee-led national survey

C. Thomas, C. Allen

Research and Audit Federation of Trainees (RAFT)

The Research and Audit Federation of Trainees (RAFT) undertook a national survey with the following aims: (i) to describe the current intraoperative use of cardiac output monitors (COMs) in operating theatres throughout the NHS; (ii) to determine the impact of NICE recommendation (NICE MTG3)1 and CQUIN payment schemes2 on COM uptake; and (iii) to test the utility of the network to undertake such a survey.

A prospective survey open to all trusts within the federation was carried out during a 2 week period commencing June 30, 2014. Requirement for research ethics approval was waived. Trainees at each site completed a questionnaire by interview with clinical or equipment leads. The survey enquired about availability of COMs and the approximate date and reason for purchase. Data were centralized using a RAFT-designed Web-based data collection system.

Data were reported from 67 sites in 11 regions. Sixty-six (99%) possessed COMs. Thirty-four sites (50%) had a recently operational COM CQUIN. Four hundred and eighty monitors were reported, averaging seven (sd 7) per hospital. On hundred and eighty-three (38%) were CardioQ Oesophageal Doppler Monitors (ODMs). Estimated date of purchase was available for 459 COMs (96%). Two hundred and seventy-one (59%) were purchased after publication of NICE MTG3 guidance (Fig. 1). The most frequent reason cited for COM purchase was ‘clinical opinion’ (129 instances, 27%). NICE MTG3 was cited as the reason for purchase in 67 (14%) instances. Thirty-seven of these (55%) were ODMs; however, uplift in the rate of procurement of ODMs after NICE MTG3 was in line with that of other COMs. The LiDCOrapid (n=32, 29%) was the most frequently purchased COM in response to a CQUIN. Twenty-eight trusts (44%) had a guideline for COM use, 36 sites (56%) provided COM training, and at 16 sites (25%) access to COM disposables was described as ‘limited’.

Cardiac output monitors are now widely available. The commonest reason advanced for COM purchase was neither CQUIN

References
nor NICE guidance, but ‘clinical opinion’. We saw no evidence of preferential ODM purchase over other COMs following NICE MTG3. Cardiac output monitor use is not standardized; access to guidelines, training, and disposables is variable.

References

The Welsh Anaesthesia Audit, Research and Engagement Network’s (WAAREN) Assessment of Ventilatory End Points (WAVE) project
J. Riddell
On Behalf of Welsh Anaesthesia Audit Research and Engagement Network (WAAREN)

In elective surgical patients at high risk of postoperative pulmonary complications, recent randomized control data from the 2013 IMPROVE trial have shown a strong association between ventilatory strategy, length of stay, and frequency of postoperative complications. The ventilatory strategy with a demonstrated benefit consists of a maximal pressure ($P_{\text{max}}$) limitation to 30 cm H$_2$O, tidal volume (V$_T$) restriction to 6–8 ml kg$^{-1}$ ideal body weight (IBW), positive end-expiratory pressure (PEEP) with a minimal level of 5 cm H$_2$O, and regular recruitment manoeuvres.

This observational multicentre study, conducted by the WAAREN group, intended to evaluate current practice compared with the emerging evidence base. The study included nine sites throughout Wales, with data collection over 9 days.

Ninety-one patients were identified, of whom 47 were at high risk of postoperative pulmonary complications (Table 4). In patients at high risk of postoperative pulmonary complications, 29.7% received a $P_{\text{max}}>30$ cm H$_2$O, 38.2% received a PEEP<5 cm H$_2$O, and 38.2% received a $V_T$ of 6–8 ml kg$^{-1}$ IBW. No recruitment manoeuvres were used to any patient observed in the study. There was significant variation in the delivery of ventilation parameters throughout the sites.

The delivery of intraoperative ventilation to elective surgical patients is heterogeneous, with a significant minority of patients receiving ventilation parameters thought to be potentially harmful. In this cohort of patients, length of stay and postoperative complications may be increased as a consequence of the ventilation strategy delivered.

Reference

Adherence to lung-protective ventilation in theatre: a multicentre audit of practice
R. Baker1, J. Patel2, C. Small2, J. Yeung3
1The Dudley Group NHS Foundation Trust, 2University Hospital Birmingham, NHS Foundation Trust, and 3School of Clinical and Experimental Medicine, University of Birmingham

Lung-protective ventilation in patients with acute respiratory distress syndrome improves mortality.1 Adopting this strategy in the perioperative period has been shown to reduce lung inflammation and now has also been shown to reduce postoperative pulmonary and non-pulmonary sepsis complications in patients undergoing major abdominal surgery.2 We conducted an audit of perioperative ventilation practice across the West Midlands Deanery to assess the use of lung-protective ventilation.

A prospective review of 406 adult ventilated patients undergoing surgery across 14 hospital trusts in the West Midlands was undertaken over a 2 day period in November 2013. Data collected included surgical specialty, patients’ biometric data, duration of procedure, grade of anaesthetist, and ventilator parameters. Lung-protective ventilation was defined as delivery of a tidal volume between 6 and 8 ml kg$^{-1}$ ideal body weight, a peak pressure of <30 cm H$_2$O, the use of positive end-expiratory pressure (PEEP) of 6–8 cm H$_2$O and hourly recruitment manoeuvres (PEEP of 30 cm H$_2$O for 30 s). Continuous data are represented as median (range).

Data were collected for 406 patients with a median age of 56 (16–91) yr. The majority of patients (78%) were having elective procedures and were being anaesthetized by a consultant. Principal surgical specialties were general (29%), trauma and orthopaedic (19%), and ENT (17%). Volume-controlled ventilation was the preferred ventilation strategy in 70% of patients. No patients were ventilated according to the guidelines above; however, peak pressure was 20 (10–43) cm H$_2$O and delivered tidal volume was 8.4 (3.5–14.5) ml kg$^{-1}$ ideal body weight. The median (range) PEEP was only 4 (0–10) cm H$_2$O, with PEEP not used in 152 patients. No recruitment manoeuvres were used.

Perioperative lung protection ventilation can improve patient outcomes from major surgery. This multicentre audit demonstrates that increasing awareness into the use of higher PEEP and the value of recruitment manoeuvres needs to be promoted as part of the concept of lung-protective ventilation.

References

Table 4. Inter-hospital variation in delivery of ventilation parameters

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Number of patients</th>
<th>PEEP&lt;5 cm H$_2$O (%)</th>
<th>$P_{\text{max}}&gt;30$ cm H$_2$O (%)</th>
<th>$V_T$&gt;10 ml kg$^{-1}$ IBW (%)</th>
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<td>C</td>
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<td>D</td>
<td>7</td>
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</tr>
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<td>23</td>
<td>60.8</td>
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Endogenous antioxidant function and oxidative stress after lung resection
B. Shelley1, J. Kinsella1, A. Macfe2, H. F. Galley3

1University of Glasgow, UK, 2Golden Jubilee National Hospital, Glasgow, UK, and 3University of Aberdeen, UK

Acute lung injury occurs in 5–10% of patients undergoing lung resection and is the leading cause of surgical mortality in this patient group. Oxidative stress has been reported to contribute to the pathophysiology of acute lung injury after lung resection.1 We hypothesized that patients presenting for lung resection may have compromised endogenous antioxidant status, making them at increased risk of oxidative stress, which may contribute to lung injury after surgery. We therefore investigated biomarkers of perioperative antioxidant status and oxidative stress in patients undergoing lung resection for lung tumours.

With research ethics committee approval and written informed consent, plasma samples were obtained before surgery and immediately after surgery were signiﬁcantly higher in lung resection patients than in age- and sex-matched control subjects (P<0.01; Fig. 2). Plasma MDA concentrations decreased after surgery (P<0.01); pairwise testing showed that concentrations immediately after surgery were signiﬁcantly lower than at baseline (P<0.01), but not different from concentrations after 24 h. There were, however, no signiﬁcant changes in plasma F2-isoprostane concentrations, and there was no association between preoperative TAC and either plasma MDA or F2-isoprostane after surgery.

We found that patients with lung cancer undergoing lung resection had elevated TAC compared with control subjects without cancer undergoing surgery and that there was no evidence of perioperative oxidative stress.

Reference

Coupling of the NOP receptor to MAP kinase
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1Department of Cardiovascular Sciences, University of Leicester, Division of Anaesthesia, Leicester Royal Infirmary, Leicester, UK, 2Department of Medical Science, Section of Pharmacology and National Institute of Neuroscience, and 3Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Italy

Opioids provide potent analgesia along with a range of adverse events, including tolerance leading to dose escalation.1 The NOP receptor is a relatively novel target for the development of analgesic drugs.2,3 Activation of the NOP receptor by nociceptin/orphanin FQ (N/OFQ) leads to activation of the MAP kinase (MAPK) pathway. This pathway is involved in a wide variety of cellular processes and may play a role in adverse effects, including tolerance. In this study, we examined the coupling of recombinant NOP receptors to MAPK and compared this with another functional assay of receptor activation, GTPγS binding.

Experiments were performed using Chinese hamster ovary cells stably expressing recombinant human NOP (CHO-NOP). Activation of MAPK was assayed using western blot analysis of phosphorylated ERK1/2 and p38; response was determined via densitometry. Receptor activation was further assessed in CHO-NOP membranes using GTPγS binding. Data are means (SEM).

N/OFQ produced a rapid phosphorylation of ERK1/2, peaking at 5 min; there was relatively less phosphorylation of p38. N/OFQ produced a concentration-dependent phosphorylation of ERK1/2 peaking at 1 µM. Analysis of concentration–response curves yielded a potency or pEC50 of 9.78 (0.24) (n=10). In GTPγS binding assays, N/OFQ produced a concentration-dependent stimulation of GTPγS binding, pEC50 of 9.27 (0.13) (n=5).

Phosphorylation of ERK1/2 in response to 1 µM of a variety of opioid ligands [PWT2-N/OFQ,4 Dmt1 N/OFQ(1-13)-NH2, buprenorphine, and Ro64-6198 (all n=6)] was further determined (Table 5). Full concentration–response curves to these ligands were produced for the stimulation of GTPγS binding, n=5 experiments, except buprenorphine, n=4.

All ligands except buprenorphine were full agonists. Buprenorphine showed a reduced Emax in terms of its ability both to cause ERK1/2 phosphorylation and to stimulate GTPγS binding; the degree of partial agonism was not statistically different between assays (P>0.05).
Telomere length progressively shortens as biological age increases and acts as a read out for ‘miles on the biological clock’.1 Telomere length shortens progressively as biological age increases. Within health care, ageing is almost exclusively described in terms of chronological age. Recent studies explored using biological age to stratify patients and predict outcomes.3 This project acts as a pilot study to investigate whether biological age is related to intensive care unit (ICU) outcomes and whether ICU patients age biologically at an accelerated rate.

This project used blood samples from a previous study where patients underwent cardiac surgery and were admitted to the ICU. Blood samples were obtained before surgery and on days 1, 2, and 3 after surgery. The database contained the following physiological parameters: haemoglobin, urea, creatinine, RIFLE score, length of ICU stay, and whether renal replacement therapy was required. Information on co-morbidities and medication was also provided. DNA was isolated using a Maxwell machine and telomere length determined via quantitative PCR.

One hundred and fifty-five blood samples from 46 patients underwent analysis. Telomere length did not differ significantly over the 4 days (P=0.662). No relationship was found between telomere length and any physiological parameter, co-morbidity, or medication. There was a trend towards significance with RIFLE score at day 3 increasing as telomere length decreased, although this was not statistically significant (P=0.09).

No relationship between telomere length and the available physiological parameters, comorbidities, or medication was found. Telomere length did not vary during ICU stay. This study was limited by its small sample size. Future studies would benefit from a larger sample size; in addition, blood samples could also be obtained at 6 months after discharge to allow gradual alterations in biological age to be determined. Recent studies give evidence that telomere length is a weak biomarker of ageing, and that more meaningful data might be obtained using superior markers, such as CDKN2A expression or expression levels of non-coding RNAs.

**References**


**Funding**

Financial support to J.O’D. from Wolfson Foundation and BJA (John Snow award from NIAA) gratefully acknowledged.

**Table 5** MAPK activation and GTPγS binding in CHO<sub>hMEC0</sub> Cells. Data are means (SEM). The $E_{\text{max}}$ values are expressed relative to 1 μM N/OFQ response in the respective experiment. ND, not determined.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>GTPγ&lt;sup&gt;[35S]&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>$pEC_{50}$</td>
<td>$E_{\text{max}}$</td>
</tr>
<tr>
<td>N/OFQ</td>
<td>9.27 (0.13)</td>
<td>1.03 (0.03)</td>
</tr>
<tr>
<td>PWT2-N/OFQ</td>
<td>10.18 (0.16)</td>
<td>1.02 (0.03)</td>
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<tr>
<td>[Dmt&lt;sup&gt;1&lt;/sup&gt;]N/OFQ(1-13)-NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>9.06 (0.26)</td>
<td>1.05 (0.02)</td>
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<td>Buprenorphine</td>
<td>6.54 (0.33)</td>
<td>0.54 (0.10)</td>
</tr>
<tr>
<td>Ro64-6198</td>
<td>8.78 (0.24)</td>
<td>1.14 (0.06)</td>
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</tbody>
</table>

**Stratifying intensive care unit outcomes based on telomere length as a biomarker of ageing: a pilot study**

H. Curley, D. McGuinness, J. Kinsella, T. Quasim, P. Shiels

University of Glasgow, UK

Biological age is a better measure of functional capacity than chronological age.1 One of the measures of biological age is telomere length. Telomeres are nucleoprotein complexes that protect chromosome ends from damage. The DNA component of telomeres progressively shortens as biological age increases and thus acts as a read out for ‘miles on the biological clock’.2 Telomere length shortens progressively as biological age increases. Within health care, ageing is almost exclusively described in terms of chronological age. Recent studies explored using biological age to stratify patients and predict outcomes.3 This project acts as a pilot study to investigate whether biological age is related to intensive care unit (ICU) outcomes and whether ICU patients age biologically at an accelerated rate.

This project used blood samples from a previous study where patients underwent cardiac surgery and were admitted to the ICU. Blood samples were obtained before surgery and on days 1, 2, and 3 after surgery. The database contained the following physiological parameters: haemoglobin, urea, creatinine, RIFLE score, length of ICU stay, and whether renal replacement therapy was required. Information on co-morbidities and medication was also provided. DNA was isolated using a Maxwell machine and telomere length determined via quantitative PCR.

One hundred and fifty-five blood samples from 46 patients underwent analysis. Telomere length did not differ significantly over the 4 days (P=0.662). No relationship was found between telomere length and any physiological parameter, co-morbidity, or medication. There was a trend towards significance with RIFLE score at day 3 increasing as telomere length decreased, although this was not statistically significant (P=0.09).

No relationship between telomere length and the available physiological parameters, comorbidities, or medication was found. Telomere length did not vary during ICU stay. This study was limited by its small sample size. Future studies would benefit from a larger sample size; in addition, blood samples could also be obtained at 6 months after discharge to allow gradual alterations in biological age to be determined. Recent studies give evidence that telomere length is a weak biomarker of ageing, and that more meaningful data might be obtained using superior markers, such as CDKN2A expression or expression levels of non-coding RNAs.

**References**


**Association of preoperative heart rate with postoperative myocardial injury**

T. Abbott<sup>1</sup>, G. Ackland<sup>2</sup>, A. Wragg<sup>3</sup>, A. Archbold<sup>3</sup>, P. Devereaux<sup>4</sup>, R. Pearse<sup>1</sup>

<sup>1</sup>Queen Mary University of London, <sup>2</sup>University College London, <sup>3</sup>Barts Health NHS Trust, and <sup>4</sup>McMaster University

New data suggest that subclinical myocardial injury occurs in as many as 12% of patients undergoing non-cardiac surgery. This is associated with death and cardiac complications during the next 30 days.1 However, the underlying physiological mechanism is poorly understood. Perioperative myocardial injury and other cardiac complications are likely to arise because of differences in coronary blood supply vs demand during and after surgery. Abnormal heart rate may directly affect cardiac function by reducing diastolic filling time and coronary blood flow, while at the same time increasing myocardial oxygen demand, leading to myocardial ischaemia.2 Current data suggest that preoperative resting heart rate is associated with mortality up to 30 days after surgery.1 However, it is unclear whether this is true of postoperative myocardial injury. We hypothesize that preoperative resting heart rate is associated with postoperative myocardial injury.

This was a post hoc analysis of the VISION study, an international observational cohort study of patients undergoing non-cardiac surgery.1 Preoperative resting heart rate was defined as the heart rate, measured at rest, in the anaesthetic room, before the induction of anaesthesia. Postoperative myocardial...
injury was defined as serum troponin T concentration >0.03 ng ml\(^{-1}\), adjudicated as resulting from an ischaemic aetiology, within 30 days of surgery. Logistic regression analysis was used to assess the association between heart rate and myocardial injury. Significance was set at \(P<0.05\).

This analysis included 15 109 patients; 51.7% were female, and 1197 patients (7.9%) had myocardial injury. Mean preoperative heart rate was 76.8 (SD 14.9) beats min\(^{-1}\). Preoperative resting heart rate was associated with postoperative myocardial injury (odds ratio 1.02, \(P<0.001\)) in a univariable model.

These results support the hypothesis that preoperative resting heart rate is associated with myocardial injury. However, the analysis needs to be repeated using a multivariable model that corrects for known risk factors, such as co-morbid disease, urgency of surgery, age, and preoperative renal function. To make these findings clinically relevant, future work will focus on identifying a preoperative heart rate threshold above which the risk of myocardial injury is significantly increased. The results could then be used in the preoperative assessment setting to identify patients at risk of perioperative myocardial injury.

References


The effect of acupuncture on bilateral bispectral index measurements and stress in healthy volunteers: a randomized, crossover pilot study

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\(^1\)Sheffield Teaching Hospitals NHS Foundation Trust, UK, and \(^2\)University of Sheffield Medical School, UK

Studies from outside the UK have demonstrated that acupuncture at the Yintang point decreases unilateral bispectral index (BIS) values\(^1\) and preoperative anxiety scores.\(^2\) We aimed to assess the effect of acupuncture on bilateral BIS and anxiety levels in a cohort of British subjects.

Ten healthy male volunteers with no medical co-morbidities were recruited. Bilateral BIS monitoring (Covidien Ltd, Dublin, Ireland) was applied, and baseline anxiety levels were assessed using the Abbreviated State Trait Anxiety Inventory (STAI; minimum 4, maximum 24) and a visual stress scale (VSS; 0, no stress; and 10, worst stress imaginable). After a 15 min period of acclimatization, volunteers were randomly assigned to receive acupuncture using semi-permanent acupuncture needles at either the Yintang point (intervention; between two medial ends of the eyebrows) or P6 (control; between tendons of flexor carpi radialis and palmaris longus, 2 cm from the non-dominant palmar crease). Bilateral BIS was then monitored for a further 15 min, after which the STAI and VSS were remeasured. During a second visit on a different day, the process was repeated with acupuncture at the other site. Data analyses were done using SigmaStat (version 3.11, Systat Software, San Jose, CA, USA). Bispectral index data were not normally distributed and are expressed as median (inter-quartile range) with Kruskal–Wallis one-way ANOVA, while STAI and VSS scores are expressed as mean (SD) with Student’s paired t-test used for comparison.

All volunteers completed the study. Mean (SD) age was 21.6 (1.91) yr. Baseline values for BIS, STAI, and VSS were similar for both interventions. Acupuncture at the Yintang and P6 point had no effect on BIS values in either cerebral hemisphere (Table 6). There were no significant differences in STAI scores after acupuncture at both points [Yintang, 7.9 (3.81) to 5.5 (1.43), \(P=0.055\); and P6, 6.6 (1.71) to 6.2 (1.75), \(P=0.583\)]. Baseline VSS values were very low, and there were no clinically meaningful changes after the interventions [Yintang, 1.64 (1.36) to 0.92 (1.17), \(P=0.03\); and P6, 2.22 (1.50) to 1.55 (1.23), \(P=0.084\)].

Acupuncture at the Yintang point in our cohort did not decrease BIS values in either cerebral hemisphere and had no effect on anxiety levels, although the low baseline anxiety may have contributed to the limited effect seen.

References


Opioid receptor expression on human vascular tissues

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Opioids are widely used, and there is evidence for a role in neovascularization, tumour growth, and immune suppression.\(^1\) In a cancer patient, this represents ‘the perfect storm’ and an ideal set of characteristics to enhance tumour survival. Classical naloxone-sensitive opioid receptors are classified as MOP (\(\mu\)), DOP (\(\delta\)), and KOP (\(\kappa\)). In addition, the non-classical receptor for nocioceptor/ orphanin FQ (N/OFQ), NOP, is a member of this family.\(^2\) The aim of this study was to explore the presence of opioid.

| Table 6 | Bispectral index (BIS) values at baseline and after acupuncture at intervention (Yintang) and control (P6) points. Values are medians (inter-quartile range) |
|---|---|---|---|---|---|
| Acupuncture site | BIS measurement side | BIS baseline (t=0) | BIS 5 min after acupuncture | BIS 10 min after acupuncture | P-value |
| Yintang | Left | 94 (92–97) | 94 (90–97) | 94.5 (89–97) | 0.243 |
| | Right | 95 (93–97) | 95 (88–96) | 94.5 (89–97) | 0.155 |
| P6 | Left | 94 (91.5–97) | 94.5 (91–97) | 95 (91–97) | 0.947 |
| | Right | 94 (91.5–97) | 95 (91–97) | 96 (93–97) | 0.315 |
receptors in tissue from human blood vessels with a view to assessing the role played by opioids in neovascularization.

Anonymized primary human umbilical vein endothelial cells (HUVECs; n=4) and human vascular smooth muscle cells (HVSMCs; n=5) were screened for expression of MOP, DOP, KOP, and NOP transcripts by quantitative real-time and gel-based PCR techniques. Additionally, both normal cadaveric (35–75 yr; 3:2, male:female) and diseased (22–77 yr; 4:1, male:female; AAA diameter 3.0–6.8 cm) aortic smooth muscle cell cultures were further tested using quantitative PCR for transcripts encoding NOP and MOP. Where appropriate, data are expressed as PCR cycle threshold (Ct) relative to the housekeeper glyceraldehyde-3-phosphate dehydrogenase, GAPDH (ΔCt).

The HUVECs and HVSMCs both expressed MOP and NOP receptors; DOP and KOP were absent (Table 7). In the case of DOP, there were issues with primer selectivity requiring a careful evaluation of expression using gel-based PCR. In non-AAA cadaveric and aneurysmal aortae, NOP but not MOP was detected.

We have demonstrated NOP expression in all tissues examined. MOP does not appear to be expressed in large primary vessels, but numbers are low. We are currently looking to describe a function for these expressed receptors and probe further for a disease signal using banked human tissues.

Funded by a small project grant from Vascular Anaesthesia Society of Great Britain and Ireland.

References
2. Dietis N, Rowbotham DJ, Lambert DG. Br J Anaesth 2011; 107: 8–18

Usability testing of the new ‘neuraxial’ ISO 80369-6 small-bore connector

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1Surgical Materials Testing Laboratory, Princess of Wales Hospital, Bridgend, UK, 2Consultant Anaesthetist (retired), 3Baxter Healthcare, Deerfield, IL, USA, and 4Surgical Materials Testing Laboratory, Princess of Wales Hospital, Bridgend, UK

After adverse events and deaths resulting from the wrong-route delivery of drugs,1 the International Organization for Standardization (ISO) has developed a range of standardized connectors (the ISO 80369 series) for medical devices, to be used for specific applications and to be non-interconnectable between applications. The ISO 80369-6 standard specifies the dimensional and performance requirements of connectors intended to be fitted to devices used in central and regional ‘neuraxial’ procedures.

To ensure clinical acceptability when deployed, usability testing was required. A multicentre observational study was devised involving simulated procedures on manikins, comparing devices fitted with ISO 80369-6 connectors and existing Luer connectors.

Thirty-eight clinicians and 17 nurses were recruited in four centres (Bridgend, Bath, Bristol, and Leicester). Each clinician completed up to two defined simulated procedures: spinal anaesthesia; intrathecal chemotherapy; cerebrospinal fluid collection and pressure measurement; and epidural anaesthesia. Clinicians performed each procedure(s) twice; once using devices fitted with Luer and once with ISO 80369-6 connectors, in a randomized order. Nurse participants carried out three procedures on a manikin simulating a PACU/ICU patient: epidural bolus and infusion; enteral feed initiation; and i.v. bolus and infusion. Participants were also asked to attempt cross-connecting both male and female ISO 80369-6 connectors with connectors on devices typically found in that environment. All procedures were recorded via video ‘glasses’ worn by participants and by static video cameras. After each procedure, both the participant and the moderator completed qualitative questionnaires. Recordings were analysed to score procedural issues such as task times and errors.

Initially, a three-way tap fitted with ISO 80369-6 connectors leaked fluid and was found to be incorrectly dimensioned. It was replaced with a compliant tap for the remainder of the study. There were no marked differences in user acceptability of the connectors. Lower levels of acceptability were seen in both connector types where associated devices (e.g. epidural catheters and connectors) were substantially different in configuration from those used in the clinician’s normal practice.

The project identified some residual cross-connections that have required further investigation and mitigation by the ISO group. This usability study was part of the evidence base that helped all national standards bodies vote for approval of the ISO 80369-6 designs.

Acknowledgements
We are grateful to M. Stacey (Bridgend), T.M. Cook (Bath), S.M. Kinsella (Bristol) and P. Sharpe (Leicester) for leading the studies, A. Ackerman for video analysis, and AAMI (Association for the Advancement of Medical Instrumentation) for organizing project funding.

References

Nociceptin/orphanin FQ receptor stimulation reduces human polymorphonuclear cell migration in vitro

M. Al-Hashimi1, J. P. Thompson1, G. Calo2, R. Guerrini3, D. G. Lambert1

1Department of Cardiovascular Sciences, University of Leicester, Division of Anaesthesia, Leicester Royal Infirmary, Leicester, UK, 2Department of Medical Science, Section of Pharmacology and National Institute of Neuroscience, and 3Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Italy

Table 7 MOP and NOP mRNA expression in human vascular tissue. Data are either full set for HUVECs (n=4) or median and full range for n=5. AAA, abdominal aortic aneurysm; ND, not detected

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<tr>
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<th>MOP ΔCt</th>
<th>NOP ΔCt</th>
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<td>HUVEC</td>
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<td>Cadaveric</td>
<td>ND</td>
<td>11.77 (10.53–13.22)</td>
</tr>
<tr>
<td>AAA</td>
<td>ND</td>
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Peripheral polymorphonuclear (PMN) white blood cells influence innate and adaptive immunity through chemotaxis, phagocytosis, cytokine/chemokine production, enzyme/peptide secretion, and reactive oxygen species production. Human PMN cells express non-classical opioid receptor (NOP) mRNA. The effect of NOP receptor stimulation on PMN migration is not fully understood. We conducted series of experiments to study migration of PMN cells collected from adult healthy volunteers in vitro with and without a range of NOP receptor agonists.

We collected venous blood from seven healthy volunteers (four male and three female, mean age 38 (range 32–50) yr). The PMN cells were harvested using a commercially available kit. Transwell migration assay was performed by loading 10^4 cells onto tissue culture plate filter inserts with 3 µm pore size. Five PMN cell populations were mixed with different concentrations of NOP agonists (N/OFQ; 300, 30, 3, 0.3, and 0.03 µM). Seven PMN cell populations were mixed with different concentrations of NOP agonists (N/OFQ; [desPhe1]N/OFQ) to compare their effects with N/OFQ on PMN cell migration. fMLP was used as a chemoattractant agent to promote PMN cell migration across filter inserts. Morphine was used as a negative control.

N/OFQ caused significant inhibition of PMN cell migration (EC_{50}=8.2 nM; Fig. 3). Compared with baseline, fMLP-induced migration was reduced to a mean of 0.85 with the novel tetra-branched highly stable analogue PWT2-N/OFQ. There were no significant differences in PMN migration compared with fMLP with the structurally inactive [desPhe1]N/OFQ and morphine.

N/OFQ stimulation causes significant inhibition of peripheral human blood PMN migration in vitro, strengthening the involvement of the N/OFQ system in immunomodulation.

**Funding**
Ernest Leach Fund – RCoA small research grant.

**References**
1. Malech HL, DeLeo FR, Quinn MT. Methods Mol Biol 2014; 1124: 3–10

**Endothelial glyocalyx disruption and lung injury after thoracic surgery**

A. Arthur^1, P. J. McCall^1, L. Jolly^1, J. Kinsella^1, A. Kirk^2, B. G. Shelley^2

^1University of Glasgow, UK, and ^2Golden Jubilee National Hospital, Glasgow, UK

Lung resection is associated with significant morbidity and mortality; the major cause of which is the development of post-lung resection acute lung injury (PLR-ALI) after up to 7% of lung resections, with a mortality of up to 88%.

Current understanding of PLR-ALI is incomplete; however, the clinical picture and pathological process appear similar to that of acute respiratory distress syndrome (ARDS). The EGL is a backbone of glycoproteins and proteoglycans adherent to the endothelial cell surface, essential in the normal homeostasis of inflammation and microvascular fluid exchange. The serum biomarkers heparan sulphate proteoglycan (HSPG) and syndecan-1 (SCD1) are widely used markers of EGL disruption and are known to be elevated after vascular and cardiac surgery but have not previously been measured in a lung resection population.

Plasma samples were collected from 16 patients undergoing lobectomy for primary lung cancer. Heparan sulphate proteoglycan and SCD1 were measured using human-specific enzyme-linked immunosorbent assay kits (USCN Life Science Inc., Wuhan, China) according to the manufacturer’s instructions in duplicate at five perioperative time points. The coefficient of variation for these measurements was 18.4 and 9.2%, respectively. Clinical outcome measures including postoperative oxygenation were recorded. One-way repeated measures ANOVA was conducted to determine whether there were differences in SCD1 and HSPG concentrations over the perioperative period.

There were significant changes in SCD1 concentration over time (P<0.001). Post hoc pairwise comparisons showed that

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**Fig 3** N/OFQ produces a concentration-dependent inhibition of PMN migration (left panel), and this was mirrored by the novel N/OFQ analogue PWT-N/OFQ but not the structurally inactive analogue Des-Phe1 N/OFQ or the MOP agonist morphine (right). Data are presented as Means (±). *PWT Aanova significant compared with fMLP (P<0.05).
SCD1 concentration was significantly elevated in the immediate postoperative period, peaking on postoperative day 2 ($P<0.001$; Fig. 4). For HSPG, one-way repeated measures ANOVA indicated significant changes over time ($P=0.04$), but post hoc pairwise comparisons revealed no significant results and examination of box plots revealed a wide distribution of results at each time point. There was no relationship found between HSPG or SCD1 concentrations and any clinical measure of PLR-ALI.

Post-lung resection acute lung injury remains a poorly understood condition, with a high mortality and limited therapeutic options. While underpowered to detect the clinical significance, this pilot study provides evidence of EGL disruption after lung resection surgery. We hypothesize that EGL disruption is involved in the pathogenesis of PLR-ALI and are conducting a larger study in a combined cardiothoracic and vascular population to investigate this further.

References
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Renal allograft ischaemia–reperfusion injury induces remote hepatic injury in rats

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Ischaemia–reperfusion injury (IRI) is an unavoidable consequence of renal transplantation and a major determinant of graft survival. Accumulating clinical evidence has identified a close relationship between renal injury and injuries to other organs, including heart, lung, and liver. The liver is particularly vulnerable to inflammatory change from the distant kidney. The aim of this study was to investigate remote hepatic injury in a rat allogeneic transplantation model.

The Brown Norway rat renal graft was stored in Soltran preserving solution at 4°C for 0–24 h and then transplanted into a Lewis rat recipient. The liver was harvested 24 h after surgery. Hepatocyte necrosis was assessed by Tunnel assay and liver inflammation by nuclear factor-$\kappa$B and CD68+ macrophage count in the samples. Liver tissue HMGB-1 and interleukin-1$\beta$ were evaluated by enzyme-linked immunosorbent assay. Data are based on four transplants.

Prolonged cold ischaemia in renal grafts greatly increased the liver injury score and necrotic hepatocytes 24 h after engraftment. Nuclear factor-$\kappa$B expression of hepatocytes and the number of CD68+ infiltrating macrophages, liver tissue HMGB-1 and interleukin-1$\beta$ were greatly increased after renal graft ischaemia–reperfusion. Administration of HMGB-1 induced hepatic injury, and the remote hepatic injury was exacerbated after this treatment.

Our data indicated that IRI in renal allograft is associated with extensive liver inflammation and hepatocyte damage after engraftment. HMGB-1 might promote the remote hepatic injury, and interventions that inhibit HMGB-1 activity may be effective in minimizing organ injury associated with renal graft IRI.

References