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# **Abstracts**

## **(ARS)**

**November 2011**

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Abstracts submitted for the President's Award for Undergraduate Research will be presented by poster; these abstracts are provided separately.

## **Isoflurane Anaesthesia impairs Remote Neocortical Memory**

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Postoperative cognitive dysfunction (POCD) is a common complication following surgery in elderly patients (1) although the responsible role of surgery-induced inflammation and/or anaesthesia on the development of POCD remains elusive. The aim of the present study was to investigate the impact of isoflurane-induced anaesthesia on hippocampal and neocortical dependent memory in mice in comparison with lipopolysaccharide (LPS)-induced inflammation which is well documented to induce a hippocampal-dependent memory impairment (2).

Young adult mice were trained as naïve with contextual fear conditioning, after which mice were randomly allocated to different experimental groups either immediately after training (experiment 1) or 3 days after training (experiment 2). The experimental groups were: Naive - no intervention; Anaesthesia – 20 minutes of general anaesthesia with isoflurane + buprenorphine for analgesia; LPS was injected i.p. at a concentration of 100 µg/kg. Mice were placed in the fear-conditioning box either 3 (experiment 1) or 32 days after training (experiment 2), to assess memory function.

*First experiment:* in the context test, mice in the LPS group displayed the greatest level of hippocampal-dependent memory impairment (35.0% ± 4.29, vs control  $p < 0.05$ ). Isoflurane-induced anaesthesia does not result in hippocampal memory impairment (49.67% ± 6.87,  $p > 0.05$  compared to control).

*Second experiment:* the control mice displayed the greatest levels of generalization of freezing; while LPS revealed a cognitive dysfunction (74.63% ± 16.09 vs control,  $p < 0.05$ ), similarly isoflurane-induced anaesthesia results in a memory deficit (62.13% ± 16.42 vs control,  $p < 0.05$ ).

Cognitive function dependent on the hippocampus, where long-term memory is initially stored, is disrupted after LPS-induced inflammation. LPS-induced inflammation and isoflurane-induced anaesthesia both have a detrimental effect on neocortical memory recall suggesting that the transference of memory between the hippocampus and the neocortex, the ultimate storage site of long-term memory, is affected by isoflurane anaesthesia or LPS.

**References:** (1) Moller JT, Cluitmans P, Rasmussen LS et al, *Lancet*. 1998; 351: 857-61; (2), Fidalgo AR, Cibelli M, White JP et al, *Neurosci Lett*. 2011; 498: 63-6

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## Magnetic resonance imaging measures of cerebral perfusion following subarachnoid haemorrhage

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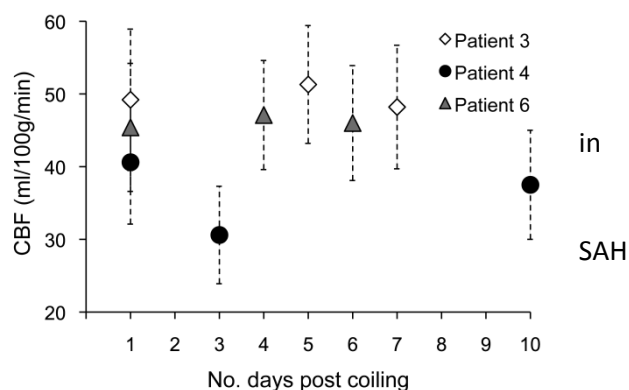
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Delayed cerebral ischaemia (DCI) is the main cause of morbidity and mortality following subarachnoid haemorrhage (SAH). Vasoconstrictive processes have been considered fundamental in the pathophysiology behind DCI. Recently, other mechanisms have been proposed.<sup>1</sup> In this preliminary study, we investigate the feasibility of using the non-invasive magnetic resonance imaging (MRI) technique, arterial spin labelling (ASL), to track CBF changes in the acute period following SAH.

6 SAH patients (5 x Grade I and 2 x Grade II, World Federation of Neurosurgeons) were scanned on a 3 Tesla Siemens MRI scanner with a 12-channel head coil. Patients were scanned on varying days post-endovascular coiling. A pseudo-continuous ASL sequence was used to assess CBF.<sup>2</sup> The sequence consisted of a 1.4 s labelling duration followed by five post labelling delays and a gradient-echo echo planar imaging (EPI) readout (TR=3.75s, TE=13ms). Additional scans included a time-of-flight angio image (1.5 min duration) and two ASL calibration scans (2 x 11 secs) to allow quantification of CBF in absolute units (ml/100g/min). CBF was quantified by fitting the data to the ASL kinetic model, using a Bayesian inference approach.<sup>3,4</sup>

The average grey matter CBF values obtained across all subjects was  $45.06 \pm 7.36$  ml/100g/min. Figure 1 shows the trend in CBF in the three patients (3, 4 and 6) that were scanned on three occasions. Patient 4 demonstrated a global CBF reduction on the second scanning day that occurred at the same time as a deterioration in clinical symptoms. This patient scored 15 points on the Glasgow Coma Scale (GCS) that is routinely used to assess SAH patients.

The preliminary study demonstrate the feasibility of using ASL MRI to reproducibly and non-invasively track changes in CBF in SAH. The CBF decrease shown in Figure 1 was not detected by routine clinical assessment. Clinical scales such as GCS are not sensitive to subtle changes in cerebral perfusion in patients that may be an important predictor of deterioration and/or the onset of DCI. The role of novel MRI techniques such as ASL in assessing SAH patients during the acute phase requires further investigation in a larger clinical study.



**Figure 1.** Cerebral blood flow measured with arterial spin labelling MRI in 3 patients following subarachnoid haemorrhage.

**References:** 1. Cahill J, Zhang JH. *Stroke* 2009; 40: S86-7; 2. Dai W, Garcia D, de Bazelaire C, et al. *Magn Reson Med* 2008; 60: 1488-97; 3. Buxton RB, Frank LR, Wong EC, et al. *Magn Reson Med* 1998; 40: 383-96; 4. Chappell MA, Groves AR, Whitcher B, et al. *IEEE Sig Proc* 2009; 45: 795-809

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## Using propofol to differentiate between mixed populations of recombinant GABAARs expressed in HEK cells

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Neuronal GABAA receptors (GABAARs) mediate the sedative, hypnotic and immobilizing effects of the general anaesthetic propofol. GABAARs are heterogenous pentameric proteins drawn from a repertoire of 19 different subunits, with the  $\alpha 1\beta 2\gamma 2$  configuration being the most abundant. However, there is increasing evidence for the existence of mixed GABAAR subtypes within individual neurones. For example, GABAARs located within the synapse have a different subunit combination and differing functional properties compared to those located extrasynaptically<sup>1</sup>. It remains unclear whether propofol affects these neuronal GABAAR subtypes in the same way, or whether different aspects of propofol's actions may be mediated through distinct receptors. In this study we examined whether functionally distinct GABAAR subtypes assemble in HEK293 cells by transiently expressing either  $\alpha 1$ ,  $\beta 2$  and  $\gamma 2$  subunits or  $\alpha 1$ ,  $\beta 3$  and  $\gamma 2$  subunits. We characterised the pharmacological properties of recombinant GABAARs using the agonists GABA and propofol in conjunction with the antagonists gabazine and bicuculline methiodide.

Single cells expressing either  $\alpha 1\beta 2\gamma 2$  or  $\alpha 1\beta 3\gamma 2$  receptors were clamped at -60 mV and activated with GABA or propofol using a rapid application technique. Under these conditions both GABA and propofol induced bicuculline- and gabazine-sensitive inward currents. Further experiments demonstrated that bicuculline could accelerate the deactivation of propofol-activated currents mediated by  $\alpha 1\beta 2\gamma 2$  receptors. However, bicuculline was less effective in this regard for  $\alpha 1\beta 3\gamma 2$  receptors. This was a surprising result as  $\beta 3$  and  $\beta 2$  subunits are structurally very similar, however  $\beta 3$  subunits contain an extracellular amino acid motif (GKER) not found in  $\beta 2$  subunits, which enables homomeric assembly<sup>2</sup>. Expression of the  $\beta 3$  subunit alone or in combination with the  $\gamma 2$  subunit produced receptors that were activated by propofol and, interestingly, also by the antagonist bicuculline. GABA displayed weak agonist and gabazine weak antagonist activity. Expression of the  $\beta 2$  subunit alone or with the  $\gamma 2$  subunit did not produce functional receptors. However, a  $\beta 2$ (GKER) mutant subunit, containing  $\beta 3$  subunit residues required for homomeric assembly, produced receptors that shared similar pharmacology with  $\beta 3$  receptors. Furthermore, bicuculline was less effective at accelerating the deactivation of propofol-induced currents mediated by  $\alpha 1\beta 2$ (GKER)  $\gamma 2$  compared to wild type  $\alpha 1\beta 2\gamma 2$  receptors.

These data suggest that cells expressing  $\alpha 1$ ,  $\beta 3$  and  $\gamma 2$  subunits are composed of a mixed population of homomeric and heteromeric receptors and those lacking  $\alpha 1$  subunits (either  $\beta 3\gamma 2$  or  $\beta 3$ ) may be distinguishable by the agonist actions of propofol and bicuculline.

**References:** 1. Farrant M, Nusser Z. *Nat Rev Neurosci* 2005; 6(3): 215-229; 2. Taylor PM, Thomas P, Gorrie GH, Connolly CN, Smart TG, Moss SJ. *J. Neurosci.*, 1999; 19(15): 6360-6371.

## **GABA immunotransmission controls macrophage function increasing vulnerability to pneumonia**

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Benzodiazepines are used by up to 10% of elderly patients<sup>1</sup> and for sedation in the critically ill<sup>2,3</sup>, transducing their neuronal effects by augmenting  $\gamma$ -amino-butyric acid (GABA) neurotransmission. Intriguingly macrophage synthesize GABA<sup>4</sup> and express some GABA<sub>A</sub> subunits<sup>5,6</sup>, yet the functional significance of a GABA “immunotransmission” system remains obscure. A previous animal study suggested that sub-sedative doses of benzodiazepines increase susceptibility to infection<sup>7</sup> however it is unclear whether the mechanism involves GABA<sub>A</sub> signaling or not; furthermore the clinical impact of this finding is unknown. Herein we uncovered evidence for cytokine and toll like receptor agonist regulated benzodiazepine sensitive ( $\alpha 1\beta 2\gamma 2$ ) GABA<sub>A</sub> receptors on macrophage (but not other immune effectors). GABA<sub>A</sub> receptor stimulation reduced alveolar macrophage TNF-alpha production, phagocytosis and bacterial killing *ex-vivo*. During infection, endogenous regulation decreased alveolar macrophage GABA<sub>A</sub> receptor expression. Opposing this reduction of GABAergic tone by augmenting GABA<sub>A</sub> signaling with anxiolytic doses of the benzodiazepine, diazepam, increased mortality from *Streptococcus pneumoniae* pneumonia in C57BL/6 mice with co-existent delayed TNF-alpha driven immune response and increases in pathogen load. The role of the GABA<sub>A</sub> receptor was confirmed using the antagonist bicuculline. The clinical impact of our findings was confirmed in a cohort of 4964 human subjects with community acquired pneumonia, where benzodiazepine use increased adjusted 30-day and long-term mortality. Our data indicate that GABAergic immunotransmission controls macrophage responses and that benzodiazepine activation of GABA<sub>A</sub> receptors during an infection opposes the endogenous regulation of GABAergic tone inhibiting an appropriate immune response. Thus benzodiazepines increase vulnerability to pneumonia.

**References:** 1. Gleason PP, Schulz R, Smith NL, et al. J Gen Intern Med 1998; 13: 243-50; 2. Pandharipande PP, Sanders RD, Girard TD, et al. Crit Care 2010; 14: R38; 3. Riker RR, Shehabi Y, Bokesch PM, et al. JAMA 2009; 301: 489-99; 4. Stuckey DJ, Anthony DC, Lowe JP, et al. J Leuk Biol. 2005; 78: 393-400; 5. Bhat R, Axtell R, Mitra A, et al. Proc Natl Acad Sci U S A 2010; 107: 2580-5; 6. Alam S, Loughton DL, Walding A, Wolstenholme AJ. Mol Immunol 2006; 43: 1432-42; 7. Laschi A, Descotes J, Tachon P, Evreux JC. Toxicol Lett 1983; 16: 281-4

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## The position of the tips of conus medullaris in Chinese adult population with low backache: an MRI imaging study

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Spinal puncture is commonly performed below the second lumbar vertebra (L2) to avoid spinal cord injury. Increasing evidence indicates that the lower end of conus is located at the body of L1 or between L1 and L2<sup>1,2,3</sup>. Therefore, the primary objective of this observational study was to determine the tip of the conus in our Chinese population using MRI.

The MRI images of 718 patients with low backache were obtained from a single centre between September 2009 and December 2009. Images were obtained in the sagittal plane using T2 weighted imaging (T<sub>2</sub>W<sub>i</sub>) and 3D-constructive interference in steady-state (CISS). Reimann positioning of the spinal cord conus was used<sup>4</sup>. Anatomical sections of each lumbar level (x) were defined as: 1. Upper vertebral body (Lx:U); 2. Middle vertebral body (Lx:M); Lower vertebral body (Lx:L) and 4. Intervertebral disc. The position of the cone tip was defined as the most distal point of the spinal cord identified in the mid-sagittal MRI image. For analysis patients were stratified into 3 groups according to age: Group A = 18 to 29 yr, Group B = 30 to 59 yr, and Group C ≥ 60 yr.

The median conus tip position for males was L1:L and L1:M for females. However, the conus tip was located at L2 and below in 190 (26%) patients and L3 and below in 12 patients. Position of the conus correlated with the age; the older the patients, the lower the conus, Spearman's correlation,  $r = 0.11$ ,  $P = 0.001$ .

The results of the study indicate that the spinal puncture should not be performed higher than the L3-L4 intervertebral space in Chinese patients with low backache unless the position of the lower end of the spinal cord is identified using the prior MRI images.

Table 2. Distribution of the tips of conus position in the three groups divided by the age

	18 to 29 yr	30 to 59 yr	≥ 60 yr
T12	8	44	10
L1	60	310	96
L2	14	111	53
L3	0	7	3
L4	0	0	1
L5	0	1	0

**References:** 1.Saifuddin A et al. Spine 1998; 23: 1452-1456. 2.Ou YL et al. Journal of Clinical Radiology 2008; 27: 544-546. 3. Fettes PD et al. Anesthesia 2006; 61: 6. 4. Thomson A. Anat physiol 1894; 29: 35-60.

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## Interobserver reliability of measurements of the supraclavicular ultrasound view of the brachial plexus

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The performance of successful ultrasound guided supraclavicular blocks currently relies upon appropriate 2-dimensional ultrasound visualisation, accurate interpretation of that image and effective operator technique. Failure to do so can result in harm (inadequate block, local anaesthetic toxicity, pneumothorax) to patients.<sup>1</sup> The aim of this study was to evaluate how the acquisition of a standardised ultrasound image and its subsequent interpretation differs amongst anaesthetists.

Four anaesthetists of differing levels of experience with these blocks independently scanned 21 volunteers' right-sided supraclavicular fossae so that the subclavian artery, 1<sup>st</sup> rib and brachial plexus were all visible. The images were saved and analysed using imageJ v1.43u. The cross-sectional areas of the artery and plexus were measured and used as surrogate markers of image interpretation. All anaesthetists interpreted their own scans as well as one set of scans from the most experienced. Analysis was made using Stata/SE v11.0.

	Interpreting one set of scans	Interpreting own scans
Mean plexus area	0.79 cm <sup>2</sup>	0.97 cm <sup>2</sup>
Mean artery area	0.35 cm <sup>2</sup>	0.33 cm <sup>2</sup>
ICC for plexus area	0.18	0.12
ICC for artery area	0.83	0.24
Estimated error of plexus area measurement	0.35 cm <sup>2</sup> (CI: 0.29 cm <sup>2</sup> – 0.42 cm <sup>2</sup> )	0.41 cm <sup>2</sup> (CI: 0.35 cm <sup>2</sup> – 0.48 cm <sup>2</sup> )
Estimated error of artery area measurement	0.035 cm <sup>2</sup> (CI: 0.029 cm <sup>2</sup> – 0.042 cm <sup>2</sup> )	0.076 cm <sup>2</sup> (CI: 0.060 cm <sup>2</sup> – 0.091 cm <sup>2</sup> )

Our data (table) shows that when interpreting one anaesthetist's scans, the intraclass correlation coefficients (ICC) for plexus area were low and for artery area were high. When interpreting their own scans the ICC was low for both measurements. When interpreting one set of scans the variability in measurements are 44% and 10% for the plexus and artery respectively; when interpreting individual scans variability for plexus measurement is similar at 42% but for the artery is higher at 23%.

Comparing these data sets suggests that the main source of error in plexus area measurement is in the interpretation rather than acquisition of the scan image. However with the artery the opposite appears to be the case. This is perhaps due to the artery being pulsatile and the plexus being a more static image to capture. Our method of standardising the image capture by ensuring all three structures (artery, rib and plexus) were in view simultaneously does not appear to result in any extra variability in plexus measurement compared to having a single anaesthetist acquire all images. Nevertheless the ICC is poor for most measurements. This could imply that what actually constitutes nerve or vascular tissue is open to interpretation when using 2-dimensional ultrasound thus needle placement and drug deposition could be variable.

**References:** 1. Bhatia A, Lai J, Chan VW, Brull R. *Anesth Analg.* 2010;111(3):817-9

## A comparison of intraneural and extraneural shear modulus in the Thiel embalmed human cadaver

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Direct nerve damage still occurs during Ultrasound Guided Regional Anaesthesia (UGRA). However, a marked disparity exists between the incidence of inadvertent intraneural injection and overt nerve damage<sup>1</sup>; the latter may be attributable to injection of small volumes of local anaesthetic into subperineural rather than subepineural tissue. Illogically perhaps, clinical testing of needle tip location relies on the injection of a 1 mL volume of local anaesthetic and the possibility exists of endoneurial or intrafascicular injection. Thus, there is a clear need for novel technology to clearly identify intraneural and extraneural anatomy in order to make regional anaesthesia safer.

Shear wave elastography is a quantitative and reproducible ultrasound technology increasingly used to differentiate between “hard” breast cancer masses and “soft” normal tissue<sup>2</sup>. Unlike strain elastography, shear wave elastography applies a non-compressive longitudinal acoustic radiation force to underlying tissues, inducing transverse shear waves. Because standard ultrasound systems cannot image shear waves, frame rates up to 20 kHz are used. By measuring the shear wave at several locations and time of travel between points, the shear wave speed is measured. Therefore the primary objective of the study was the comparison of shear modulus in intraneural and extraneural tissue in Thiel embalmed human cadavers. Secondary objectives included measurement of shear modulus and reproducibility of shear modulus between raters.

B-mode imaging was overlaid with a colour map of shear wave modulus (Supersonic Imagine, Aix-en-Provence, France) and two paired circular regions of interest (ROI) were selected over the appropriate nerves and adjacent muscle. The paired ROI measures were defined as the statistical units for this study in cadavers. Two anaesthetists measured the shear modulus for intraneural and extraneural pairs at the same three anatomical block sites – interscalene, median and sciatic. Two cadavers were selected for imaging and 20 paired measures taken of each block site by both anaesthetists for the first cadaver. Twenty-five paired measurements were taken in the second cadaver. As the standard deviation of data increased with the modulus, log transformation of data was also undertaken. Linear mixed models with maximum likelihood estimation (MLE) were used to assess effects. Significance was defined at  $P < 0.05$  (two-tailed).

A total of 167 measurements was eligible for analysis. The results are shown in Table 1. Significant effects were identified for cadaver, operator, block site and intraneural versus extraneural measures, the latter having the largest effect. Intraclass correlation coefficient was 0.73 amongst raters.

Table 1. Shear modulus as geometric mean (95% confidence interval)

Intra/extra neural	kPa	Block Site	kPa
Intraneural	26.8(24.6–29.2)	Interscalene	25.6 (23.3–28.3)
Extraneural	6.2 (5.7–6.8)	Median	24.3 (21.8–27.0)
		Sciatic	3.5 (3.0–4.0)

In conclusion, differences exist in shear modulus for intra and extra neural measures and for different block sites. Further studies in human volunteers and patients are required to determine if shear modulus can be used to detect and avoid accidental intraneural injection and damage.

**References:** 1. Liu SS et al. Incidence of unintentional intraneural injection and postoperative neurological complications with ultrasound-guided interscalene and supraclavicular nerve blocks. *Anaesthesia* 2011;66:168-74. 2. Evans A et al. Quantitative shear wave ultrasound elastography: initial experience in solid breast masses. *Breast Cancer Res* 2010;12:R104

## Development and validation of a quantitative phenotype model for malignant hyperthermia susceptibility

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Phenotype-genotype analyses strongly suggest that some *RYR1*-variants only partially contribute to malignant hyperthermia (MH) risk<sup>1</sup>. We previously used four separate quantitative phenotypes derived from data collected during the diagnostic *in vitro* contracture testing (IVCT) to explore phenotype-genotype correlations.<sup>1</sup> These previous analyses showed that if we wished to use IVCT data to estimate the contribution of mutations to the MH susceptibility phenotype it would be preferable to develop a composite quantitative phenotype. We have conducted and published a similar study previously<sup>2</sup> but that was confounded by the need to use the IVCT itself to define true positive and true negative cases, thus invoking a circular argument. We are now in a position to use *RYR1* mutation status of individuals from families with identified causative mutations to define “true” positive and negative cases.

We selected 301 patients who had undergone IVCT testing and had been tested for a familial *RYR1* mutation associated with MH susceptibility. Using data from 137 of these patients we generated logistic regression probability (backward conditional and forward conditional) models for a composite quantitative phenotype. For construction of each model the dependent variable was *RYR1* mutation status and the predictor variables entered were the pre-drug twitch heights and the muscle contractures at each concentration of test agent for each of the static halothane, dynamic halothane and static caffeine tests ([www.emhg.org](http://www.emhg.org)). The model providing the optimal combination of face validity and best fit was then prospectively validated using the data from the remaining 164 patients. The accuracy of the models was determined using receiver operating characteristic (ROC) curves. SPSS v19.0 (IBM) was used for analyses.

The model generated using the backward conditional algorithm classified 93.6% of cases correctly but the forward conditional model produced fewer anomalies and classified 92.6% of cases correctly. The ROC curves for this model in the two sets of patients are shown in the figure.

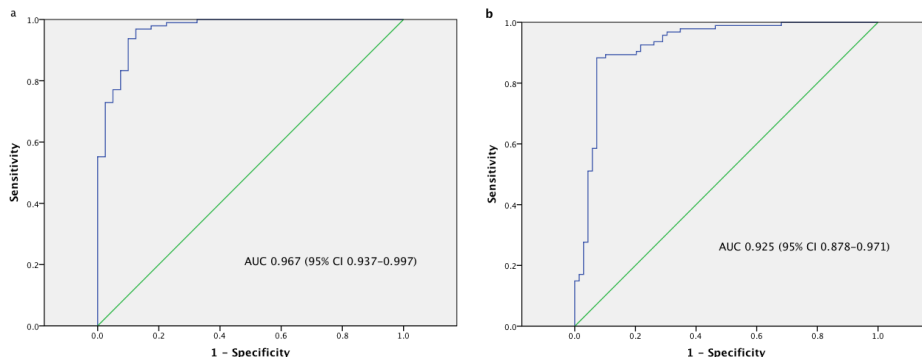


Figure: ROC curves for (a) model generation and (b) test datasets

Using the validated model we will next apply quantitative linkage analyses to families with uncharacterized *RYR1* variants in order to estimate the contribution of these variants to the phenotype.

**References:** 1. Carpenter D, et al. *Br J Anaesth* 2009 103: 538-48; 2. Hopkins PM, et al. *Anesth Analg* 1997; 84: 648-56

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## Do malignant hyperthermia susceptible patients have higher baseline core body temperature?

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Preliminary data suggest that mutant *RYR1* transgenic knock-in mice susceptible to malignant hyperthermia (MH) have a higher baseline core body temperature than wild type mice and this is associated with increased energy expenditure (*IN Pessah, PD Allen personal communication*). The aim of this study was to compare overnight rectal temperature measurements in patients testing positive for MH and those testing negative.

For the first 20 years (1971-91) of our MH diagnostic service we used a rectal probe to monitor the core body temperature of patients attending for muscle biopsy from 21.00 hr the evening before biopsy until discharge from the recovery room the following morning. The temperature was recorded every 1-2 hr by the nursing staff. For the purposes of this study, preoperative temperature data were extracted from the MH Unit records of 130 patients (MH positive, n=65, MH negative, n=65) and entered into an anonymised database for analysis. We compared the mean and maximum temperatures as well as the range for each patient between the groups (Mann Whitney U test, IBM SPSS 20 software).

The patients' ages, sex and temperatures are shown in the table.

	MH positive	MH negative	P value
Age (yr, mean, range)	29.7, 5-75	26.5, 5-75	0.26
Sex (m:f)	29:36	35:30	0.38
Mean temperature (°C, median, IQR)	36.83, 36.68 - 37.0	36.69, 36.67 - 36.7	0.013
Maximum temperature (°C, median, IQR)	37.4, 37.0 - 37.7	37.25, 37.0 - 37.6	0.41
Temperature range (°C, median, IQR)	1.0, 0.6-1.3	1.17, 0.89-1.49	0.028

Although this was not a tightly controlled thermoregulatory study our data suggest that MH positive patients may have higher average core body temperatures than MH negative patients. The differences we observed are small and of no direct relevance to the clinical context of these patients but our findings are consistent with a growing body of evidence that the metabolic profile of MH muscle is altered even in the absence of triggering drugs.

## Is the Nociceptin Orphanin FQ peptide (N/OFQ) / Nociceptin Orphanin FQ receptor (NOP) system dysregulated in asthma?

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The Nociceptin Orphanin FQ (N/OFQ) receptor (NOP) is a non-opioid member of the opioid receptor family. N/OFQ is the endogenous ligand for NOP and exerts a variety of physiological effects in the nervous system (central and peripheral), the cardiovascular system, the airways, the gastrointestinal tract, the urogenital tract and the immune system<sup>[1]</sup>. Asthma is a chronic inflammatory airway disease characterised by variable degree of airflow obstruction and airway hyper-responsiveness<sup>[2]</sup>. Current evidence from animal model studies suggests that N/OFQ reduces airway hyper-responsiveness and thus could potentially play a key role in regulating airway inflammation<sup>[3]</sup>. To date there is no data on N/OFQ-NOP expression in structural and immune cells from the normal or diseased human airways. Therefore the potential role of N/OFQ-NOP system in asthma is unknown. The main objective of this project was to determine NOP and N/OFQ precursor prepro-nociceptin (ppN/OFQ) mRNA and protein expression in primary inflammatory and structural cells from the normal and asthmatic airways and then investigate their functional role.

RNA extracted from the airway cells were specifically probed with nociceptin receptor, ppN/OFQ and GAPDH (housekeeping gene) TaqMan primers by qRT-PCR. The data was expressed as difference in cycle threshold relative to GAPDH mRNA expression. To determine NOP receptor protein expression, radioligand saturation binding assays were performed using [<sup>3</sup>H]UFP-101 and [<sup>125</sup>I]N/OFQ where there was sufficient tissue.

No ppN/OFQ mRNA expression could be detected in any of the human airway cells. Average  $\Delta C_T$  values recorded for NOP mRNA expression was  $11.37 \pm 1.25$  (mean  $\pm$  SD; n=6) in normal human airway smooth muscle cells (HASMs) and  $10.77 \pm 1.04$  (mean  $\pm$  SD, n=7) in asthmatic HASMs. However, using radioligand saturation binding assays we failed to detect NOP receptor protein expression on normal and asthmatic HASMs (n=4 each). As a control for these experiments we were able to detect high levels of expression in cell line expressing recombinant human NOP. With human bronchial epithelial cells,  $\Delta C_T$  values observed in normal cells for NOP mRNA were 11.39, 11.36, 8.12, and 8.10 (mean  $\Delta C_T$  = 9.75, n=4) and those recorded in asthmatic cells were 12.12, 9.61, 10.31 and 10.46 (mean  $\Delta C_T$  = 10.63, n=4). Similarly  $\Delta C_T$  values observed for human lung mast cell NOP mRNA were 4.63, 7.65 and 6.95 (mean  $\Delta C_T$  = 6.41, n=3) and those recorded in human lung fibroblasts were 4.10, 4.70 and 5.01 (mean  $\Delta C_T$  = 4.60, n=3).

This is the first study to investigate the expression of NOP receptors on human airway structural and immune cells. These studies revealed that human lung mast cells and lung fibroblasts express relatively higher amounts of NOP mRNA expression. None of the cells expressed ppN/OFQ mRNA. Further functional studies on these cells would reveal their physiological role in regulating inflammation within the airways. This could potentially identify novel molecules for the management of airway inflammatory diseases including asthma.

**References:** 1. Lambert DG. *Nat Rev Drug Discov.* 2008;7(8):694-710; 2. Siddiqui S, Hollins F, Saha S *et al.* *Eur Respir J.* 2007;30(6):1043-56; 3. D'Agostino B, Orłotti D, Calò G, *et al.* *Am J Respir Cell Mol Biol.* 2010;42(2):250-4

**Acknowledgements:** Funded by Asthma UK

## A randomised crossover trial comparing a single-use PVC laryngeal mask with a single-use silicone laryngeal mask made by the same manufacturer

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Single-use polyvinyl chloride (PVC) laryngeal masks (LMs) have increased in use since their introduction in 1997, mainly due to concerns regarding possible prion transmission with reusable silicone LMs [1, 2]. Silicone potentially offers increased flexibility when compared to PVC, which may reduce airway trauma [3]. A number of single-use silicone LMs are now available, but are more expensive than PVC versions. We compared a single-use PVC (pLM) with a single-use silicone (sLM) laryngeal mask, both produced by Flexicare Medical and identical in design except for the material from which they were manufactured.

After local ethical approval, 72 ASA one and two patients, aged 18-79, undergoing elective surgery and suitable for LM insertion, were recruited. Intravenous access and full monitoring was instituted before induction of anaesthesia with fentanyl  $1\mu\text{g kg}^{-1}$  and propofol 1%, titrated until loss of the eye lash reflex. Sevoflurane was titrated until jaw relaxation was achieved. The LM size was chosen and inserted according to the manufacturer's guidance. The order of insertion was randomly assigned. Insertion success, insertion time, leak pressure, position (Brimacombe score [4]), subjective ease of insertion, and ease of ventilation were recorded, as were pre- and post- insertion vital signs. After three minutes of steady state anaesthesia the first LM was removed, the second LM inserted and identical tests performed. Intra- and postoperative complications were recorded.

The mean (SD) age was 39 (17) years and body mass index was  $25.9 (4.9) \text{ kg m}^{-2}$ . Male: female ratio was 54:18 and the ASA one: two ratio was 52:20.

Table 1: 1<sup>st</sup> time insertion rate (n=72)

	pLMA	sLMA
Success	68 (94%)	64 (89%)
Failure	4 (6%)	8 (11%)

McNemar's test did not demonstrate a significant difference for first time insertion rate ( $p=0.39$ ). There was no difference between the performance of the LMs with respect to Brimacombe score, insertion time or ease of ventilation. The mean seal pressures for the sLM was higher ( $p=0.017$ , difference of  $1.6\text{cm H}_2\text{O}$ ). The pLM was easier to insert ( $p= 0.025$ ).

In conclusion we did not find a difference in the first time insertion rates of single-use PVC and silicone LMs made by the same manufacturer. The higher seal pressure for the sLM is unlikely to be clinically significant. Subjectivity the pLM was easier to insert, which may be due to user familiarity.

**References:** 1. Smith G. *The Royal College of Anaesthetists Bulletin* 2001; May 7: 302–4; 2. Parker MRJ, Day CJE. *Anaesthesia* 2000; 55: 388–90. 3. Wilkes T, Crawford D. *Buyer's guide: Laryngeal masks*. NHS Purchasing and Supply Agency, July 2008 <http://www.wales.nhs.uk/sites3/Documents/443/CEP08010%20Laryngeal%20masks%20BG.pdf>; 4. Brimacombe J, Berry A. *Anesthesia and Analgesia* 1993; 76: 457.

## Dexmedetomidine pretreatment reduces the cardiac adverse events of intravenous administration of ropivacaine in rats

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Cardiac toxicity is a serious side effect of amide local anaesthetics such as ropivacaine. Our hypothesis in this laboratory study was that dexmedetomidine, an  $\alpha_2$ -adrenoceptor agonist, prevented cardiac adverse effects during the administration of ropivacaine in a small animal model<sup>1 2 3 4</sup>.

Forty Wistar rats were randomly allocated to four groups of increasing concentration of dexmedetomidine infused via a femoral vein over 10 min and monitored with ECG and MAP. The groups were: A (0 $\mu$ g/kg); B (5 $\mu$ g/kg); C (10 $\mu$ g/kg) and D (15 $\mu$ g/kg). Thereafter, ropivacaine 1%, was infused at 1ml/h via a femoral vein until an adverse cardiac event occurred, defined as: QRS >20% of the baseline, cardiac arrhythmia or MAP or heart rate < 25% of the baseline. The plasma concentration of ropivacaine was measured at the time of the cardiac adverse event.

In the control group, cardiac adverse events occurred at mean (SD) 846.7(124.7)s after ropivacaine infusion in the control group. In contrast, cardiac adverse events occurred later in groups B, C and D respectively (Table 1).

These results show that the dexmedetomidine pretreatment can delay the onset of cardiac adverse events in a dose dependent manner during ropivacaine intravenous administration. However, further investigation is required to determine the optimal concentration of dexmedetomidine<sup>5</sup>.

Table 1. Mean (SD) ropivacaine dose, plasma concentration and time to onset of cardiac adverse event. \* P <0.05 compared with control group A, ANOVA

	A	B	C	D
Ropivacaine dosage(mg)	2.36 (0.34)	3.98 (0.17)*	3.44 (0.34)	3.63 (0.57)*
Ropivacaine concentration in plasma ( $\mu$ g/kg)	0.59 (0.07)	3.36 (0.49)*	2.78 (0.43)	3.50 (0.40)*
Time to onset of cardiac adverse event	847 (125)	1433 (66)*	1235 (124)*	1300 (209)*

**References:** 1. Tanaka K et al. *Anesth Analg* 2005; 100: 687-96; 2. De Kock M et al. *Anesthesiology* 1993; 79: 282–9; 3. Hanci V et al. *Reg Anesth Pain Med* 2009; 34:565-8; 4. Okada H et al. *Resuscitation* 2007; 74: 538-45; 5. Snapir A et al. *Anesthesiology* 2006; 105: 902 - 10.

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**Patients` inability to perform a preoperative cardiopulmonary exercise test risk predicts inferior medium term mortality following major colorectal surgery**

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Patients with poor functional capacity secondary to comorbidity or physical de-conditioning may be at higher risk of mortality after major surgery<sup>1</sup>. We studied the outcomes of patients whose functional capacity was characterised by cardiopulmonary exercise testing (CPET) and of those who were unable to perform the test.

All patients scheduled for elective major colorectal surgery at our Colorectal Specialist Unit undergo pre-operative CPET to assist in the planning of peri-operative care. With ethics committee approval we followed the outcomes of 238 patients stratified into “Fit” (Group 1, n=161), “Unfit” (Group 2, n=62) & “Very Unfit” (Group 3, n=15) on the basis of their CPET results and a further 17 patients who were unable to cycle a stationary bicycle at all or sufficiently long to provide an interpretable result, “Unable to CPET” (Group 4, n=17). All patients were followed to 500 days after surgery.

Seven patients from Group 4 were unable to cycle due to lower limb osteoarthritis, seven due to general physical infirmity, two from perineal pain and one refused.

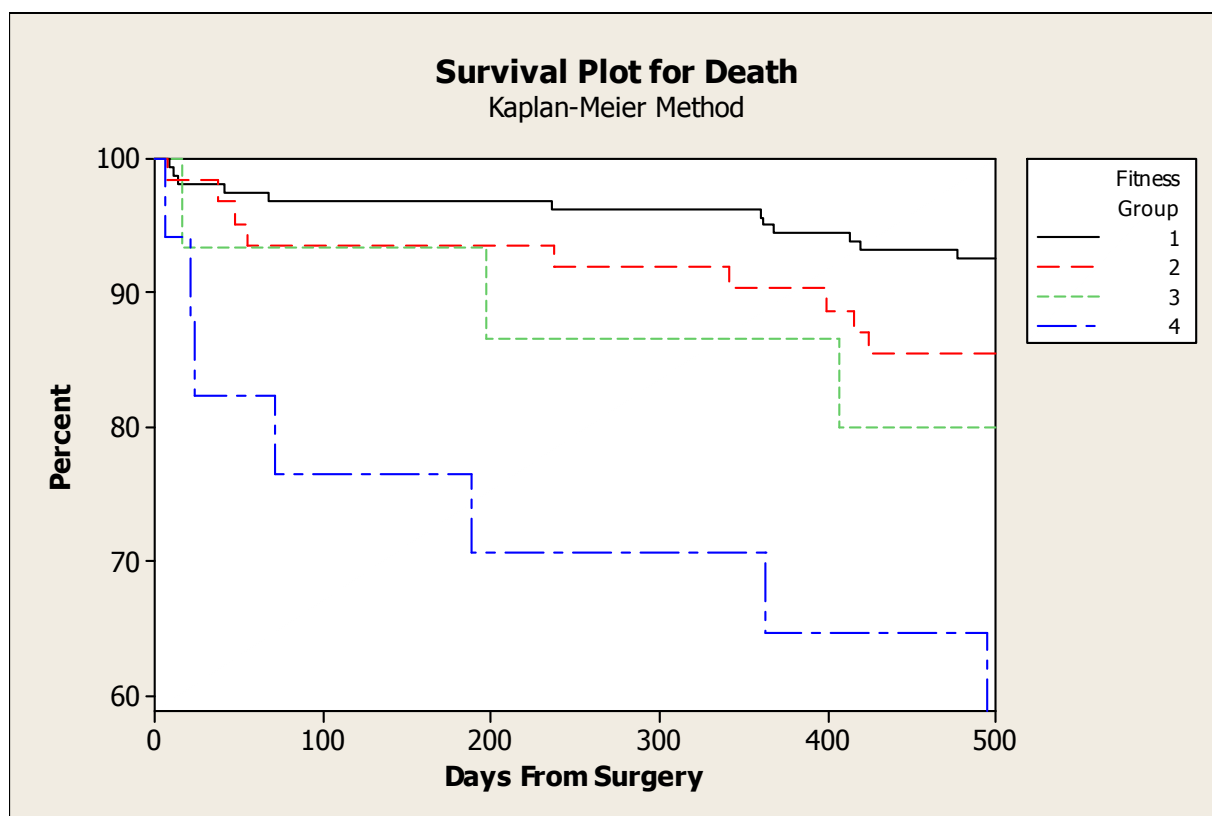


Table 1 Kaplan Meier survival plot stratified by subgroup. (p < 0.001 Log Rank test )

In this study, patients who were unable to perform a CPET had appreciably high medium term mortality following elective major colorectal surgery. This is an important consideration when consenting such patients for surgery.

**References:** 1. Wilson RJT, et al. Br J Anaesth 2010;105:297-303

## **Independent preoperative predictors of mortality in major joint arthroplasty: the influence of time interval between an acute coronary syndrome and the operation**

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Present guidelines do not advocate a prolonged delay following an acute coronary syndrome (ACS)<sup>1</sup> though recent data suggest delaying operations by 8 weeks<sup>2</sup>. The Hospital Episode Statistics database was analyzed for elective admissions for total hip or knee replacement (THKR) surgery between 2006/7 and 2009/10. Patient factors influencing mortality (including the timing of ACS) were identified by logistic regression. 414,985 THKRs (mortality: 0.2%) were included. Heart failure, renal failure, liver disease, peripheral vascular disease, arrhythmia, previous stroke, valvular heart disease, respiratory disease, diabetes mellitus, previous cancer and previous ACS (OR: 1.73 [95% CI: 1.33 to 2.25]) increased the odds of mortality. Compared with more delayed surgery, THKR surgery performed within six months of an ACS (OR: 3.81 [95% CI: 1.55 to 9.34]) increased the odds of mortality. The effect of ACS persisted up to 12 months (OR: 1.99 [95% CI: 1.02 to 3.88]). The odds ratios for the timing of ACS were not altered by exclusion of patients who received percutaneous coronary intervention or coronary artery bypass grafting for treatment of their ACS. Overall prior ACS exerted a modest effect on mortality from THKR surgery (number needed to harm (NNH) 1:700), however if surgery was conducted within six months (NNH 1:64) or 12 months (NNH 1:183) of an ACS, the risk was augmented. Multiple risk factors increase the risk of perioperative death. THKR surgery conducted too soon (up to 12 months) after an ACS is associated with increased mortality and therefore consideration must be given to delaying surgery: Current guidelines are too permissive regarding the timing of surgery following ACS for major joint arthroplasty.

**References:** 1. Fleisher LA, Beckman JA, Brown KA, et al. J Am Coll Cardiol 2007; 50: 1707-32; 2. Livhits M, Ko CY, Leonardi MJ, Zingmond DS, Gibbons MM, de Virgilio C. Annals of surgery 2011; 253: 857-64.

**Acknowledgments:** AAGBI/Anaesthesia Department Project Grant

## Protocol presentation: evaluation of a device to detect early respiratory deterioration

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We have developed a small non-invasive device that senses body movement and reliably measures respiratory rate in patients after abdominal surgery.<sup>1</sup> Respiratory rate is a good marker of developing illness<sup>2</sup> and can predict ITU referral and outcome.<sup>3</sup> Intensive surveillance with pulse oximetry can reduce emergencies and ITU admission.<sup>4</sup> If reliable frequent measures of respiratory rate are included into a routine physiological warning score, it is possible that:

- the “weak link” in the early detection of deterioration might be strengthened
- early detection would allow prompt escalation of care and improve outcome.

We present the plans we have for testing these hypotheses. We propose:

- validation of the device in acute medical patients  
(problem: consent in acute illness)

In this time period we hope to obtain CE marking and MHRA approval.

- A feasibility study to define several aspects of use of a new device:
  - Staff attitude, response, and use of a new monitor
  - Influence of more intensive monitoring on interventions
  - Methods to measure outcome

Population: we plan to study “level 1” i.e. patients receiving ward based care, because patients considered at risk of substantial postoperative morbidity are generally given higher levels of care which include more intensive monitoring. Patients would be studied before and after routine and emergency colorectal and urological surgery (we have two suitably sized local units) with a phased introduction and assessment using the following:

Surgical Apgar, P-Possum, Charlson Age-Comorbidity index, Duke Activity Status Index, Scottish Index of Multiple Deprivation 2009 followed by measures after surgery, using:

Calls to Hospital at night team, Postoperative Morbidity Score, EuroQol EQ-5D and SF-12, dependency-weighted LOS and 28 day mortality, TrakCare’ electronic patient record system, and other clinical management indicators.

We would value general comments but specifically comments on consent procedures, assessment tools, and study design.

**References:** 1. Drummond GB, Bates A, Mann J, Arvind DK.. *Br J Anaesth* 2011; 107: 462-9; 2. Duckitt RW, Buxton-Thomas R, Walker J, *et al. Br J Anaesth* 2007; 98: 769-74; 3. Cuthbertson BH, Boroujerdi M, McKie L, Aucott L, Prescott G. *Crit Care Med* 2007; 35: 402-9; 4. Taenzer AH, Pyke JB, McGrath SP, Blike GT. *Anesthesiology* 2010; 112: 282-7

## The radial artery to digit pressure transit time is affected by low pass filter features

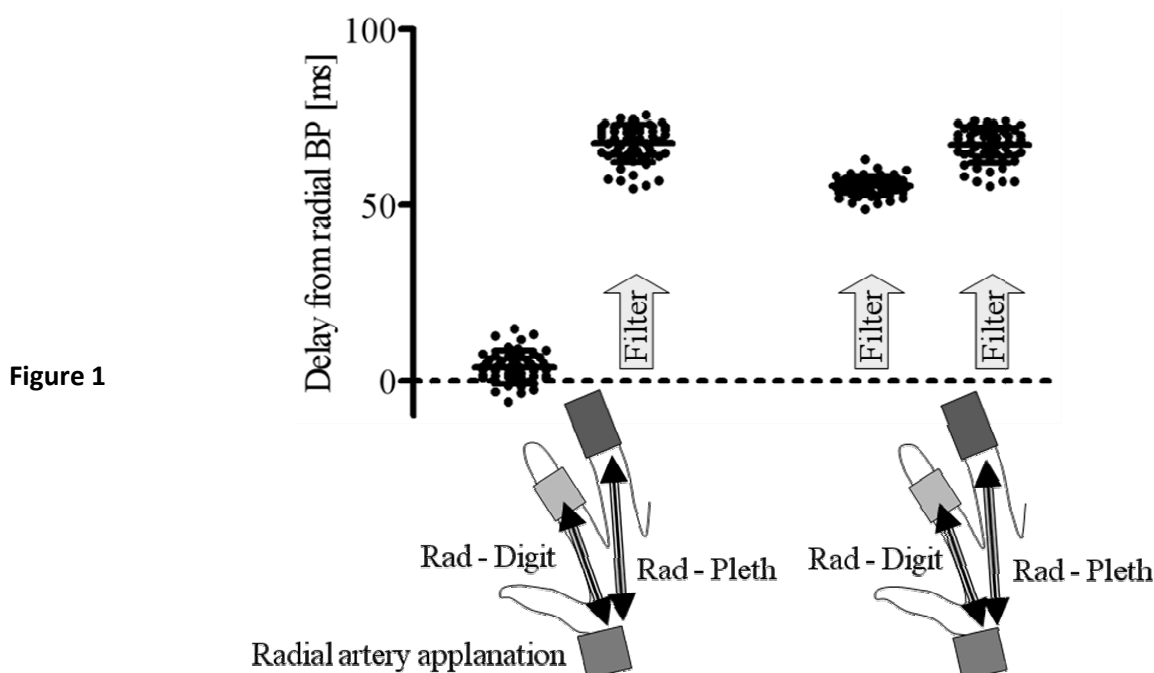
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We are studying the timing of vascular events in the hand to allow non-invasive measurements of arterial pressure<sup>1</sup> and assessment of vascular responses in the finger. We found that measurements are substantially affected by processing of the signal. Our previous study used recordings of non-invasive radial artery pressure (Colin CBM-700), and finger photoplethysmograph in 12 volunteers. Signals were digitised at 10 KHz. We detected waveform troughs and peaks using second derivatives. Data were analysed with Octave and Prism5 (GraphPad). The plethysmograph device we used had no high pass filter but contained a low pass filter (2-pole Butterworth, 8.5 Hz) to remove 50 Hz noise.

We measured time delay, using the upsweep of the radial artery pressure and the corresponding point recorded in a non-compliant pressure cuff applied to the finger. The wrist to digit delay was much less than the delay in the plethysmograph signal. The delay from radial artery to plethysmograph was 68 (5) ms but the delay from radial artery to digital pressure changes was only 4 (5) ms. To assess the impact of the low pass filter on the plethysmograph signal, we applied an equal filter to the digital pressure recordings.

Figure 1 shows a representative subject. Low pass filtering caused a substantial delay in the digital pressure wave. Measurements of peripheral arterial transmission time depend substantially on the characteristics of the signal processing. One useful application of DC plethysmograph measurements is generating pressure-volume plots for finger vessels, but this requires accurate knowledge of exact timing of events distal to the radial artery. Previous studies have simply aligned pressure and volume signals using a recognisable marker such as the turning point.<sup>2</sup> Our measurements show that delays in all parts of the measurement system should be evaluated before accurate measurements are possible.



**References:** 1. Allen J. *Physiological Measurement* 2007; 28: R1-R39; 2. Shelley KH Murray WB Chang D. *Journal of Clinical Monitoring* 1997; 13: 223-8

## Dexamethasone prolongs the duration of brachial plexus block: a meta-analysis

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There has been recent interest in using adjuncts to local anaesthetics to prolong analgesia following peripheral nerve blockade for surgical procedures.<sup>1</sup> Dexamethasone has been an adjunct of particular focus in a number of prospective randomised controlled trials (RCTs) examining its efficacy in brachial plexus block. This meta-analysis examines the findings from these RCTs.

The keywords: human, brachial plexus, interscalene, supraclavicular, infraclavicular, nerve block and dexamethasone were used to search Medline, EMBASE (from 1980-2011) and Google Scholar to identify RCTs and published abstracts from scientific meetings. No language restrictions were applied. The Jadad Scale<sup>2</sup> was used to assess the quality of the RCT's. RevMan statistical software<sup>®</sup> utilised inverse variance and a random effect model to calculate weighted mean difference (WMD) with 95% confidence intervals for continuous variables. The primary outcome measure was duration of analgesia, with the secondary outcomes, times to onset of maximum motor and sensory block, and to recovery of motor function.

Six studies comprising 563 patients published from 2006-11 were included. The Jadad score for the studies was 1-5. Addition of dexamethasone to the local anaesthetic (levobupivacaine, mepivacaine, lidocaine +/- epinephrine, or a combination) increased the duration of postoperative analgesia. Recovery of motor function was delayed in patients who received dexamethasone but there was no significant difference in time to onset of sensory or motor block (Table 1).

The addition of dexamethasone to brachial plexus blocks increases the length of analgesia with no delay in time to onset of sensory or motor block. A delay in recovery of motor function may occur. Dexamethasone has a role as an adjunct in brachial plexus blockade.

Table 1: Times in minutes

	Number of studies / Patients	Mean difference and CI	p value
Duration of analgesia	5/503	-418.3 (-555.4, -281.2)	<0.00001
Onset of sensory block	5/259	1.49 (-0.06, 3.04)	0.16
Onset of motor block	5/259	0.97 (-0.4, 2.3)	0.06
Recovery motor function	3/180	-487.6 (-728.8, -246.5)	<0.0001

**References:** 1. Thornton PC, Grant SA, Breslin DS. *Int Anesthesiol Clin* 2010; 48; 59–70; 2. Jadad AR, Moore RA, Carroll D, et al. *Controlled Clin Trials* 1996; 17; 1-12

## Effects of goal directed fluid therapy during colorectal surgery on the sublingual microcirculation

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1 Directorate of Anaesthesia 2 Directorate of Gastroenterology, Derriford Hospital, 3 Peninsula Medical School, Plymouth

We have previously reported that intraoperative goal directed fluid therapy, GDT, had no impact on clinical outcomes for 179 patients having major elective colorectal surgery<sup>1</sup>. We performed side stream dark field imaging of the sublingual capillaries at specified perioperative time points on 28 of these patients to investigate the effects of GDT on microcirculatory blood flow.

Side stream dark field imaging was undertaken using a microcamera (Microscan, Microvision, Amsterdam) at three specified time points: T0 immediately prior to anaesthesia, T1 immediately following surgery and T6-12, between 6 and 12 hours post-operatively. The first three images suitable for study at each time point were analysed according to consensus methodology<sup>2</sup> using AVA 3.0 software (Microscan, Microvision, Amsterdam).

Images were available at all time points for 15 patients and for four more at 2 of 3 time points

	n	Perfused Vessel Density*			Boerma flow index*			Stroke volume (mls)		Intra-op fluid (ml/kg)	Length of stay (days)	Pts with Day 5 POMS score >0
		T0	T1	T 6-12	T0	T1	T 6-12	pre-op	end-op			
Control	9	19.02	17.92	18.68	2.93	2.03	2.83	60	79	38	6.0	4
GDT	10	17.89	19.60	18.77	2.92	2.92	2.67	67	103	77	7.5	5

Table 1. Perioperative microvascular flow indices, haemodynamic measurements and selected clinical outcomes. Data are presented as medians. \* NS, repeated measures Anova analysis for comparison of mean perfused vessel density and Boerma flow index at any time periods, between and within Control vs GDT groups.

This pilot work illustrates the difficulties involved acquiring microvascular images of sufficient quality studies in awake patients. The results mirror the clinical outcomes of our previous study<sup>1</sup>, however power is limited. These pilot data have been employed in the power calculation of a follow up GDT randomised trial on 220 patients undergoing major abdominal surgery.

**References:** 1. Challand C, Struthers R, Sneyd JR, et al. Br J Anaesth 2011 Aug 26. [Epub ahead of print]; 2. De Backer D, Hollenberg S, Boerma C, et al. Crit Care 2007; 11:R101

**Acknowledgements:** Funded by AAGBI through the NIAA, & South West Regional Innovation Fund

## Assessment of a non-invasive haemoglobin monitor (Masimo SpHb) in infants and small children undergoing craniofacial surgery

H Gill\*, M Sury

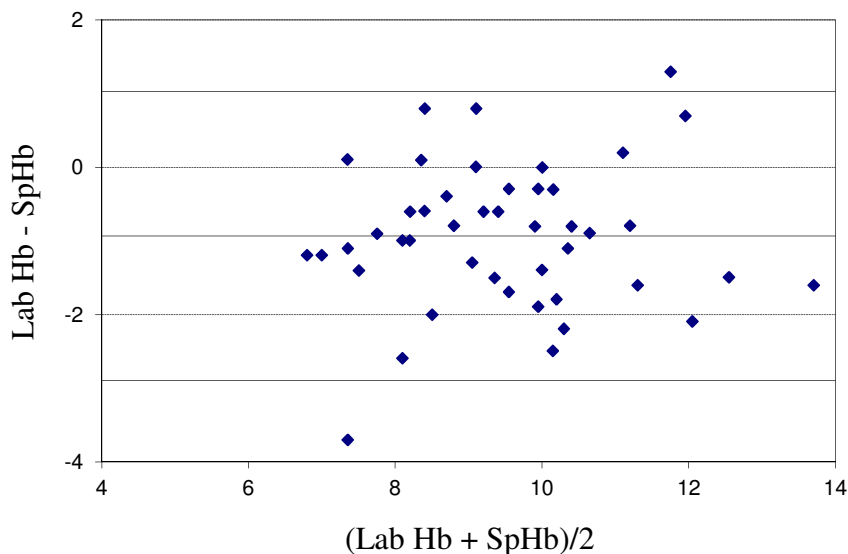
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Major haemorrhage and haemodilution are common during craniofacial surgery in small children and may be better managed with a continuous monitor of haemoglobin concentration (Hb). The Masimo Pulse CO-Oximeter™ is a pulse oximeter that monitors SpHb® yet its accuracy during haemorrhage is uncertain. A recent study in 20 adults showed that 22% of laboratory Hb (LabHb) were > 2.0 g/dL different to SpHb; no patients had Hb < 7.5 g/dl. We present our preliminary data comparing LabHb with SpHb during craniofacial surgery.

This is a prospective observational study in children less than six years of age and under 20kg. Transfusion practice was not changed by the study. Ethics committee approval was obtained and parents gave written informed consent. Timing of blood samples was dictated by clinical judgment. The SpHb probe was attached to a toe and SpHb data was stored on a PC for analysis later. The monitor was hidden from the clinical team. We aimed to determine the confidence interval of the limits of agreement when LabHb was less than 7gd/L. Assuming the difference between SpHb and Lab Hb was <1g/dl we estimated we needed to study > 40 children.

Twelve patients have been studied; mean weight was 11.34kg (range 9.65-14.1). 45 Hb pairs were analysed. The range of LabHb was 5.5-12.9g/dl. Five children had at least one LabHb below 7g/dl. Using all Hb pairs, the mean bias of SpHb was 0.93g/dl (SD=0.98). In one patient the SpHb trace failed to identify a LabHb of 5.5g/dl.

Figure: Bland Altman plot showing mean at -0.93g/dl (2SDs either side at -2.89 & 1.03g/dl)



The level of agreement was wide although in most patients the SpHb followed the trend of the LabHb. On average, the SpHb was 1g/dl higher than LabHb. More data are needed.

**References:** 1. Miller et al. *Anesth Analg* 2010, 112, 858-86

## Differences in the lumbar epidural pressure between full-term pregnant and non-pregnant women

HC Ma<sup>1\*</sup>, L Nan<sup>1\*</sup>, XG Yang<sup>1\*</sup>, YH Feng<sup>1\*</sup>, DY Wang<sup>1\*</sup>, GA McLeod<sup>2</sup>

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The loss of resistance technique is routinely used to indicate Touhy needle placement during epidural block. Epidural pressure is one variable influencing loss of resistance and may change with pregnancy<sup>1,2</sup> and position<sup>3</sup>. Therefore the aim of this study was to compare epidural pressure in full term pregnant and non-pregnant women during epidural block<sup>4,5</sup>.

Twenty full-term pregnant and 15 non-pregnant women were included in this study. Epidural block was performed in the left lateral position at the L2-3 interspace using a 16G Touhy. Epidural pressure was measured on 4 occasions: (T0) Tuohy needle entering the epidural space; (T1) 90-second after placement of the epidural catheter; (T2) after returning to the supine position; and (T3) after injection of local anaesthetics into the epidural space.

No differences in mean (SD) epidural pressure existed between groups at T0 16.1(3.1) vs 17.1 (2.0),  $P > 0.05$ . However differences existed between groups at T1, T2 and T3 (Table 1). Epidural pressure increased in both groups after turning the patients into supine position and after injection of local anaesthetics, but increased more in the pregnant group.

Table 1. Mean (SD) epidural pressures (mmHg) measured at four time points in full-term parturient (n=15) and non-pregnant women (n=20) during epidural block \*  $P < 0.05$

	T0	T1	T2	T3
Pregnant	17.1(2.0)	14.3(0.6)	24.0(1.0)	23.8 (1.2)
Nonpregnant	16.1(3.1)	11.7(1.0)*	20.5 (1.8)*	20.2(1.7)*

This study showed higher pressure in the epidural space in the full-term pregnant patient compared to the non-pregnant women.

**References:** 1. Igarashi T et al. *Anesthesiology* 2000; 92:1631-6; 2. Messih MNA. *Anaesthesia* 1981; 36: 775-82; 3. Moon JY et al. *Anesthesiology* 2010; 113: 666-71; 4. Shah JL. *Br J Anaesth* 1984; 56:1373-7; 5. Thomas PS et al *Reg Anesth* 1992; 17: 212-5

## Endogenous brain oscillations during sedation: Initial results of a MEG and FMRI study

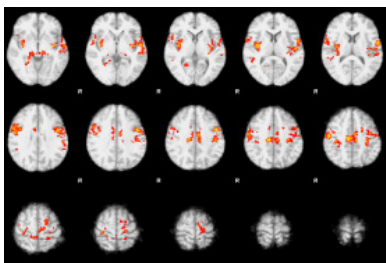
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We investigated the modulation of endogenous brain activity during mild sedation using a multimodal approach: magnetoencephalography and functional magnetic resonance imaging. As the thalamus plays a pivotal role in sedation and anaesthesia<sup>1</sup>, we focus on its role in brain oscillations measured electrophysiologically (MEG) and haemodynamically (FMRI).

Eight healthy male volunteers [age {mean (SD)}; 27.5years (7.2)] underwent (eyes-closed) 5 min resting-state whole-head MEG scans (CTF-275 channel gradiometer system). Five of these undertook 8 min of resting-state FMRI over 1 week later (3T GE HDx system). MEG and FMRI scans were performed both before and during mild sedation (TCI propofol to achieve OAA/S score 4). **MEG analysis;** Power spectral density analysis was calculated for 1-80 Hz using Fourier transforms in Matlab. **MRI analysis;** Images were acquired using a blood oxygen level dependent weighted imaging sequence (TR=3s, TE=35 ms, matrix=64x64, 50 slices). FMRI data was analysed using FSL (fmrib.ox.ac.uk/fsl). Images were corrected for movement, normalised to stereotaxic coordinates of MNI and smoothed. **Resting-state functional connectivity (fc):** between thalamus and the rest of the brain was evaluated by extracting individual subjects' mean BOLD signal time series from the thalamus. Within-subject statistical comparisons of functional connectivity were performed at the group level between sedated and un-sedated conditions (Z statistic images with cluster thresholding).

Increased power of the central delta, frontal alpha, central and frontal gamma, and central, frontal and temporal beta rhythms was seen during sedation with MEG. Seeding in the thalamus revealed increased FMRI functional connectivity in a network involving both deep brain structures and cortical areas. Sedation (figure) increased the connectivity between the thalamus both with areas of the neocortex and with the rostral brainstem. There was increased connectivity between the precentral gyrus (primary motor cortex), postcentral gyrus (primary somatosensory cortex), and juxtapositional lobule cortex (supplementary motor area).



Increases in functional connectivity between motor/somatosensory cortices have been attributed to an uneven modulation of cortico-thalamic feedback by anaesthetic agents<sup>2,3</sup>. Our resting state MEG results provide complementary information as this increased connectivity parallels an increase in beta and alpha oscillations thought to originate from those areas. The increases in functional connectivity seen with fc-FMRI may represent an increase in synchrony of thalamic and cortical neurons involved in the MEG-recordable oscillations.

**Figure;** Increases in functional connectivity of brain regions with thalamus during mild sedation

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