Potential role of the PI3K pathway on renal cell carcinoma progression \textit{in vitro}

L. L. Benzonana*, N. J. S. Perry* and D. Ma

Anaesthetics, Pain Medicine and Intensive Care Section, Department of Surgery and Cancer, Chelsea and Westminster Hospital, Imperial College London, UK

Most cancer patients have to undergo at least one surgery during the course of their disease. The surgery itself along with the anaesthetic used could influence cancer recurrence, metastatic potential, or both. Previous work in our lab has determined that isoflurane up-regulates HIF-1$\alpha$, HIF-2$\alpha$, and phospho-Akt, and increases the rate of proliferation of renal cell carcinoma cells (data not shown here). The aim of this project was to investigate the potential impact of isoflurane on tumour progression \textit{in vitro}.

Renal cell carcinoma (RCC4) cells both containing and lacking the Von-Hippel–Lindau (VHL) gene were exposed to 2\% isoflurane under normoxic atmospheric conditions at 37°C. HIF-1$\alpha$, p-Akt, and PHD2 protein levels were measured by western blot analysis at various time points after gas exposure (0–24 h). Akt was inhibited by an Akt inhibitor LY294002 and cells were then exposed to 2\% isoflurane; HIF-1$\alpha$ and p-Akt were then measured. Relative rate of cell proliferation was measured by an MTT assay and a trypan blue exclusion assay. Finally, cell migration was measured using an Oris cell migration assay.

Isoflurane activated the phosphatidyl-inositol-3-kinase (PI3K) pathway, indicated by significantly raised levels of p-Akt from 4 to 24 h, with maximal levels at 8 h [1.64 (0.06) vs 1.00 of control; $P<0.001$], and decreased levels of p-Akt [0.64 (0.09) vs 1.77 (0.10) of isoflurane-treated cell group; $P<0.001$], and HIF-1$\alpha$ [1.33 (0.11) vs 2.16 (0.05) of isoflurane-treated cell group; $P<0.001$], when the Akt signal was inhibited by LY294002. Cell proliferation was inhibited by Akt inhibitor treatment ($P<0.001$). HIF degradation did not seem to be affected as there were no changes in HIF-1$\alpha$ in RCC4 cells that had the VHL gene re-introduced, and there were no changes in the amount of PHD-2 in RCC4 (VHL deficient) cells. Finally, cell migration assays showed an increased migration of isoflurane-treated cells 8 h post-exposure in three different conditions (collagen, fibronectin, and tissue culture-coated plates) ($P<0.001$).

Isoflurane at clinically relevant concentrations increases the rate of RCC4 cell migration \textit{in vitro}, which is mediated through the PI3K-HIF pathway.

Acknowledgements

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Functional electrical impedance tomography by evoked response: a new device for the study of human brain function during anaesthesia

A. Bryan$^1$, C. J. D. Pomfrett$^{1,2}$, J. Davidson$^3$*, B. J. Pollard$^1$, T. Quraishi$^1$*, P. Wright$^3$*, R. Robinson$^3$*, S. T. Ahsan$^3$* and H. McCann$^3$*

$^1$Division of Clinical and Scientific Services, Department of Anaesthesia, CMFT, $^2$School of Biomedicine and $^3$School of Electrical and Electronic Engineering, University of Manchester, Manchester M13 9PL, UK

The objective of this project was to develop a non-invasive and portable brain imager, based on electrical impedance tomography, for use by anaesthetists. Functional electrical impedance tomography by evoked response (FEITER) gives the 100 frames per second resolution needed to study sub-second mechanisms underlying consciousness.$^1$

FEITER met the requirements of the Medical Device Directive, received MHRA ‘no objection’, and a favourable ethical opinion from S. Manchester LREC (ISRCTN 93596854). All subjects gave written, informed consent. FEITER injected a sinusoidal current (1 mA pk–pk, 10 kHz) between opposite electrode pairs (ZipPrep, Covidien, UK), pseudo-randomly selected from 32 electrodes positioned using the 10–20 montage. Non-current injection electrodes were used for
>500 voltage measurements during each 10 ms measurement frame. Flash stimuli were presented using fEITER. Stage 1 of the study (awake, completed) required the recruitment of 20 ASA I volunteers. Twenty ASA I or II patients undergoing elective surgery with BIS monitoring are being recruited now for stage 2 (anaesthetized).

The rheoencephalograph was time-locked to the ECG but with different latencies depending on the position of the recording on the head. Sub-second responses to single flashes were of sufficient magnitude to reconstruct as 3D maps of conductivity change that highlighted the visual cortex and frontal lobes in temporal ranges expected for visual processing. Large, sub-second changes in transcerebral impedance were noted during propofol induction (Fig. 1).

Acknowledgements
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References

Tissue oxygenation during permissive hypercapnia in critically ill patients
S. Chillistone*, K. R. Corrie* and J. G. Hardman
Division of Anaesthesia and Intensive Care, University of Nottingham, Nottingham, UK

Small tidal volumes with permissive hypercapnia reduces ventilator-associated lung injury in critically ill patients. There may also be a beneficial effect of the hypercapnia per se, which has been shown to improve tissue oxygenation in some situations. The aim of this study was to investigate the effects of hypercapnia in the face of varying oxygen delivery through alterations of haemoglobin (Hb) and cardiac output (CO). Additionally, we looked to see how altering the inspired oxygen fraction (FiO₂) affected the trends.

Using the Nottingham Physiology Simulator (NPS), we configured 90 virtual patient scenarios. The NPS is a validated computational model of integrated cardiovascular and respiratory systems which has been described in detail elsewhere. Version NPSv039 was used in this study. The lungs were configured to create a moderate ventilation/perfusion mismatch simulating acute lung injury. Physiologically, the patients were identical except for Hb which was varied across the range 6–14 g dl⁻¹ and CO which was varied across the range 3–9 litre min⁻¹. All patients were ventilated with volume-controlled ventilation at FiO₂ 0.8 and 0.5. Tidal volumes were set at 350, 450, and 650 ml. Tissue oxygen tension (PtO₂) was recorded. The results at FiO₂ 0.8 and 0.5 are shown in Figure 2.

Reducing oxygen delivery reduced PtO₂. When Hb and CO were < 8 g dl⁻¹ and 3 litre min⁻¹, respectively, the reduction in PtO₂ became marked and the gradient increased. Permissive hypercapnia improved tissue oxygenation, except during low oxygen delivery states when the FiO₂ was 0.5, where it reduced PtO₂. The deleterious effect of hypercapnia at low oxygen delivery was not seen at FiO₂ 0.8.

In conclusion, it appears that organ oxygenation may become critical below Hb 8 g dl⁻¹ and CO 3 litre min⁻¹. When tissue oxygenation is critical, permissive hypercapnia may worsen tissue hypoxia. This effect may be attenuated by increasing the inspired oxygen fraction.

References
Exact model for the oxyhaemoglobin dissociation curve
R. S. Cormack and G. G. Lockwood

1Department of Anaesthesia, Northwick Park and St Marks Hospital, Harrow, UK. 2Department of Anaesthesia, Hammersmith Hospital, UK

Hill argued that the oxyhaemoglobin dissociation curve (ODC) can be defined simply as a sum of terms each reflecting a different compound of haemoglobin with oxygen. He derived his equation (A) from the text-book equation for the law of mass action, which leads to a hyperbolic series, but it does not fit the best ODC data.

Our model follows Hill, but exponential terms replace hyperbolic.

Our model:

\[ y = S_M - S_1 e^{-K_1 x} - S_2 e^{-(K_2 x)^2} - S_3 e^{-(K_3 x)^3} - S_4 e^{-(K_4 x)^n} \]  

where \( x \) is the measured \( P_{O_2} \); \( y \) the calculated saturation (%); \( S_M \) the maximum saturation; \( S_1 \) to \( S_4 \) the contribution of each term to total saturation; and \( K_1 \) to \( K_4 \) the equilibrium constants. It fits the ODC perfectly within the physiological range of saturation; the scatter round the curve matches the measurement error; the residuals pass the most rigorous tests. It is amenable to manual calculation and easily put into clinical software.

The flaw in Hill’s model may be the assumption that measured values reflect active mass, which may not be true at high saturations. The exponential model does not start from that law, but is consistent with it. Our conjecture is that \( \frac{dy}{dx} \) is proportional to \((S - y)\), the number of free haemoglobin-binding sites for oxygen:

\[ \frac{dy}{dx} = K(S - y) \]

Integration leads to an equation which we label a geometric exponential series, because consecutive terms contain increasing powers of \( x \). That distinguishes it from a fixed exponential series, where each term has the same \( x \), but a new \( S \) and \( K \), as in motor learning. It seems likely that many physiological processes have a similar origin, for example, in motor learning \( \frac{dy}{dx} \) is proportional to the number of synapses that can potentially be recruited. Consequently, exponential series generally fit better than hyperbolic. Preliminary studies suggest that our approach fits other dose–response processes (e.g. anaesthetizing luminous bacteria) better than existing methods.

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In silico validation of ventilatory ratio as a tool to monitor ventilatory efficiency
K. R. Corrie, P. Sinha, N. Soni and J. G. Hardman

1Division of Anaesthesia and Intensive Care, University of Nottingham, Nottingham, UK. 2Magill Department of Anaesthesia, Intensive Care Medicine and Pain Management, Chelsea and Westminster Hospital, UK
Although there are several indices to assess the efficiency of oxygenation at the bedside, such an index does not exist for ventilation. Recently, a method by which to monitor ventilatory efficiency has been described. A ventilatory ratio (VR) is an easily calculated unitless index ratio that reflects ventilatory efficiency at the bedside. Calculation of VR requires values for minute ventilation and $P_{aCO_2}$. Its value is influenced by the magnitude of CO$_2$ production and pulmonary deadspace. VR is calculated as:

$$
VR = \frac{V_{Emeasured} \times P_{aCO_2measured}}{V_{Epredicted} \times P_{aCO_2predicted}}
$$

The Nottingham Physiology Simulator (NPS) was used to validate the VR equation’s ability to reflect ventilatory efficiency ex vivo. NPS is a previously validated computational model of human cardiopulmonary physiology. Three virtual patients were configured within the NPS, representing healthy lung configuration, acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease. VR was calculated while minute ventilation, ventilation rate, and VCO$_2$ were each varied in isolation.

Mean calculated VR for the normal patient was 0.9 (0.85–0.95). There was a significant correlation between VR and physiological deadspace fraction ($Vd/Vt_{phys}$) at constant VCO$_2$ ($P<0.0001$, $r=0.99$). Similarly, VCO$_2$ had a linear relationship with VR at constant $Vd_{phys}/Vt$. With VCO$_2$ 150–250 ml min$^{-1}$ and $Vd_{phys}/Vt$ 0.22–0.7, VR range was 0.61–2.62 (Fig. 3).

Both VCO$_2$ and deadspace affect VR. In patients with a stable metabolic rate, the ratio may be a useful indicator of deadspace fraction. However, in the critically ill patient, VR is more than a simple deadspace indicator. Hypermetabolism and increased $Vd_{phys}/Vt$ are equally important factors in the increased demand for pulmonary ventilation associated with ARDS. VR can quantify the efficiency with which the patient clears CO$_2$ in the face of the hypermetabolic state and increasing deadspace fraction found in ARDS.

### References

### Effect of resvaratrol, rutin, and quecertin on mitochondrial function and endogenous glutathione in endothelial cells cultured under conditions of sepsis

**N. H. Driver**, D. A. Lowes and H. F. Galley

Academic Unit of Anaesthesia and Intensive Care, School of Medicine and Dentistry, University of Aberdeen, Aberdeen, UK

The mortality rate of critically ill patients with sepsis remains high. Mitochondria are a major source of reactive oxygen species in a resting cell and oxidative stress occurs in these patients. Dietary antioxidants which provide protection against oxidative stress have been widely acclaimed for their many positive health benefits. Resvaratrol is found in wine, while rutin and quercetin are flavonoids found in many plants. We investigated whether resvaratrol, rutin, and quercetin were able to protect against mitochondrial dysfunction in endothelial cells cultured under conditions of sepsis.

Human endothelial cells were exposed to 2 $\mu$g ml$^{-1}$ lipopolysaccharide (LPS, from *Escherichia coli* 0111:B4) plus 20 $\mu$g ml$^{-1}$ peptidoglycan (PepG) for 24 h and 7 days in the

**Fig 3** VR as influenced by $Vd/Vt_{phys}$ in a 70 kg healthy individual with constant VCO$_2$.

**Fig 4** Glutathione levels in endothelial cells exposed to resvaratrol for 7 days. Fluorescence expressed as a percentage of the mean for untreated cells ($n=6$). Box and whisker plots show median, inter-quartile, and full range. **P**$<0.01$ compared with untreated cells (Mann–Whitney). $P$-value displayed is Kruskal–Wallis.
presence of resvaratrol or rutin at a range of concentrations. Mitochondrial membrane potential was measured using the fluorescent cationic dye JC-1; mitochondrial metabolic activity was measured using AlamarBlue™; opening of mitochondrial permeability transition pores was measured with calcien AM; and glutathione concentration was measured with mono-bromobimane. Six separate replicate experiments were performed.

Cells exposed to LPS/PepG had lower GSH levels ($P < 0.05$) and evidence of mitochondrial dysfunction compared with untreated cells ($P < 0.01$), but these changes were not attenuated by any concentration of resvaratrol, rutin, or quercetin. Moreover, at higher concentrations, the antioxidant treatments resulted in lower GSH levels ($P < 0.05$) and increased mitochondrial dysfunction ($P < 0.05$) (Fig. 4).

At the concentrations used, resvaratrol, rutin, and quercetin appeared to behave in a pro-oxidant fashion creating additional oxidative stress within the cells. This pro-oxidant effect probably contributed to greater mitochondrial damage and dysregulation. In contrast to reported antioxidant properties and beneficial effects, rutin, resvaratrol, and quercetin failed to protect against LPS/PepG-induced mitochondrial dysfunction in endothelial cells.

A specific amino acid in the glycine-binding site of the N-methyl-D-aspartate receptor is involved in xenon inhibition of the N-methyl-D-aspartate receptor


Biophysics Section, Blackett Laboratory, Imperial College London and Department of Anaesthetics, Pain Medicine and Intensive Care, Imperial College, UK

The noble gas xenon is a general anaesthetic and shows potential as a neuroprotective treatment for ischaemic brain injury. Until relatively recently, no targets had been identified that could mediate xenon’s anaesthetic and neuroprotective properties. However, work in our laboratory showed that xenon inhibits N-methyl-D-aspartate (NMDA) receptors.\(^1\) NMDA receptor antagonism is plausible as a mechanism underlying xenon anaesthesia and we have recently shown that inhibition of the NMDA receptor plays a role in xenon neuroprotection against ischaemia. Using molecular modelling and patch-clamp electrophysiology, we showed that xenon competes for the binding of the co-agonist glycine at the glycine-binding site on the NR1 subunit of the NMDA receptor and we identified 12 amino acids that may be involved in the binding of xenon at the glycine site.\(^1\) In the current study, we show that one of these amino acids, Phe758, is critical for the binding of xenon at the glycine site. We use site-directed mutagenesis to mutate the Phe758 residue of the NR1 subunit. The mutant NR1/NR2A receptors are expressed in HEK293 cells and the effect of the mutation is assessed functionally using patch-clamp electrophysiology. Inhibition of mutant and wild-type (WT) receptors by xenon is compared at a range of glycine concentrations. We show that in WT receptors, xenon inhibition increases as glycine concentration decreases, consistent with xenon competing with glycine at the glycine site. However, when the Phe758 residue is mutated to a leucine or alanine residue, the glycine dependence of the inhibition is abolished.

These findings provide additional evidence that xenon binds to the glycine site of the NR1 subunit of the NMDA receptor. Attenuation of xenon inhibition of the Phe758Leu and Phe758Ala mutants suggests that an interaction between xenon and the aromatic ring of the phenylalanine residue is important in the xenon binding to the WT NMDA receptors (Fig. 5).

Fig 5 Inhibition of WT and mutant NR1/NR2A receptors by 80% xenon as a function of glycine concentration. Glycine concentrations are normalized to EC$_{50}$ for that particular receptor. Glycine EC$_{50}$ values are: 5.7 (1.5), 30.1 (2.6), and 30.0 (2.5) μM for the WT, F758L, and F758A receptors, respectively. Data shown are means from an average of eight cells at each concentration. Error bars represent standard error.
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References

Does elective ‘aftercare’ contribute to surgical outcome?
E. Haberman*, S. Barnett* and D. Dutta
Princess Alexandra Hospital NHS Trust, Hamstel Road, Harlow, Essex, UK

The ideal patient journey should constitute admission to hospital for elective procedure and should represent minimal disruption to the patient’s life. Measurements of the quality of perioperative care have traditionally been in terms of outcomes and length of stay (LOS) has been expressed in the form of league tables. However, our perspective of quality of care may be different from that of patients. Assessing patient comfort in the perioperative period may help us to identify the shortcomings in care delivery, which may in turn have an impact on outcome. Thus, the patient experience may be different even being in the better outcome group. Also a surgeon as an individual may have a limited influence on how the aftercare is delivered by the organization.

We devised a scoring system to measure patient comfort objectively in a purpose-built elective centre in a district general hospital. Data were collected prospectively for a month in two separate settings. We used objective case note analysis and a five-question patient survey by 50 randomly selected patients. The primary objective was to ascertain the patient comfort level after having had elective surgery. The secondary objective was to identify factors that caused patient discomfort and delayed discharge, particularly looking at anaesthetic, surgical, and staffing factors.

The majority of the patients were pain free (86% had VAS score <5). 92% had no postoperative nausea and vomiting (PONV). 50% of those patients who reported sickness received no anti-emetic after operation. The average length of postoperative fasting was 3.5 h.

On review only 34% of patients had something to eat after the operation (despite well-controlled pain 86% and no PONV 92%). 56% of patients had no desire to pass urine after operation (possibly due to dehydration). No significant surgical and anaesthetic shortcomings were identified.

Measurements of patient comfort are a positive indicator of quality of care.

The development of a comfort score, like pain scores or an early warning system, may trigger an action if a certain threshold is reached. The good outcome of a surgical procedure is dependent on the multidisciplinary team working together to provide a common and positive healthcare goal. Each member of the multidisciplinary team plays a crucial role towards a positive outcome. It is probably not entirely dependent on the surgical procedure or its technique.

Effects of ketamine anaesthesia on brain orexin-A contents in rats
K. Hirota, T. Kushikata* and M. Kudo*
Department of Anesthesiology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

Central orexinergic neurones have been reported to play an important role in general anaesthesia. We previously reported that ketamine inhibited orexinergic neurones via an interaction with N-methyl-D-aspartate receptors.1 In the present study, we have determined whether ketamine anaesthesia affects brain orexin-A (OXA) content in rats.

After approval of our protocol by our University animal ethics committee, 22 rats were assigned into three groups: K0 (n=8), K20 (n=8), and K60 (n=6). In the K0, K20, and K60 groups, rats were decapitated 0, 20, and 60 min after i.p. ketamine (100 mg kg⁻¹), respectively. The brain was quickly removed, and the pons, hypothalamus, hippocampus, and cerebrocortex were dissected from internal structures and weighed. Each brain region was immediately sonicated in 10× brain tissue weight of Krebs–Ringer bicarbonate buffer solution. The supernatant was collected and stored at −70°C until OXA extraction was performed. OXA concentration was measured using a commercial enzyme-linked immunosorbent assay kit. All data are mean (±SEM). Statistical analysis was by one-way ANOVA followed by the Student–Newman–Keuls test. P<0.05 was considered significant.

When rats were decapitated, all were anaesthetized in the K20 group and awake within 15 min after emergence from ketamine anaesthesia in the K60 group. In the hypothalamus and the hippocampus, OXA contents were significantly lower in the K20 group than those in the K0 and K60 groups (Table 1). No significant changes in OXA contents between the groups were observed in the pons and the cerebrocortex.

A previous report2 suggested that orexinergic neurones could affect exit from but not entry into the anaesthetized state. However, in the present study, brain OXA contents significantly decreased during ketamine anaesthesia and returned to the baseline immediately after emergence. Therefore, central orexinergic activity may be modulated by anaesthesia.
The innate immune system mediates the early localized inflammatory response to infection that is essential in clearing pathogens. However, excessive release of inflammatory mediators may trigger a systemic inflammatory response with organ injury (sepsis). During infection, the activation by microbial components of two main components of innate immunity, Complement and the Toll-like receptors (TLRs), plays a critical role in the release of pro-inflammatory mediators. Co-stimulation via both TLRs and the receptor for the pro-inflammatory complement component C5a (C5aR, a G-protein-coupled receptor) has a synergistic effect in the release of inflammatory mediators. This synergy is an attractive target for attenuating excessive release of inflammatory mediators without abrogating the appropriate inflammatory response. Here we report the findings of our study on this synergy and its underlying mechanism.

Peripheral blood mononuclear cells (PBMCs) or human whole blood cells were pre-exposed to TLR ligands, washed and exposed to C5a, temporarily separating the two stimuli in order to assess the relative contributions of each. An ex vivo model used blood cells from mice deficient in TLR signalling (n = 5) previously injected with the TLR4 ligand bacterial lipopolysaccharide (LPS, endotoxin). Production of inflammatory mediators was assessed by ELISA, qPCR for mRNA and western blot. C5a receptor expression was assessed by flow cytometry (FC) and qPCR. Ca²⁺ mobilization experiments were conducted by FC. Levels of the activated transcription factor NF-κB were assessed by ELISA.

IL-8 release by PBMC in response to simultaneous stimulation with LPS and C5a was greater than additive compared with either alone. This synergy was reproduced by the pre-exposure (LPS)/exposure (C5a) model in both PBMC and whole blood, suggesting that the synergy is at least partly due to an enhancing effect of TLR activation on cell sensitivity to C5a for PBMC C5a alone (10 nM) mean IL-8 (SD) was 2.7 ng ml⁻¹ (0.1) compared with 7.5 (0.2) mg ml⁻¹ (P < 0.01). Pre-exposure to a variety of TLR ligands resulted in C5a-induced IL-6 and IL-8 mRNA levels higher than those in cells not pre-exposed, indicating that the TLR-induced enhancement in sensitivity to C5a occurs at a transcriptional level. Similarly, C5a-induced levels of NF-κB, a key regulator of inflammatory gene transcription, were also higher in TLR-activated cells, suggesting that a range of inflammatory mediators is affected. The use of TLR4 signalling-deficient mice confirmed that intact TLR signalling is necessary for the LPS-induced enhancement in sensitivity to C5a. Mechanistically, TLR-induced hypersensitivity to C5a is not due to up-regulation of C5aR expression. Furthermore, no effect on Ca²⁺ mobilisation was observed, suggesting that TLR activation does not affect the C5a-triggered G-protein signalling pathway. Rather TLR stimulation was found to inhibit the expression and activity of the second C5a receptor, C5L2, which is a negative modulator of C5aR. Cell pre-exposure to LPS inhibited the C5a-induced C5L2-mediated release of the late inflammatory mediator, HMGB1, and qPCR experiments showed a significant LPS-induced reduction in C5L2 mRNA. Notably, pre-incubating PBMC with a C5L2 blocking antibody reproduced the effect of LPS in inducing hypersensitivity to C5a while inhibiting HMGB1 release. These findings indicate that TLR activation induces cell hypersensitivity to C5a, at least in part, by inhibiting C5L2, itself an inhibitor of C5aR activity. Unravelling the pathways regulating this effect may reveal novel therapies for sepsis.
knees and encourages forward flexion of the lumbar spine. Our aim was to assess, using ultrasound measurements, the effect of lateral table tilt on the height of the ‘target area’ (visible part of the ligamentum flavum in the longitudinal view) for intrathecal anaesthesia.

We performed lumbar ultrasound (US) scans on healthy pregnant women, at or beyond 36 weeks gestation, in order to measure the height of the ‘target area’ (TA) and the interlaminar distance (ILD) at the L3/L4 interspace. Each subject was scanned in random order, by two operators and in three positions (0°, 8°, and 15° of lateral table tilt). A clinically significant increase was considered to be a minimum of 1 mm increase in TA height. Using an SD of 1 mm from previous pilot data, at 90% power, a minimum of 16 women were required to find a 1 mm difference as significant at \( P < 0.017 \) (Bonferroni’s correction for three positions). Data were analysed using repeated-measures analysis of variance (RMANOVA) with the Tukey–Kramer multiple-comparison test. Data are presented as mean (SD).

We enrolled \( n = 20 \) women: age 27.7 yr (4.89), weight 86.2 kg (14.81), height 1.64 m (0.06), and body mass index 32.2 (5.32). There were no significant effects with respect to operators. The US measurements (Table 2) demonstrate significant increases in TA with increasing tilt but with no significant effect on ISD. There was a significant trend to increasing TA with tilt (\( P < 0.0001 \)) and the Tukey–Kramer tests were significant for all TA tilt comparisons (\( P < 0.05 \)).

Our study showed that both 8° and 15° of lateral table tilt significantly increase the height of the TA and exceeded 1 mm for the 15° position. The data suggest that using table tilt in obstetric patients may be of help in the siting of neuraxial needles for anaesthetic procedures and that further clinical research is required.

### Table 2 Effect of table tilt on TA height and ILD

<table>
<thead>
<tr>
<th>US measure</th>
<th>Degree of table tilt</th>
<th>RMANOVA, P-value</th>
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<tr>
<td></td>
<td>0°</td>
<td>8°</td>
</tr>
<tr>
<td>TA (mm)</td>
<td>10.6 (1.27)</td>
<td>11.6 (1.31)</td>
</tr>
<tr>
<td>ILD (mm)</td>
<td>32.0 (3.30)</td>
<td>32.8 (3.24)</td>
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Activation of the enzyme Sphingosine kinase 1 (SphK1) generates the lipid mediator sphingosine-1-phosphate (S1P).\(^1\) Puneet and colleagues showed up-regulation of SphK1 expression in septic patients compared with healthy volunteers, and that SphK1 inhibition protects against LPS-induced endotoxic shock in mice, illustrating the potential of SphK1 and S1P as targets for novel therapies to treat sepsis.\(^2\) Here we have measured SphK1 mRNA in polymorphs from septic patients with their own recovery sample acting as a control.

With REC approval and informed consent, we recruited patients admitted to the intensive care unit with a diagnosis of sepsis. Fifteen millilitres of blood were collected into EDTA tubes from each patient within 24 h of diagnosis of sepsis (day 1), 24 h later (day 2), and on clinical recovery from sepsis. Polymorphonuclear leucocytes (PMNs) were isolated using gradient methodology (polymorph prep, Axis Shield). Total RNA was isolated using a mirVana™ miRNA Isolation Kit and treated to remove DNA contamination (Turbo DNA-free). Total RNA was converted to copy DNA by reverse transcription and samples assayed for SphK1 gene expression by quantitative PCR using a commercially available TaqMan® probe from Applied Biosystems. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an endogenous control.\(^3\) Data are presented as \( \Delta C_t \) (difference between SphK1 and GAPDH cycle threshold, \( C_t \) where one cycle is a doubling of start material and low \( C_t \) equates to high expression).

Data from 12 patients (aged 32–79 yr, six males) are presented. Twenty-four-hour APACHE II scores ranged from 15 to 30. Documented source of sepsis was the chest (5) or abdomen (7). PCR data are presented in Table 3.

The higher \( \Delta C_t \) values indicate that gene expression of SphK1 in PMN cells was significantly lower during sepsis compared with values after clinical recovery. Further studies are required to establish the effect of this reduction in mRNA on SphK1 activity and S1P concentrations and to reconcile these data with those of Puneet and colleagues.\(^2\)

### Table 3 \( \Delta C_t \) for SphK1. Median (range, \( n = 12 \)). *\( P < 0.05 \) (ANOVA with Bonferroni’s correction for multiple comparisons) compared with ICU admission (day 1)

<table>
<thead>
<tr>
<th></th>
<th>Day 1 sepsis</th>
<th>Day 2 sepsis</th>
<th>Recovery</th>
</tr>
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<tbody>
<tr>
<td>SphK1 (( \Delta C_t ))</td>
<td>11.07 (9.60–13.09)</td>
<td>10.63 (9.05–12.12)</td>
<td>9.65* (8.39–11.61)</td>
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**Sphingosine kinase 1 mRNA expression in polymorphs from intensive care unit patients with sepsis**

N. Ladak, A. Serrano-Gomez, J. McDonald, J. P. Thompson and D. G. Lambert

Division of Anaesthesia, Critical Care and Pain Management, Department of Cardiovascular Sciences, University of Leicester at Leicester Royal Infirmary, Leicester, UK
Xenon reduces apoptosis, γ- and β-secretase expression in an in vitro model of Alzheimer’s disease

D. Lloyd*, M. Vizcaychipi*, C. Pac-Soo and D. Ma

Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Imperial College London, Chelsea and Westminster Hospital, UK

Alzheimer’s disease is the most common cause of dementia in old age and is associated with the accumulation of Amyloid-β, the product of sequential cleavage of Amyloid Precursor Protein (APP) by γ- and β-secretase enzymes. A link between Alzheimer’s pathogenesis, general anaesthesia,1 and apoptosis2 has been established but is poorly understood. We hypothesize that xenon, an emerging anaesthetic agent with known neuroprotective properties,3 causes less apoptosis than isoflurane at clinically relevant concentrations, through a mechanism related to Alzheimer’s pathogenesis.

Neuroglioma cells stably transfected with human wild-type APP (H4 APP cells) were exposed for 6 h to (i) no treatment, (ii) 70% xenon, (iii) 75% nitrous oxide, or (iv) 2% isoflurane, with 21% O₂ and 5% CO₂ balanced with nitrogen. The level of the functional executor of cellular apoptosis Caspase-3 fragment, APP, γ- and β-secretase, present in cell lysate isolated immediately post-exposure, was determined by western blotting. Densitometric analysis was performed and the data were normalized by internal control to α-tubulin. Data are presented as mean (SEM) (n=3).

Caspase-3 fragment was significantly reduced after xenon exposure, when compared with cells exposed to Isoflurane [0.46 (0.36)-fold reduction. γ-Secretase expression was significantly inhibited after xenon compared with isoflurane exposure [0.44 (0.35)] and untreated control [0.41 (0.35)] (Fig. 6) β-Secretase expression was significantly reduced in the xenon group [0.29 (0.11)] when compared with untreated control. Nitrous oxide was not shown to produce any significant effect.

Our results indicate that xenon has cytoprotective effects and down-modulates some aspects of Alzheimer’s disease pathogenesis. The implication of our data may suggest that anaesthetics such as xenon produce favourable effects when used in clinical practice in an ageing population at risk of Alzheimer’s pathology.

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Effects of mitochondria-targeted antioxidants on mitochondrial dysfunction in paclitaxel-treated dorsal root ganglion neuronal cells: implications for neuropathic pain

D. A. Lowes¹, A. Hoke²*, N. R. Webster¹, M. P. Murphy³* and H. F. Galley¹

¹Academic Unit of Anaesthesia and Intensive Care, School of Medicine and Dentistry, University of Aberdeen, Aberdeen, UK.
²Neuromuscular Division, Johns Hopkins University, Baltimore, MD, USA. ³MRC Mitochondrial Biology Unit, Cambridge, UK
Chemotherapy-induced peripheral neuropathic pain is an unpleasant side-effect of chemotherapeutic agents such as paclitaxel and limits the doses which can be used. Mitochondria produce energy from oxygen via oxidative phosphorylation, but during this process, oxygen-derived reactive species are released, which are toxic and can damage mitochondria. There is evidence that paclitaxel-induced neuropathy is caused by mitochondrial damage. Antioxidants which specifically protect mitochondria against oxidative stress may be able to prevent paclitaxel-induced mitochondrial damage. We assessed the effect of MitoVitE and melatonin on paclitaxel-induced mitochondrial damage in a dorsal root ganglion (DRG) neuronal cell line. These cells extend neurites when differentiated, express receptors characteristic of small sensory neurones, generate action potentials when depolarized, and respond to capsaicin.

Cells were cultured in 96-well plates in neurobasal medium containing 20% glucose, 0.2 M l-glutamine, fetal calf serum and B27 supplement devoid of antioxidants, to 50% confluence. To initiate differentiation, 75 μM forskolin was added and neurite outgrowth started 2–3 h later. After 24 h, paclitaxel at 0, 1, 5, 10, or 100 μM was added, along with 1 μM MitoVitE or melatonin or vehicle control. Cells were cultured for 24 h. Mitochondrial membrane potential was analysed using the fluorescent probe JC-1 and metabolic activity was measured using Alamar Blue. Total glutathione was analysed using the fluorescent probe JC-1 and metabolic activity was measured using acid phosphatase. The effect of the antioxidants on paclitaxel-mediated killing of cancer cells was assessed in the breast cancer cell line MCF7. Our data are presented in Figure 7.

We have shown that antioxidants which accumulate in mitochondria can protect against paclitaxel-induced damage. This may have implications for treatment of neuropathy in the future.

Acknowledgement

This work was funded by the Association of Anaesthetists of Great Britain and Ireland.

Autonomic tone in patients undergoing coronary artery bypass surgery requiring cardiopulmonary bypass: does it predict postoperative atrial fibrillation?

M. T. H. Lowry 1*, A. Ronald 2 and N. R. Webster 1

1Academic Unit of Anaesthesia and Intensive Care, School of Medicine and Dentistry, University of Aberdeen, Aberdeen, UK.
2Department of Anaesthesia, Aberdeen Royal Infirmary, Aberdeen, UK.

Atrial fibrillation (AF) is the most common arrhythmia after coronary artery bypass grafting (CABG) operations with an incidence of 17–33%. It has a significant impact on patient morbidity, mortality, and hospital resources. Effective prophylactic treatment strategies are available, but as of yet no accurate method for identifying those patients at highest risk of developing the arrhythmia is available. The autonomic nervous system (ANS) plays a key role in the pathogenesis of AF and can be assessed using heart rate variability (HRV) analysis. It was hoped that such analysis could identify patients at an increased risk of developing AF, thus allowing targeted prophylaxis to take place.

A Holter monitor was used to record a 10 min ECG on four separate occasions in 32 patients undergoing CABG: 24 h before operation, 1 h after operation, 24 h after operation, and 48 h after operation. Offline analysis was then performed using R peak detection software and HRV parameters that assessed the overall variability of the heart (mean R–R interval) and calculation of other specific vagal and sympathetic influences.

Twelve (38%) patients developed AF within 48 h. Mean R–R interval was decreased and heart rate increased (P<0.04) significantly in the patients who developed AF compared with those who remained in sinus rhythm 1 h after operation. No other differences in HRV parameters between those who developed AF and those who did not were found.

In patients undergoing CABG, a significant change in markers of sympathetic tone was found regardless of whether patients developed AF. However, higher heart rate and lower mean R–R interval 1 h after operation was associated with subsequent AF. Since decreased HRV has been shown to be a risk factor for adverse cardiac events in the non-surgical population, this study may indicate a potential
role for HRV analysis in the risk stratification of post-cardiac surgery patients.3

References

Computational fluid dynamic modelling of airway gas flow with tracheal intubation

A. B. Lumb1, A. D. Burns2,3*, D. B. Ingham2* and M. Pourkashanian2*

1School of Medicine and 2Centre for Computational Fluid Dynamics, University of Leeds, Leeds, UK. 3Ansys UK, Abingdon, UK

A clinical report of unequal ventilation of the right and left lungs during anaesthesia with a tracheal tube (TT) suggested that a Coanda effect could occur in the airway, resulting in preferential ventilation of one lung.1 When ventilating via a TT, maintenance of alveolar ventilation requires the use of similar gas flow rates to normal breathing, despite delivering this via a TT of 7–9 mm diameter compared with 20–30 mm for the trachea. These two observations led to our hypothesis that airway gas flow patterns would be abnormal when using a TT. We have used computational fluid dynamics (CFD) to investigate our hypothesis.

A three-dimensional model of a human airway was provided by ANSYS UK. The model was originally produced by mesh generation algorithms that convert 3D medical images into a geometric model, and represents the airway from the start of the trachea to 21 segmental bronchi. The commercial CFD package ANSYS CFX was used to compute the flow during constant flows of 0.5 and 1.0 litre min−1 to correspond to peak inspiratory flow rates during resting breathing and mild hyperventilation, respectively. The results were post-processed by plotting flow velocity vectors along streamlines of the flow. Visualizations were generated with no TT, and then with a 7 mm TT positioned in the centre and to one side of the airway.

Our model is at an early stage of development and has limitations. The tip of the TT is more proximal than in clinical use, and we used constant flow rather than tidal flow. Our results show that with normal breathing, there is uniform, and approximately equal, flow to both lungs. In contrast, with a TT, a high velocity jet of gas causes flow to pass along the inferior aspect of the main bronchi reducing flow to both upper lobes. When the tube is to one side of the trachea, there is preferential flow to the lung on the same side and the flow exhibits a small degree of unsteadiness, with flow exit ratios oscillating around a mean value of 70:30%. Our results show that gas flow patterns are abnormal when ventilated via a TT (Fig. 8).

Acknowledgement
We wish to thank ANSYS-UK for providing the airway model mesh.

Reference
1 Qudaisat IY. Br J Anaesth 2008; 100: 859–60
Patients with tracheostomies are increasingly common in hospital. Hospital wards may lack appropriate infrastructure and resources to care for this vulnerable group of patients. The aim of this study was to compare the levels of harm occurring on hospital wards or in critical care.

We identified and analysed post-placement tracheostomy incidents reported to the UK National Patient Safety Agency (NPSA) between October 1, 2005, and September 30, 2007, using key letter searches. Incidents were stratified into three strata; completely or partially displaced and obstructed. Outcomes were defined as the frequencies and types of harm occurring. Analyses included the Mantel–Haenszel chi-squared test for stratified data and Fisher’s exact test for within-stratum comparisons. The expanded Fisher–Freeman and Armitage trend tests were used for within-location analyses. Results are presented as frequencies and odds ratios (ORs) with 95% confidence intervals (CIs). Significance was defined at P<0.05 (two-sided).

n=494 post-placement tracheostomy incidents were identified and classified by location into ‘Intensive Care/High Dependency’ (n=218) or ‘Hospital ward’ (n=276). The overall risk of harm was significantly greater in the ward setting (pooled OR 7.1; 95% CI 3.7–14.7; P<0.0001 Mantel–Haenszel test). Results stratified for incident are shown in Table 4. There was a significant trend (slope 15%; 95% CI 7–23) to increasing risk of harm across the strata in the ICU setting from complete through partial displacement to complete obstruction.

Searching the NPSA database has allowed us to compare tracheostomy incidents occurring in wards and critical care areas. Incidents may be due to potentially remedi able problems and simple education, guidelines, and equipment could be expected to reduce harm. Our study demonstrated that ward patients have a significantly higher chance of coming to harm when a tracheostomy incident occurs when compared with critical care patients.

### Table 4 Results stratified for incident

<table>
<thead>
<tr>
<th>Type</th>
<th>Ward Harm</th>
<th>Ward No Harm</th>
<th>ICU Harm</th>
<th>ICU No Harm</th>
<th>Odds ratio (95% CI) Fisher’s exact P-value</th>
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<tr>
<td>Complete</td>
<td>112</td>
<td>3</td>
<td>51</td>
<td>35</td>
<td>25.6 (7.4–134.0)</td>
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<td>Partial</td>
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<td>3</td>
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<tr>
<td>Obstructed</td>
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<td>7</td>
<td>39</td>
<td>5</td>
<td>2.2 (0.5–8.7)</td>
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<td>Expanded Fisher’s P-value</td>
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<td>Trend P-value</td>
<td>0.31</td>
<td>0.0003</td>
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</tbody>
</table>

References
3 Thomas A, McGrath B. Anaesthesia 2009; 64: 358–65
Antioxidants are known to affect cytokine production and NF-κB activation. This study shows that antioxidants directly decrease phosphorylation of MSK1 and increase pCREB activation presumably via PKA pathways, which may contribute to the reduction in NF-κB activation and reduced pro-inflammatory cytokine expression.

Is the impact of intraoperative goal-directed fluid therapy on length of stay after major elective colorectal surgery related to patients’ aerobic fitness?

G. Minto1,3*, C. Challand2,3, J. R. Sneyd1,3, N. Mellor2*, K. B. Hosie2*, P. Erasmus1* and R. Struthers1,3*

1Department of Anaesthesia and 2Department of Surgery, Plymouth Hospitals NHS Trust, UK. 3Peninsula Medical School, University of Plymouth, Plymouth, UK

Intraoperative goal-directed fluid therapy (GDT) has been shown to reduce length of stay and decrease morbidity in elective colorectal resections.1 We hypothesized that the benefit of GDT might apply particularly to unfit patients.

We recruited 179 patients characterized by preoperative cardiopulmonary exercise test on a stationary bicycle as aerobically fit (anaerobic threshold, AT > 11 ml O₂ kg⁻¹ min⁻¹), n=123, or unfit (AT 8.0–10.9 ml O₂ kg⁻¹ min⁻¹), n=56, into a single-centre double-blind randomized controlled trial of GDT vs standard intraoperative fluid therapy. Oesophageal Doppler probes were placed in all patients: measurements were visible only to an investigator. Control fluid therapy was at the discretion of the anaesthetist. GDT patients were given additional algorithm-directed colloid (Voluven, Fresenius) by the investigator with the anaesthetist and surgeons blinded.

Patient characteristics and surgical details were comparable between the groups. Intraoperative GDT had no impact on length of hospital stay (medians 8.9 vs 6.7 days, GDT vs control, P=0.221, t-test) or on the incidence of severe complications (9.0% vs 12.2%, GDT vs control, P=0.48 x² test) (Table 5).

LOS was increased in fit patients undergoing colonic resection who received GDT. n=32 GDT, n=37 control (median LOS 8.7 vs 4.9 days; P=0.007).

Algorithm-directed colloid-based GDT was not superior to standard perioperative fluid management.

Acknowledgement

Supported by AAGBI through the National Institute of Academic Anaesthesia.

Reference

1 Noblett SE, Snowden CP, Shenton BK, Horgan AF. Br J Surg 2006; 93: 1069–76

Effect of a thoracic epidural bolus and subsequent intravenous phenylephrine infusion on gastric tube blood flow during oesophagectomy

D. Pathak1, S. H. Pennefather1*, G. N. Russell1, R. D. Page2 and O. Al Rawi1

1Department of Anaesthesia and 2Department of Thoracic Surgery, Liverpool Heart and Chest Hospital, UK

Ischaemia of the gastric tube is a major cause of anastomotic leak and mortality after oesophagectomy. A relationship between low laser Doppler flux measured at the gastric anastomotic site and subsequent anastomotic leak has been shown. We have shown that a thoracic epidural bolus results in a decrease in gastric tube blood flow and that this decrease is reversible by an epinephrine infusion.1 In this study, we investigated the effect of the vasoconstrictor, phenylephrine on blood flow in the gastric tube.

With ethics approval, patients undergoing an oesophagectomy were recruited. An arterial cannula and a mid-thoracic epidural catheter were inserted. No epidural test dose was given. Anaesthesia was induced with fentanyl and propofol. Placement of a double-lumen tube was facilitated with succinylcholine. Anaesthesia was maintained with isoflurane in an oxygen/air mixture. Neuromuscular block was
maintained with atracurium. A pulmonary artery catheter was inserted. Fluid management was standardized. After formation of tubularized stomach, laser Doppler flow probes (DP8C, Moor Instruments, Axminster, UK) were sutured to the fundal (anastomotic) and pyloric end and then attached to a monitor (DRT4, Moor Instruments). Data were archived. Surgery was stopped for the study. Data were collected during 3 and 5 min periods. During the baseline period, the flux trace was marked and then three thermodilutional cardiac output measurements were made and averaged. After 5 min, the flux trace was re-marked and haemodynamics remeasured. Patients then received a 0.1 ml kg\(^{-1}\) bolus of epidural 0.25% levobupivacaine. The epidural study period commenced when the systolic arterial pressure had decreased by 30%, the flux trace was marked, and haemodynamic measurements made as above. The patients then received an i.v. infusion of phenylephrine titrated to achieve an arterial pressure of 30% above baseline. When the target arterial pressure was achieved, the phenylephrine study period started. The Doppler flux trace was marked and haemodynamic measurements were made as described above.

Eighteen patients were recruited. One patient was excluded because of failure to site the epidural; six patients were excluded because of corruption/loss of flux data; and one patient was omitted because of failure to capture flux data. The haemodynamic and flux changes of the remaining 10 patients are summarized in Table 6. We have shown that the epidural bolus induced reduction in gastric flux was reversed by a phenylephrine infusion.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Epidural</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>57 (39–339)</td>
<td>41 (30–112)</td>
<td>67 (24–345)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>80 (65–95)</td>
<td>57 (47–64)</td>
<td>96 (80–122)</td>
</tr>
<tr>
<td>SVR (dyne s(^{-1})cm(^{-5}))</td>
<td>815 (483–1665)</td>
<td>619 (441–1160)</td>
<td>1064 (773–2335)</td>
</tr>
</tbody>
</table>

Reference
1 Al Rawi O, Pennefather SH, Page RD, Dave I, Russell GN. Anaesth Analg 2008; 106: 884–7

**Functional electrical impedance tomography by evoked response: monitoring cerebral auto-regulation during the Valsalva manoeuvre**

T. Quraishi\(^1\)*, C. J. D. Pomfrett\(^1,2\), J. Davidson\(^3\)*, R. Robinson\(^3\)*, P. Wright\(^3\)*, S. T. Ahsan\(^3\)*, A. Bryan\(^1\), B. J. Pollard\(^1\)* and H. McCann\(^3\)*

\(^1\)Division of Clinical and Scientific Services, Department of Anaesthesia, CMFT, UK. \(^2\)Cardiovascular Research Group, School of Biomedicine and \(^3\)School of Electrical and Electronic Engineering, University of Manchester, Manchester, UK

Functional electrical impedance tomography by evoked response (fEITER) is a novel imaging device which monitors changes in cerebral impedance across the whole brain. We aimed to evaluate haemodynamic and electrophysiological changes across the brain in response to volunteers performing the Valsalva manoeuvre (VM).

Each volunteer had 32 ZipPrep\(^\text{TM}\) (Covidien, UK) electrodes placed on the scalp using the 10–20 system. The VM was initiated at 10 s and released at 25 s. Sinusoidal current of 1 mA pk–pk was injected at 10 kHz; continuous voltage data were recorded from all electrodes excluding the
current injection pair, for 60 s at a temporal resolution of 10 ms. The VM was performed by 15 volunteers at CMFT.

The upper trace shows sub-second cerebral transimpedance changes in response to the VM. Pooled voltage measurements beginning at 5 s were compared with measurements at 8 s for an epoch of 40 ms; no significant differences were observed during this reference period before the VM being initiated. Voltage measurements during the VM at 20 s were significantly different from those taken at 5 s for an epoch of 40 ms (Wilcoxon’s signed-rank, \( P < 0.05 \)).

Sub-second transimpedance changes signify neural mechanisms involved in cerebral auto-regulation during the most distinct phases of the VM (I and III). The cerebral transimpedance waveform (Fig. 10) is similar to those obtained from middle cerebral artery recordings previously performed using transcranial Doppler.¹ These findings show FEITER has the potential to monitor haemodynamic regulation across the brain.

**Acknowledgement**

This study was funded by the Wellcome Trust.

**Reference**


**Application of sono-elastography to clinical peripheral nerve block**

A. Satapathy¹*, S. Munirama¹, G. A. Corner²*, S. Cochran³* and G. A. McLeod⁴

¹Department of Anaesthesia and ²Department of Medical Physics, Ninewells Hospital and Medical School, Dundee, UK. ³Institute for Medical Science and Technology and ⁴Institute of Academic Anaesthesia, University of Dundee, Dundee, UK

Ultrasound has become the standard modality for real-time imaging of peripheral nerve block. Unfortunately, B-mode ultrasound has clinical limitations: good needle visibility is restricted to specific angles out-of-plane (60°–75°) and in-plane (15°–30°); spread of local anaesthetic, particularly using small 0.5–1 ml test volumes, is difficult to visualize; and differentiation between intra- and extraneural placement and intravascular injection cannot be guaranteed. A need arises to develop a means of readily detecting local anaesthetic spread with a small test volume before injection of larger aliquots. Our group has previously reported the development and application of sono-elastography on the Thiel cadaver model.¹ Using a range of volumes from 0.25 to 1 ml, we were able to demonstrate cadaver perineural spread of local anaesthetic for interscalene, median, and femoral block. We now wish to present the first human application of sono-elastography applied to three patients undergoing interscalene, axillary, femoral, and sciatic block.

Caldicott guardian approval was given by NHS Tayside. All blocks were performed using a Zonare Ultra ultrasound machine, Zonare, Mountain View, CA, USA, using linear probes with B-Mode and elastography split imaging. The interscalene block was conducted with a 10/5 MHz probe, needle in-plane, and 15 ml 0.375% levobupivacaine, and axillary block was conducted with a 10/5 MHz probe, needle out-of-plane, and 25 ml 0.375% levobupivacaine. The femoral and sciatic blocks were undertaken on the same patient using a 10/5 MHz probe for the femoral block and 8/3 MHz for the sciatic block, both needle out-of-plane and 20 ml 0.24% ropivacaine. The B-mode image was used to place the tip of the needle as close to the intended nerve as possible. A test dose of 1 ml local anaesthetic was injected around each nerve block followed by increments of 5 ml. Video recording was started before injection and continued for 30 s.

During injection of the 1 ml test dose, spread of fluid was visible in all blocks as an orange hue surrounding the
relatively incompressible nerve, which was visible in blue. Injection of a further 5 ml of local anaesthetic generated a larger orange/red elastogram (Fig. 11). In all patients, there were characteristic patterns of fluid spread, but no expansion of intraneural tissue.

Our group is currently undertaking validation of sono-elastography in the Thiel cadaver model before validation in humans.

Reference

Can commonly available non-invasive temperature measurement methods be used as a surrogate of core temperature and reliably compared with each other?

O. L. Takats*, D. Turnbull and J. Andrzejowski*
Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

Maintaining core body temperature during surgery is considered to be an important component of quality anaesthesia—and the initial postoperative temperature measurement can be used to index the performance of perioperative temperature management. While core temperature is frequently monitored through a surrogate measure, the reliability of the non-invasive temperature measurement methods available in post-anaesthesia care units (PACUs) is questionable. Our objective was to investigate how three of these non-invasive methods can be used for comparisons against each other or as a surrogate of core temperature.

Data from 95 patients—collected during our postoperative temperature audit—were used to determine the agreement between infrared tympanic membrane, infrared temporal artery, and electronic axillary measurements. Tympanic temperatures were recorded in both ears and we made comparisons using both the average of the two sides (trying to increase accuracy) and the greater of the two readings (trying to decrease the effect of the most common operator error of not properly directing the head of the probe and getting a lower reading from the aural canal wall). Subsequently, we collected data from another 21 patients and compared the better agreement between the different temperature measurement methods. AT, average tympanic; MT, maximum tympanic; TA, temporal artery; AX, axillary; BL, bladder

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Mean (SD)</th>
<th>95% CI of Mean</th>
<th>95% Limits of Agreement</th>
<th>95% CI of 95% LA</th>
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<tbody>
<tr>
<td>95 patients</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AT vs TA</td>
<td>−0.40 (0.48)</td>
<td>−0.49 − −0.30</td>
<td>−1.34, 0.54</td>
<td>−1.51 − −1.17, 0.37 − 0.72</td>
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<tr>
<td>MT vs TA</td>
<td>−0.25 (0.50)</td>
<td>−0.35 − −0.15</td>
<td>−1.23, 0.73</td>
<td>−1.60 − −1.05, 0.55 − 0.90</td>
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<tr>
<td>AT vs AX</td>
<td>0.20 (0.73)</td>
<td>0.05 − 0.35</td>
<td>−1.24, 1.64</td>
<td>−1.50 − −0.98, 1.37 − 1.90</td>
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<tr>
<td>MT vs AX</td>
<td>0.34 (0.73)</td>
<td>0.20 − 0.49</td>
<td>−1.08, 1.77</td>
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<tr>
<td>AX vs TA</td>
<td>−0.59 (0.83)</td>
<td>−0.76 − −0.09</td>
<td>−2.22, 1.03</td>
<td>−2.51 − −1.92, 0.74 − 1.33</td>
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<tr>
<td>21 patients</td>
<td></td>
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<tr>
<td>AT vs TA</td>
<td>−0.35 (0.48)</td>
<td>−0.57 − −0.13</td>
<td>−1.30, 0.60</td>
<td>−1.69 − −0.91, 0.21 − 0.98</td>
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<td>MT vs TA</td>
<td>−0.26 (0.51)</td>
<td>−0.49 − −0.02</td>
<td>−1.26, 0.75</td>
<td>−1.67 − −0.85, 0.34 − 1.16</td>
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<tr>
<td>AT vs BL</td>
<td>−0.26 (0.38)</td>
<td>−0.43 − −0.09</td>
<td>−1.00, 0.48</td>
<td>−1.30 − −0.69, 0.18 − 0.78</td>
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<td>MT vs BL</td>
<td>−0.16 (0.39)</td>
<td>−0.34 − −0.02</td>
<td>−0.92, 0.60</td>
<td>−1.24 − −0.61, 0.29 − 0.91</td>
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<tr>
<td>TA vs BL</td>
<td>0.10 (0.42)</td>
<td>−0.09 − 0.29</td>
<td>−0.72, 0.91</td>
<td>−1.06 − −0.39, 0.58 − 1.25</td>
</tr>
</tbody>
</table>
agreeing two non-invasive methods (as demonstrated by our earlier results) to core temperature readings obtained by bladder catheter probes. We used the Bland–Altman method for evaluation and like other authors, we chose 0.5 °C as a clinically relevant temperature deviation. Therefore, we defined that two methods clinically agree if their estimated 95% limits of agreement are within ±0.5 °C range. We also calculated the 95% confidence intervals for our results. Table 7 summarizes the results.

None of the pairwise comparisons of the non-invasive methods fulfilled our clinical agreement criteria. The tympanic membrane and temporal artery measurements, however, had a better agreement with each other than axillary readings. In patients with invasive core temperature measurement, these two non-invasive techniques both had similar levels of agreement with bladder temperature, but none of them was within the predefined ±0.5 °C range.

On the basis of the analysis of our data, commonly available non-invasive temperature measurement methods cannot be used as a reliable estimate of core temperature and cannot be compared with each other. It is important to clearly understand the limitations of these measurement methods when trying to use them as individual or institutional performance indices.

### References

2. Duggan J, Sinha VK. Anaesthesia 2010; 65: 1042–3

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**Table 8** Times are shown as hh:mm:ss

<table>
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<tr>
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**Did the introduction of safe surgery checklists affect theatre productivity?**

A. Vats* and P. K. Gupta

Academic Unit of Anaesthesia, University of Leeds, Leeds, UK

The National Patient Safety Agency (NPSA), in collaboration with a multi-professional expert reference group, has adapted the World Health Organization checklist for use in England and Wales to improve the safety of surgery by reducing deaths and complications. The published evidence for introduction for this checklist is not very robust. We assessed the impact of introduction of this checklist at theatre start time at our local orthopaedic surgery hospital.

The checklist was introduced in the hospital in January 2010. The hospital has four operating theatres and each of these has an electronic tracking system whereby the time of arrival into anaesthetic room, time of skin incision, etc. is recorded by the theatre ODP. The completion of theatre checklists is mandatory before the anaesthetist induces the first patient. We collected the data of all theatre sessions for the period January to May (years 2009 and 2010). We compared the induction time for the first patient for the months January and May for these years, that is, before and after the introduction of the checklists. Our null hypothesis was that the introduction of checklists had no impact on theatre start time.

In total, 241 sessions took place in four theatres over this period. Table 8 shows the mean start time, standard deviation, and the number of theatre sessions for these months. We found that the lists started earlier in six theatre sessions (range 2–7 min approximately) and late in two theatre sessions (range 15 s to 7 min approximately).

A study of the checklist in nearly 8000 surgical patients has been shown to reduce the risk of deaths and other complications. The conduct of checklists requires the presence of the full-theatre team (i.e. surgeon, anaesthetist, ODP, and scrub staff) who go through a questionnaire which takes between 15 s and 2.5 min. Our study suggests that this does not have any significant impact on theatre start time (i.e. productivity).
Investigating high-frequency jet ventilation in a simulated bronchopleural fistula

M. J. Wood, J. P. Thompson and E. S. Lin
Division of Anaesthesia, Critical Care and Pain Management, Department of Cardiovascular Sciences, University of Leicester, Leicester Royal Infirmary, Leicester, UK

High-frequency jet ventilation (HFJV) is used in the management of patients with a bronchopleural fistula (BPF), but variables such as distal pressures, entrained volumes, and leaks cannot be reliably monitored. These are crucial as barotrauma and volutrauma are recognized complications of HFJV.1 We recently presented work to the ARS showing that when using HFJV with a simulated BPF in a test lung, tidal volumes are lower than when ventilating a test lung with no BPF, with the largest differences seen at lower ventilator frequencies.2 In this study, we used HFJV in cadaveric pig lungs with a simulated BPF.

Using an Acutronic Monsoon HFJV ventilator, we performed HFJV (60–350 bpm, 1.5 bar driving pressure) in a cadaveric pig lung model with a left pneumonectomy and simulated BPF. We recorded total measured flow, entrained flow, airway pressures, and leak volumes with differential and gauge pressure sensors (Freescale MPX10DP and MPX10GP) attached to a laptop-based four-channel oscilloscope (Picoscope 4464, Pico- tech, UK). The effects of different ventilator frequencies between 60 and 350 bpm and different anatomical sites (proximal, middle, and distal) of the BPF relative to the tip of the tracheal tube were studied (n=6) (Fig. 12).

All measured volumes were lower at higher HFJV frequencies with both distal and proximal simulated BPF. Expired volumes were lower but entrained and leak volumes were higher for a given ventilator frequency when ventilating a proximal compared with a distal BPF. Further work is to look at the effect of different driving pressures on these volumes.

References

Xenon preconditioning protects renal graft against ischaemia–reperfusion injury in rats

H. Zhao and D. Ma
Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea and Westminster Hospital, London, UK

In clinical settings, renal graft inevitably undergoes various periods of hypothermic storage before engraftment is carried out. Ischaemia–reperfusion injury (IRI) after cold storage is responsible for the delayed graft function and has been considered to contribute to the occurrence of acute rejection and progression of chronic graft nephropathy.1 Therefore, an organo-protective strategy needs to be developed urgently to minimize graft injury from IRI and to prolong the survival of the transplanted kidney. The anaesthetic gas xenon has been demonstrated to protect against renal IRI.2 The aim of the current study is to explore whether xenon preconditioning can ameliorate renal IRI and hence prolong graft survival in a rat model of kidney transplantation.

The syngeneic Lewis-to-Lewis rat renal transplant model was used in this study. Donor animals were preconditioned with 30% O₂ and 70% xenon for 2 h while control donor animals were treated with 30% O₂ and 70% N₂ for 2 h. The donor graft was taken out 24 h after gas exposure and then underwent 16 or 24 h cold ischaemia in 4°C Soltran...

Fig 12 Effect of HFJV frequency on mean (±SD) n=6 entrained, expired, and leak volumes with a simulated BPF in different anatomical sites.
preserving solution. After transplant surgery, the graft was harvested at various time points (1–28 days) for further analysis.

The survival of renal graft with 24 h cold ischaemia was significantly prolonged with xenon preconditioning (maximal survival for 17 days in the control kidney grafts compared with up to 28 days in the xenon-treated grafts).

Preconditioning with xenon protects renal graft against ischaemia–reperfusion, this is likely mediated through HIF-1 alpha activation.

Acknowledgement

MRC DPFS grant.

References