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ABSTRACTS

The College of Anaesthetists of Ireland: Delaney Medal Competition 2014

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

The College of Anaesthetists of Ireland established the Delaney Medal competition 16 yr ago to allow trainees to present their research work annually and get critical feedback. It is named after the late Dr Edmund Delaney who worked in Dr Steeven's Hospital in Dublin from 1957 to 1979. This competition is the premier research event in the College's calendar, attracting high-quality laboratory and clinical papers. The judging panel comprises leading Irish academics, with an external peer reviewer as chairperson. Winning presentations have always been of a very high standard, and consistently, the winners have published their findings in major international peer-reviewed journals.

The *BJA* is now the official journal of the Irish College and last year, for the first time, the *BJA* published the short-listed abstracts which were presented. The external judge this year was Prof. Martin Leuwer and he, along with the entire panel, commented on the high-quality of the abstracts presented. They represent a snap-shot of the academic research being carried out presently in Ireland. The winning abstract was presented by Dr Stephen Fröhlich and entitled 'The CREB transcription factor mediates pulmonary hypoxic responses; implications for a novel therapeutic strategy in acute respiratory distress syndrome'. Dr Fröhlich held an Irish Health Research Board (HRB)-funded academic fellowship. The College of Anaesthetists of Ireland has developed a high academic standing and, despite our small size currently, hold one-quarter of the Irish HRB-funded academic fellowships. We are delighted that the *BJA* has agreed to publish these abstracts as it will further increase the popularity of the Delaney Medal, our premier research competition in Ireland. This and the adoption of the *BJA* as the official journal of the College of Anaesthetists of Ireland has helped to further enhance the academic standing of anaesthesia in Ireland.

CREB transcription factor mediates pulmonary hypoxic responses; implications for a novel therapeutic strategy in acute respiratory distress syndrome

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Alveolar hypoxia in isolation results in expression of a pro-inflammatory phenotype in the lung. Interestingly, this pulmonary inflammatory response to hypoxia occurs in response to oxygen levels in the lung much higher than those encountered in systemic organs, suggesting unique pulmonary transcriptional mechanisms must be mediating these responses. We have previously reported that CREB1 is activated in the lung in response to alveolar hypoxia but not in other organs, and plays a key role in pulmonary homeostatic vascular responses to hypoxia. This work aimed to elucidate the role of the CREB transcription factor in mediating pulmonary inflammatory responses in hypoxic lung diseases such as acute respiratory distress syndrome (ARDS).

Wild-type mice, mice lacking the alpha and delta isoforms of CREB ($CREB^{\alpha\Delta-/-}$), and completely CREB-deficient mice ($CREB^{-/-}$) were exposed to hypoxia (F_{IO_2} 0.10, $F_{IO_2}<0.01$) to examine the effects of CREB deficiency on pulmonary inflammatory responses. A further group of wild-type mice were stimulated with the cAMP activators Forskolin and NKH477 to examine the effects of CREB activation on pulmonary hypoxic gene expression. An extensive panel of inflammatory genes were examined at RNA and protein level in each model. Furthermore, four isolated pulmonary cell types were exposed to hypoxia and CREB pathway manipulation to further investigate responsible signalling mechanisms *in vitro*.

Follistatin expression was increased in response to hypoxia in both wild-type and CREB-deficient mice; however, the increase was greater in both $CREB^{\alpha\Delta-/-}$ and $CREB^{-/-}$ mice than in wild-type controls. CXCL12 was similarly increased in response to hypoxia in wild-type and CREB-deficient mice; in the $CREB^{\alpha\Delta-/-}$ mice, there was no difference in hypoxic response, but in the complete CREB knockout ($CREB^{-/-}$), the response of CXCL12 and its receptor, CXCR4, to hypoxia was attenuated. In the *in vitro* cell model, CXCL12 was similarly elevated in response to hypoxia; this increase was attenuated using the AMP kinase inhibitor dorsomorphin.

We have demonstrated for the first time that the unique lung-specific pulmonary responses to hypoxia are, at least in part, CREB-dependent. The factors CXCL12 and Follistatin are altered in response to hypoxia in the lung as a result of AMP kinase-mediated CREB up-regulation. This novel finding provides a new therapeutic paradigm that may provide a unique pathway to target in ARDS therapies.

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Reference

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Xenon and sevoflurane effects on migration and expression of angiogenesis factors in breast adenocarcinoma cells *in vitro*

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Anaesthetic agents may influence residual cancer cell function and development of metastasis.[1] Volatiles have been implicated in metastasis-enhancing effects; however, the noble gas xenon has never been evaluated. We investigated the effect of xenon and sevoflurane on migration and expression of angiogenesis biomarkers in breast adenocarcinoma cell lines *in vitro*.

MDA-MB-231 and MCF-7 breast cancer cells were exposed to experimental or control gas concurrently in two hermetic chambers. Xenon cylinder contained O_2—25%, CO_2—5%, xenon—70%; control gas contained O_2—25%, CO_2—5%, N_2—70%. Sevoflurane 2.5% was administered in O_2—60%, N_2—37%, or in control gas. Cell viability was determined using an MTT assay. Migration was determined using the Oris Cell Migration Assay™. Secretion of angiogenesis factors into conditioned medium was measured using a membrane-based sandwich immunoassay array.

Xenon reduced MDA-MB-231 migration to 59 (13)% of control after 1 h exposure, $P=0.02$; 64 (10)% after 3 h, $P=0.01$; 71 (9)% after 5 h, $P=0.04$, without affecting viability. Similarly, MCF-7 migration was significantly reduced at all three timepoints [57.5 (12.0)%, 64.75 (12.1)%, and 64.7 (11.9)%]. Sevoflurane, delivered in control gas, did not affect migration. *N*-methyl-D-aspartate (NMDA) receptor co-factor glycine reversed the inhibitory effects of xenon on migration. Expression of pro-angiogenesis cytokine, RANTES, was reduced in conditioned medium from xenon-exposed cells compared with cells exposed to either control gas or sevoflurane [mean dot density 2.05 (0.20) *vs* 2.95 (0.07) and 3.1 (0.28), respectively, $P=0.02$].

Xenon, but not sevoflurane, inhibits migration in both ER+ and ER− breast adenocarcinoma cells by an NMDA receptor-mediated mechanism. Furthermore, xenon decreases the release of the pro-angiogenic cytokine, RANTES, from MDA-MB-231 cells.

Serum from women undergoing breast cancer surgery, randomized to distinct anaesthetic techniques, exerts different effects on healthy Natural Killer cell anti-tumour activity

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Animal inoculation models and retrospective clinical data suggest that certain anaesthetic techniques may attenuate immunosuppression and minimize metastasis after cancer surgery.[1–4] Natural Killer (NK) cells are a critical component of the anti-tumour immune response. We investigated the effect of serum from women undergoing primary breast cancer surgery, randomized to propofol-paravertebral (PPA) or sevoflurane-opioid (GA) anaesthetic technique, on healthy human donor NK cell function and cytotoxicity against oestrogen and progesterone receptor-positive breast cancer cells (HCC1500).

Ten patients who donated serum before operation and 24 h after operation in an ongoing randomized prospective trial (NCT 00418457) were randomly selected. Serum from PPA ($n=5$) and GA ($n=5$) was co-cultured with HCC1500 and healthy primary NK cells. NK cell activating receptors (NKp30, NKp44, NKp46, 2b4, CD16, NKG2D), cytokine production, NK CD107a expression, and subsequent cytotoxicity towards HCC1500 were examined.

Serum from PPA patients did not alter normal NK marker expression or secretion of cytokines. Serum from patients receiving GA reduced NK cell activating receptor CD16 [from mean (SEM)%, 82 (2) to 50 (4), $P=0.001$], IL 10 [from 1700 (80) to 1200 (92) pg ml^{-1}, $P=0.001$] and IL1β [from 68 (12) to 19 (4) pg ml^{-1}, $P=0.01$]. A significant increase in NK cell CD107a [mean (SEM)%, 23 (2) to 37 (3), $P=0.007$] expression and apoptosis of HCC1500 [11 (1) to 21 (2), $P=0.0001$] was observed with PPA, but not GA serum-treated NK cells.

Serum from women with breast cancer undergoing surgical excision, who were randomized to receive PPA anaesthetic technique, preserved human donor NK cell cytotoxicity *in vitro* to a greater extent than patients who received GA.

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The effect of the Oxford Head Elevating Laryngscop Pillow (O/HELP) on subarachnoid local anaesthetic spread in elective Caesarean section: a randomized controlled trial

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The Oxford Head Elevating Laryngoscopy Pillow (O/HELP) places a patient in a ramped posture, which maximizes the view of the larynx during laryngoscopy.[1] In our institution, the (O/HELP) is used pre-emptively for regional anaesthesia in parturients with BMI >30. In our study, we aimed to investigate the effect of the O/HELP on the spread of local anaesthetic injected during subarachnoid anaesthesia. We hypothesized that the O/HELP impairs the cephalad spread of local anaesthetic resulting in an inadequate block for Caesarean section.

One hundred parturients presenting for elective Caesarean section under combined spinal epidural anaesthesia were prospectively randomized. They were placed in either the standard supine position with lateral displacement (control group) or in the supine position on the O/HELP (intervention group). Both groups received 11 mg of hyperbaric bupivacaine+100 μg morphine+15 μg fentanyl intrathecally. Patients were assessed for adequacy of sensory block (T6 or higher) at 10 min and the need for the epidural top-up or conversion to general anaesthesia.[2]

Satisfactory sensory block was achieved in 65.9% of parturients in the intervention group *vs* 95.7% in the control group ($P<0.05$). The requirements for epidural top-up or conversion to general anaesthesia because of discomfort were higher in the intervention group.

The use of the O/HELP in parturients undergoing elective Caesarean section was associated with a significantly increased incidence of subarachnoid block failure.

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Stroke volume and systolic pressure variation for prediction of fluid responsiveness during major pancreatic surgery

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Stroke volume variation (SVV) and systolic pressure variation (SPV) have been shown to be reliable predictors of fluid responsiveness (FR) in a variety of clinical settings. The aim of this study was to evaluate their efficacy in major pancreatic surgery.

Thirty-five patients undergoing elective major pancreatic surgery were enrolled in this study. The patients were monitored using a radial artery catheter connected to Flo Trac™/Vigileo™ system. Fluid boluses of 7 ml kg^{-1} of Geloplasma

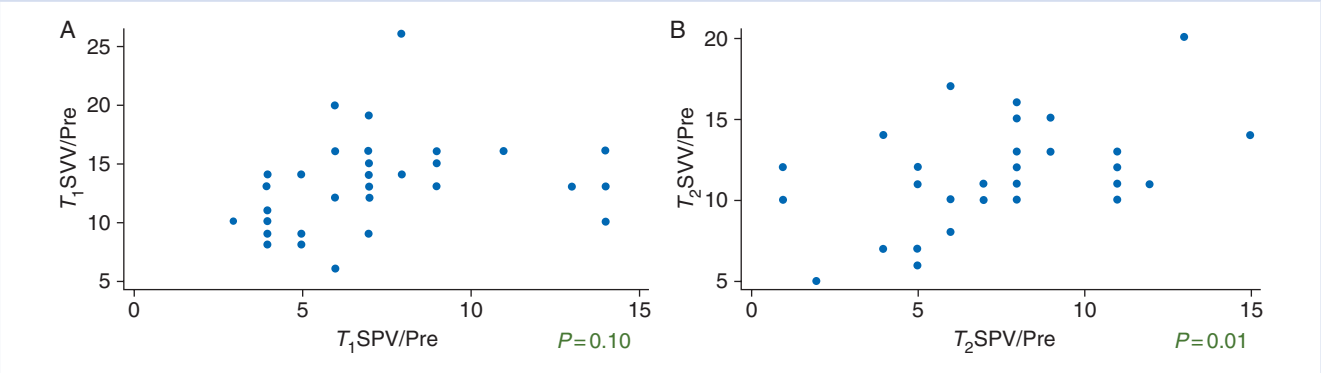

Fig 1 (A) SPV–SVV relationship: baseline. (B) SPV–SVV relationship: laparotomy.

were administered after induction of general anaesthesia (T_1) and during steady state of surgery with open abdomen (T_2). SVV, SPV, cardiac index (CI), and stroke volume index (SVI) were measured before and after each fluid bolus. FR was defined as a 15% increase in SVI.

Volume responders (VR1, VR2) had similar patient characteristics to non-responders. Pre-treatment CVP and SVR did not differ. CI, SVI, and mean arterial pressure were univariate predictors of volume responsiveness (VR1, VR2). SPV correlated inconsistently with SVV and did not predict volume responsiveness in either phase (Fig. 1). SVV did not predict VR1, but was a univariate (P=0.04) and multivariate (P=0.057) predictor of VR2. The specificity of SVV was low for both phases.

SPV and SVV both lack consistency, depending at least partly on the timing of volume loading. SVV predicts cardiac output responses to volume but is an inconsistent, weak predictor of targeted increases. Goal-directed decisions about fluid therapy based on SVV data should probably be based on context (patient risk for organ failure *vs* lung injury)—a 'grey zone' approach.[1] Our data suggest that the 'grey zone' also includes varying reliability of SVV measurements over time.

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