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Abstract Book

Non-invasive bilateral auricular nerve stimulation reduces perioperative pain through autonomic neuromodulation in patients undergoing orthopaedic trauma surgery: randomised, sham controlled trial.

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Noxious stimuli activate central autonomic pathways, which modulate both descending analgesic pathways and adaptive autonomic responses to pain. Activation of the arterial baroreflex, which is impaired by inflammation/surgery,[1] reduces pain in experimental models and causes hypoalgesia in humans.[1] We hypothesised that non-invasive bilateral auricular nerve stimulation reduces pain after trauma surgery through autonomic activation.

This RCT was registered (researchregistry7566) and approved by NHS Research Ethics (21/LO/0272). Participants aged >18y scheduled for orthopaedic trauma surgery under general and/or regional anaesthesia were randomly allocated to receive single-blinded, active or sham bilateral transcutaneous auricular nerve stimulation (TAN) for 50 minutes at the same time of day, before and 24h after surgery. The primary outcome was absolute change in pain, using the 100mm Visual Analogue Score (VAS), 24h after surgery immediately following TAN. Secondary outcomes included the proportion of patients achieving a >10mm reduction in VAS (defining the minimal clinically important difference; MCID)[2] after surgery. Autonomic modulation of heart rate was assessed by Holter-derived heart rate variability measures. Sample size was estimated by having a 90% chance of detecting (significant at the 1% level) a 11mm decrease in mean VAS between groups (SD:12mm), allowing for 10% dropout.

86 patients were randomly assigned to active (n=43) or sham (n=43) TAN, who had similar characteristics before surgery. 79/86 (92%) participants (49y; 45% female) completed both interventions. 24h after surgery, active TAN reduced VAS by 19mm (95%CI:12-26), compared with 10mm (95%CI:3-17) reduction by sham TAN (mean difference:9mm (95%CI:2-16); p=0·017). MCID was achieved in 31/43 (72%) participants after active TAN, compared with 18/43 (42%) receiving sham TAN (30% absolute risk reduction (95%CI:11-52); p=0·004). Only active TAN increased heart rate variability, as indicated by increased low frequency power (+0·19 ms^2 (95%CI:0·01-0·37); p=0.033) reflecting greater baroreflex sensitivity. Local ear skin irritation occurred more frequently in 6/43 participants who received active stimulation, with no other adverse events reported.

Bilateral TAN reduces pain following orthopaedic trauma surgery through autonomic modulation. These proof-of-concept data support a non-pharmacological, generalisable approach to reduce pain, which may potentially reduce opioid prescribing.

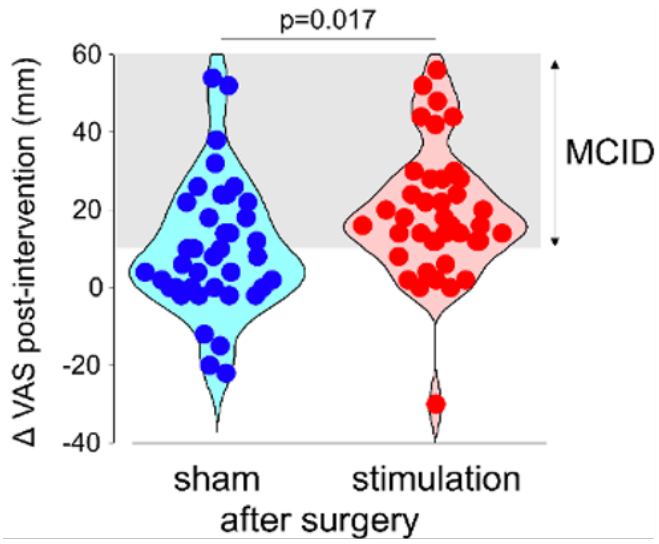

Figure 1. Violin plots showing changes in VAS after sham or active bilateral auricular nerve stimulation 24h after surgery. Patients achieving MCID reside in grey shaded area.

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Feasibility of Right Ventricular Free Wall Longitudinal Strain Assessment of Contractile Reserve in Patients Undergoing Lung Resection

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Lung cancer is the second most common cancer in the UK; though lung resection is potentially curative, it results in a burden of post-operative dyspnoea and functional limitation. Previous work by our group demonstrated right ventricular (RV) function impairment at day-2 and 2-months post-lung resection[1]. During exercise, the normal physiological response is an increase in RV function termed RV contractile reserve (CR). Previous studies have suggested that RV-CR is impaired postoperatively and additionally associated with increased cardiopulmonary complications post-operatively[2] (though their methodologies have since been challenged). RV free-wall longitudinal strain (RVFWLS) can identify subtle RV dysfunction and may therefore be a superior method of RV assessment. We examined the feasibility of RVFWLS assessment of RV-CR in patients pre- and post-lung resection.

With ethical approval (RECref 17/EE/0134) and informed consent, seven patients undergoing lung resection underwent exercise stress echocardiography (semi-supine cycle ergometer with incremental workload) pre-operatively and 2-months post-operatively. To evaluate RV-CR, we assessed the relationship between percentage of predicted maximal heart rate (ppHRmax: a measure of exercise intensity) and RVFWLS, and RVFWLS strain-rate (R). Tolerability was defined as the patient's ability to physically exercise at a given workload. Feasibility was defined as the percentage of echocardiography scans of adequate quality for RVFWLS analysis.

Pre-operatively all patients tolerated exercising up to 45W, at 60W two patients withdrew due to dyspnoea and knee pain. Post-operatively 6/7 patients tolerated exercise at 45W, but only 3/7 tolerated 60W. RVFWLS feasibility was 87.9% (29/33) pre-operatively, and 71.4% (20/28) post-operatively. ppHRmax was not associated with RVFWLS pre- or post-operatively (r=0.02, p=0.95, and r=0.16, p=0.58 respectively). Pre-operatively, a significant correlation was observed between ppHRmax and RVFWLS-R (r=0.58, p=0.03), which was abolished post-operatively (r=0.05, p=0.87).

RVFWLS assessment of RV-CR in lung resection patients is highly feasible pre-operatively, and well tolerated up to 45W workload. It is less feasible and tolerable post-operatively. RVFWLS did not identify RV-CR pre- or post-operatively. RVFWLS-R demonstrated the expected RV-CR response pre-operatively which was abolished post-operatively suggesting loss of RV-CR. Future research is needed to examine if impaired RV-CR (assessed by RVFWLS-R) is associated with postoperative complications and/or functional limitation in this population.

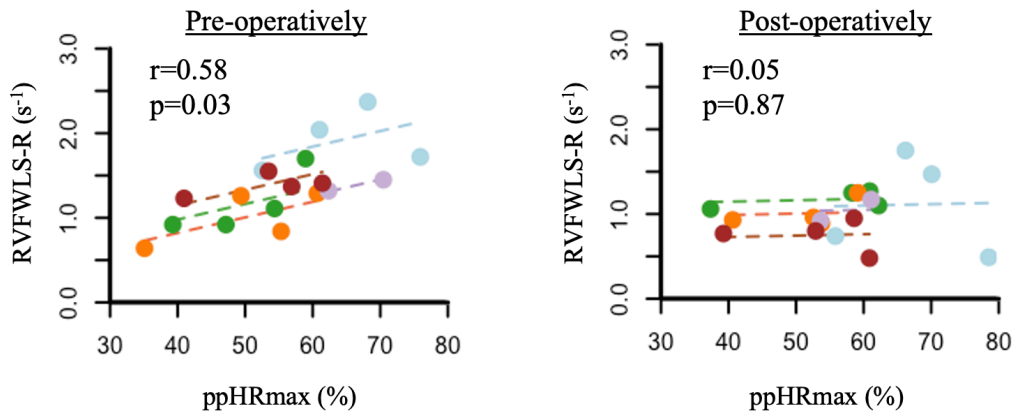

Figure 1. Pre- and Post-Operative Contractile Reserve Assessed by RVFWLS-R
Correlation co-efficient calculated with analysis of co-variance (ANCOVA) to account for within-subject correlation

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Two-dimensional modelling of tracheostomy Above Cuff Vocalisation (ACV) using Computational Fluid Dynamics.

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Above Cuff Vocalisation (ACV) involves retrograde delivery of gas via the subglottic suction port of a tracheostomy tube, independent of lung ventilation. Whilst ACV facilitates speech in around 75% of uses, the characteristics of laryngeal flows have not been studied under ACV.[1,2] We aimed to model and characterise ACV flows along the subglottic suction tube and throughout the upper airway, in order to corroborate observed safe operating parameters, and to predict ACV flows for optimal voice.

Anonymised two-dimensional median sagittal Computed Tomography scans of a tracheostomised male with normal upper airway anatomy (from a previous study) were imported into Ansys Fluent modelling software (R1, 2022; Ansys,USA). ACV flows of 2, 5 and 10 $L.min^{-1}$ were modelled, including velocity and pressure at the inlet/outlet of the subglottic port, and at the external lip. As gas traverses the larynx at different velocities (depending on ACV flowrates), modelling can predict and characterise the potential for vocalisation.[1]

The simulations predicted that airway velocity was directly proportional to ACV flow. For flows of 2, 5 and 10 $L.min^{-1}$, exhaled velocities were calculated as 3.21, 8.40 and 16.83$m.s^{-1}$ respectively. A pressure-drop of approximately 66% was calculated from the external port of the subglottic tube (position-3, Figure 1a) to the external lip (position-1, Figure 1a). A modelled ACV flowrate of 2.17 $L.min^{-1}$ generated exhalation flows/pressure levels comparable to a healthy (non-tracheostomised) airway.[3] Pressure contour analysis demonstrated significant turbulence within the upper airway, predicting pressure levels of -19.75, -151.92 and -718.40 Pa for ACV flows of 2, 5 and 10 $L.min^{-1}$ respectively.

Our modelling suggests ACV flows of around 2 $L.min^{-1}$ are sufficient to reproduce the physiological pressures in the upper airway associated with normal speech in a healthy airway. However, most patients requiring tracheostomy following critical illness do not have normal airways. Further research using three-dimensional modelling and in-vivo measurements should be conducted to validate these calculations.

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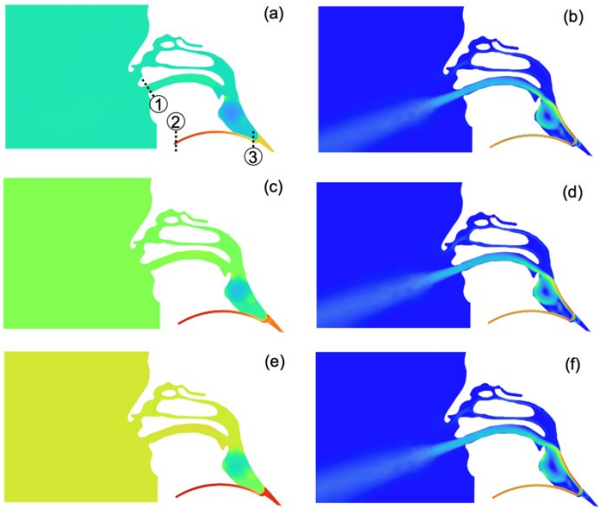
Figure: Pressure [Pa] ((a), (c), and (e)), and velocity [$m.s^{-1}$] contours ((b), (d), and (f)), for ACV on a cuffed tracheotomy tube: (a) and (b) at 2 $L.min^{-1}$, (c) and (d) at 5 $L.min^{-1}$, (e) and (f) at 10 $L.min^{-1}$.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Incidence and Risk factors of Postoperative Cardiac Complications: An International Prospective Cohort Study

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Background

Postoperative cardiac complications (PCC) after major surgery remain heterogeneously reported. This international prospective cohort study aimed to define incidence and risk factors for PCC after major abdominal surgery in Europe, Ireland, and UK.

Methods

A prospective, international cohort study was performed between January 23 and May 1, 2022. Data were collected on consecutive patients undergoing major abdominal surgery in 446 hospitals from 28 countries of Europe. The primary outcome was postoperative cardiac complications (PCC) as defined by Standardised Endpoints and COMs for Perioperative and Anaesthetic Care (STeP-COMPAC) to 30-days after surgery. The secondary outcome was 30-day postoperative mortality.

Results

This study included 24,260 patients, of whom 611 (2.5%) developed PCC and 458 (1.9%) died within 30-days of surgery. Of patients who died, 123 (26.9%) were related to cardiac causes. Mortality rates were higher in patients who developed PCC than those who did not (19.8% vs 1.4%, p<0.001). On adjusted analyses, age ≥65 years (OR: 2.47, 95% CI: 1.99-3.06), ASA grade III-V (OR: 1.95, 95% CI: 1.58 - 2.40), emergency surgery (OR: 1.62, 95% CI: 1.31 - 2.00), and contaminated/dirty surgery (OR: 1.60, 95% CI: 1.15 - 2.23) were risk factors for PCC.

Interpretation

PCC are infrequent after major abdominal surgery, yet death from cardiac causes was higher than previously reported in adults undergoing major abdominal surgery. Targeting high-risk groups at risk of PCC and death warrant holistic interventional trials as future research focus.

Long-term healthcare use after postoperative complications: A prospective analysis of linked primary and secondary care routine data.

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Postoperative complications are associated with reduced long-term survival, we characterised healthcare use changes after postoperative complications.

We linked primary and secondary care records for patients having elective surgery at four East London hospitals from 2012 – 2017, with at least 90 days of postoperative follow up. We captured pre-specified complications (wound or urinary tract infection, pneumonia, new stroke, new myocardial infarction) using codes recorded within 90 days in primary or secondary care records. Outcomes were change in days of healthcare contact in the two years before and after surgery ('contact days'), and death in two years. We report change as rate ratios (RaR) with 95% confidence intervals, age as median [interquartile range], and adjusted for preoperative healthcare use and confounders with a negative binomial model.

We included 49,913 patients (age 49 years [34 – 64]), of whom 27,958 (56.0%) were female. Among 3,883 (7.8%) patients who suffered a complication (age 58 years [43 – 72]) there were on average 18.4 contact days per year before surgery and 25.3 days after surgery (RaR: 1.38 [1.37 – 1.39]). Patients who did not suffer complications (age 48 years [33 - 63]), had 12.3 contact days per year before surgery and 14.0 days after surgery (RaR: 1.14 [1.14-1.15]) (Table 1). The adjusted incidence rate ratio of days in contact with healthcare associated with complications was 1.67 (1.49 – 1.87). Some 391 (10.1%) patients with complications died in two years, compared to 1428 (3.1%) without.

	Total healthcare encounters (per patient year)		
	Before	After^{+}	Rate ratio
All	12.8 (12.7 - 12.8)	14.9 (14.9 - 14.9)	1.17 (1.16 - 1.17)*
Presence of postoperative complication			
Absent	12.3 (12.3 - 12.3)	14.0 (14.0 - 14.1)	1.14 (1.14 - 1.15)*
Present	18.4 (18.3 - 18.5)	25.3 (25.2 - 25.4)	1.38 (1.37 - 1.39)*

Table 1: Total healthcare encounters per patient year, stratified by the presence of complications (* is p<0.05 using rate-ratio test).

Patients suffering postoperative complications have greater preoperative healthcare use, but still have greater absolute and relative increases in healthcare use than patients who do not suffer complications.

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Title: Investigating candidate modifier loci in malignant hyperthermia susceptibility using CRISPR/Cas gene editing.

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Previous studies indicate more than one gene may be involved in determining susceptibility to malignant hyperthermia (MH) in individuals.[1,2] Thus a threshold model of MH, whereby several genes may contribute to phenotype through both major and modifier effects, may be more suitable than a classical single gene disorder model. We have previously found that variants in both *PYGM* and *CPT2* are over-represented amongst individuals susceptible to MH. We aimed to examine whether loss of function in these genes has a modifying effect on caffeine-induced calcium release in mouse skeletal muscle cells modelling the *RYR1* variant most commonly associated with MH in the UK.

CRISPR/Cas gene editing was used to knockout *Cpt2* or *Pygm* in primary mouse myoblasts heterozygous for the *Ryr1* p.G2435R variant.[3] The mutations are generated due to the inherent error rate of non-homologous end joining DNA repair, with a high likelihood of leading to loss of function. Plasmids containing CRISPR guides targeting exons common to all transcripts of *Cpt2* or *Pygm* were transfected using lipofection followed by puromycin selection and serial dilution to generate monoclonal colonies. These were validated using Sanger sequencing, RT-qPCR, western blotting, and enzyme activity assays. Caffeine induced responses of myotubes generated from the knockout colonies were assessed using live cell calcium-imaging with 5µM Fluo4-AM.

Colonies exhibited homozygous deletions in the target exons resulting in low expression. *Cpt2* knockouts displayed decreased sensitivity to caffeine, whilst *Pygm* knockouts were not significantly different compared to p.G2435R heterozygous myotubes. Ongoing calcium release assays using halothane will provide additional insights into the relationship between these genes and MH. This novel study in MH highlights the value of CRISPR/Cas gene editing as a tool to generate new cell lines with mutations of interest for functional characterisation.

Table: Mouse myotube responses to caffeine

Genotype	Caffeine EC_{50} (mM)	95% CI	n	P-value
Cpt2 KO + *Ryr1* p.G2435R Het	4.1	4.7 – 3.5	57	p < 0.001
Pygm KO + *Ryr1* p.G2435R Het	3.4	3.8 – 3.1	75	ns
Ryr1 p.G2435R Het	2.5	3.4 – 1.8	30	Reference
Wild Type	4.6	5.4 – 3.9	38	p < 0.0001

Acknowledgements
Funded by BJA/RCoA joint studentship

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Melatonin and sleep parameters in patients with chronic pain: first results from the DREAM-CP trial

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Chronic pain is associated with sleep disturbance and melatonin may improve both sleep and pain.[1] We undertook a double blind randomised controlled crossover trial of melatonin in patients with non-cancer severe chronic pain.[2] The trial was prospectively registered (ISRCTN12861060).

After ethical approval, clinical trial authorisation and written informed consent, 60 adult patients (aged 31-79, 36 female, 24 male), with an average pain intensity score of 7 or more were randomised and 51 completed both treatment arms. Participants received either melatonin (Circadin™, Flynn Pharma) 2mg daily at night or placebo for 6 weeks, followed by a washout period, then a further 6 weeks of placebo or melatonin. The primary outcome measure was sleep disturbance measured using the Verran Snyder Halpern (VSH) sleep scale.[1,2] Secondary outcome measures included pain scores, sleep latency, efficiency and supplementation, plus Pittsburg Sleep Quality Index (PSQI) and pain and sleep questionnaire-3 (PSQ-3) scores.[1,2] Crossover, intention-to-treat analysis was performed using mixed effects linear models with baselines as covariates for treatment, period and sequence effects using Stata 17 and NCSS 2020 with $P<0.05$ (two-sided) taken as being significant.

There were no significant differences in baseline measures between those receiving melatonin or placebo first. Sleep disturbance was elevated in all participants. There was a transient decrease in sleep disturbance during melatonin treatment ($P<0.001$) not seen during placebo, but no significant difference between the treatment periods. Pain scores decreased during both melatonin and placebo treatment periods (both $P<0.001$) but with no difference between treatment periods. Sleep latency ($P=0.016$), PSQI ($P=0.012$) and PSQ-3 scores ($P=0.03$) were significantly lower during melatonin compared to placebo treatment. Transient effects on wake after sleep onset ($P=0.024$) and latency ($P<0.001$) during the melatonin treatment period were seen. Adverse events were similar during both treatment periods and there were no serious adverse events related to drug treatment.

We showed that treatment with melatonin 2 mg per night did not improve sleep disturbance but had beneficial effects on other sleep parameters. In addition, during trial participation, patients with chronic pain report lower pain intensity scores.

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