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The effect of hydrogen sulfide synthesized by cystathionine-gamma-lyase on inflammation and liver sinusoidal endothelial cells in polymicrobial sepsis in mice

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Aims: Hydrogen sulfide (H_2S), produced by cystathionine-gamma-lyase (CSE), is a key mediator of inflammation in sepsis.[1] The liver sinusoidal endothelial cells (LSECs) are important target and mediator of sepsis.[2] This study was aimed to investigate role of CSE-derived H_2S on inflammation and LSEC fenestrae in CLP-induced sepsis using CSE-KO mice.

Methods: Sepsis was induced by CLP, and mice were sacrificed after 8 hours. Liver, lung and plasma were processed to measure CSE expression, H_2S synthesis, MPO activity, NF-kB, ERK1/2 and cytokines/chemokines. Diameter, frequency, porosity and gap area of liver sieve were calculated from scanning electron micrographs of the LSECs.

Results: An increased CSE expression and H_2S synthesis in wild-type mice following CLP-induced sepsis. This was associated with an increased MPO activity, TNF-α, IL-6, IL-1β, MCP-1 and MIP-2. Conversely, CSE-KO mice had decreased H_2S synthesis, MPO activity and cytokine/chemokines following sepsis. ERK1/2 and NF-κB became activated following CLP in wild-type mice but not in CSE-KO mice. In addition, CLP-induced defenestration/damage to the LSEC was reduced in CSE-KO mice.

Conclusion: Gene deletion of CSE, an H_2S synthesizing enzyme, protects mice against CLP-induced sepsis and associated inflammatory response through ERK/NF-κB pathway as evidenced by reduced inflammation, defenestration and gaps formation in the LSECs.

1. Badiei A, Chambers ST, Gaddam RR, Bhatia M. Journal of Biosciences, 2016;41:87–95.
2. La Mura V, Pasarín M, Rodriguez-Vilarrupla A, García-Pagán JC, Bosch J, Abraldes JG. Journal of Hepatology, 2014;61:1321–1327.

Activation of immune cells in live carotid plaque

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Aims: Ex-vivo carotid plaque (CP) tissue provides a complex and realistic model in which to test how inflammatory processes in atherosclerosis are occurring. To evaluate the ability of cells within excised tissue to produce 7,8-dihydroneopterin, a biomarker of immune cell activation and inflammation in atherosclerotic plaque,[1] we stimulated CP tissue with phorbol 12-myristate 13-acetate (PMA), phytohemagglutinin (PHA) and interferon-γ. Neopterin, the oxidised form of 7,8-dihydroneopterin, was also measured.

Methods: Live CP tissue obtained from carotid endarterectomy were cut into sections and cultured in RPMI 1640 media plus 10% human serum four days. Media was changed every 24 hours and analysed for neopterin and total neopterin by HPLC. PMA, PHA or interferon-γ was added to the media after 24 hours. Tissue viability was measured by a lactate assay.

Results: Stimulation of plaque with PMA, PHA and interferon-γ resulted in the activation of T-cells and macrophages within the excised tissue while unstimulated plaque showed no immune cell activation. The concentration of neopterin and 7,8-dihydroneopterin released varied between sections in each plaque.

Conclusions: Immune activation can be measured and modelled within the plaque using PMA, PHA and interferon-γ. Levels of 7,8-dihydroneopterin oxidised to neopterin indicate that oxidative stress is occurring in the plaque.

1. 1) Gieseg SP, Leake DS, Flavall EM, Amit Z, Reid L, Yang Y. Macrophage antioxidant protection within atherosclerotic plaques. Frontiers in Bioscience 2009;14:1230–1246.

Cognitive impairment in Parkinson's disease: a study of early-phase amyloid PET and arterial spin labeling perfusion MRI

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Aims: There is a need to identify biomarkers of imminent conversion to dementia in Parkinson's disease. This study compared early-phase [^{18}F] Florbetaben (FBB) PET, a novel perfusion measure, with arterial spin labeling (ASL) perfusion MRI. We aimed to assess association between perfusion and risk of conversion to dementia.

Methods: 50 PD patients were assigned a summary global cognitive score and Parkinson's disease dementia risk score (PDDRS) from the results of neuropsychological testing. FBB PET and ASL MRI data were acquired, pre-processed and analysed for association with these measures using the general linear model and a network-based approach.

Results: Cognitive decline and increased PDDRS were found to be significantly associated with distinct regions of cortical hypoperfusion, as quantified by the ASL data. FBB-derived images did not exhibit any significant association with cognition or dementia risk and did not correlate significantly with ASL perfusion measures. A network based approach using principal component analysis identified networks of cortical hypoperfusion in the ASL data that related significantly to cognition and PDDRS.

Conclusions: The physiological information provided by early-phase PET remains a worthwhile area of further investigation. The PDDRS-related perfusion network developed here presents a potential biomarker of imminent conversion to dementia in Parkinson's disease.

1. Melzer TR, Watts R, MacAskill MR, Pearson JF, Rüeger S, Pitcher TL, Livingston L, Graham C, Keenan R, Shankaranarayanan A, Alsop DC, Dalrymple-Alford JC, Anderson TJ. Arterial spin labelling reveals an abnormal cerebral perfusion pattern in parkinson's disease. Brain. 2011;134:845–855.

The effect of irreversibly electroporated cell dynamics on drug transport in electroporated tissue

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Aims: Recent developments in the modelling of the cellular uptake of drug by electroporation (EP) have enabled for the prediction of dynamic behaviour of electroporated cells. Statistical analysis shows that tissue elecroporation can simultaneously result in reversibly (RE) and irreversibly (IR) electroporated cells.[1] The influence of IR cell dynamics on drug uptake of neighbouring RE cells is investigated.

Methods: First principles approach is used to develop the theoretical model describing post EP cell dynamics and diffusion behaviour of the drug. The resulting set of coupled PDEs are evaluated numerically in a fully implicit parametric investigation.

Results: By varying the mass transfer coefficient of the irreversible cells it was shown that the dynamics of the IR cells did not make a significant difference to the RE cell concentrations. The influence of the presence of IR cells on the drug uptake of viable cells was found to be less than 4%.

Conclusion: The dynamics of irreversibly electroporated cells does not greatly influence the rate of drug delivery to viable cells.

1. Puc M, et al., Quantitative model of small molecules uptake after in vitro cell electropermeabilization. Bioelectrochemistry. 2003;60:1–10.

Preventing lung damage via automation and optimisation of mechanical ventilation for critically ill patients in the third world

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Aims: Critically-ill adult patients in the third-world can require breathing support during power outages. However, existing manual ventilation methods can lead to ventilator induced lung injury (VILI) if poorly applied.[1] Automated ventilation of patients which remains operational off-grid could improve consistency of care and patient outcomes.

Methods: Volume controlled mechanical ventilation utilises tidal volumes between 600mL and 400mL. However, in patients with high elastance, set tidal volumes can cause overdistension. Pressure centric control can lead to insufficient oxygenation of patients with high elastance.[2] Respiratory rate is affected in order to maintain a healthy gas exchange.

A generic pressure-volume domain was designed to facilitate ventilation of heterogeneous third world

ICU patients. All patients receive PEEP of 10cmH2O. The domain has a tidal volume of 600mL up to peak inspiratory pressure (PIP) of 30cmH2O; a tidal volume of 300mL when PIP is between 40cmH2O and 50cmH2O; a diagonal line (PIP=50–0.033ΔV) links the 'tidal-volume' domains.

Results and Conclusions: The proposed envelope contrasts existing volume-controlled, pressure-controlled or minimum-elastance mechanical ventilation strategies. The domain for automated ventilation provides a universally applicable approach that requires minimal calibration and expertise. The proposed domain would be suitable for adult ICU patients and will reduce the burden on ICU staff.

1. Hickling KG: The Pressure-Volume Curve Is Greatly Modified by Recruitment: A Mathematical Model of ARDS Lungs. American Journal of Respiratory and Critical Care Medicine. 1998;158(1):194–202.
2. Laufer B, PD Docherty, A Knörzer, YS Chiew, R Langdon, K Moller JG Chase. Performance of variations of the dynamic elastance model in lung mechanics. Control Engineering Practice, 2016. In press.

Amyloid imaging for cognitive impairment in Parkinson's disease

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Aims: Parkinson's disease (PD) is a neurodegenerative movement disorder, but cognitive impairment and dementia ultimately become the greatest burden for patients. The accumulation of misfolded amyloid protein, an Alzheimer pathology, can also occur in PD and may contribute to cognitive impairment. Here, we examined amyloid accumulation in the brain, using Positron Emission Tomography (PET) imaging as a potential cognitive biomarker in PD.

Methods: 50 participants with PD completed Florbetaben PET to measure amyloid burden in the brain. A battery of neuropsychological tests was used to produce (1) a global measure of current cognitive ability and (2) a dementia risk score (four-year probability of future dementia). PET images were evaluated clinically and standard uptake value ratio (SUVR) images were derived to assess the association between amyloid accumulation and cognition/dementia risk.

Results: Eleven participants (22 %) received a radiological visual evaluation of abnormally increased amyloid accumulation. Across all patients, there was a significant (corrected $p<0.05$) association between amyloid accumulation (SUVR) and global cognitive ability in multiple brain regions. Widespread amyloid accumulation was also associated with the dementia risk score.

Conclusions: Amyloid accumulation in the brain provides a suitable biomarker of cognitive ability and risk of future dementia in PD.

Homogenisation Theory Applied to Coupled Mammalian Cells

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Aims: Migraine pain is often preceded by disturbed vision known as an 'aura'. Visual auras are thought to be caused by a wave of calcium moving slowly across the occipital lobe of the brain. This wave is termed Cortical Spreading Depression (CSD). The temporary high calcium concentrations cause electrophysiological hyperactivity followed by inhibition.

Methods: We modelled calcium wave propagation across a coupled cell model using a homogenised implementation of the model by Goldbeter *et al.* Spatially coupled cells were initially simulated with simple linear diffusion and then with added electro-diffusion terms. The outcomes were compared to a 'toy-model' approach with sinusoidal inputs.

Results: Interesting wave shapes emerged and resulted in waves propagating into regions where theoretical analysis implies oscillations should not exist. Electro-diffusion exhibited minimal contrast to the simpler linear diffusion model. In contrast, the 'toy model' approach yielded no such wave propagation.

Conclusions: We have determined that the shape of cell fluxes instigate wave propagation. In particular, waves with non-linear tendencies lead to wave propagation, whereas sinusoidal waves ameliorate wave propagation. This unique insight may lead to an improved understanding of CSD and lead to novel treatments for migraines that target the non-linear elements of intracellular calcium fluxes.

Reuse, disposal, and partial remanufacturing of medical devices

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Aims: A device may be designed for single use, but reprocessed, contrary to the designer's original expectations. Reprocessing and reusing of single-use devices (SUDs) occurs frequently. Product reprocessing may lead to degradation of medical devices, adversely affect patient health and reduce the productivity of the medical staff and operations. Need: Different stakeholders (product designers, surgeons, theatre managers) have different priorities regarding single use or reusable medical devices. These expectations are not always congruent. Purpose: This work

investigates the multiple reuse scenarios that occur in medical devices, and the decision thinking of stakeholders.

Methods: The main phases are: (1) Question stakeholders to determine the motivations for reprocessed SUDs and the key issues. (2) Develop a model of the decision process and the health risk. (3) Validation against medical device failure databases.

Results: Initial findings are that SUDs can be more financially expensive and environmentally costly than reusable ones. We propose a conceptual systems framework for the lifecycle risks of a medical device, see Figure 1.

Conclusions: The reprocessing is not a simple case of reuse vs. disposal, but a complex hybrid process of partial remanufacture where the decision appears to be determined by situational variables (e.g. country, cost, perceived risks).

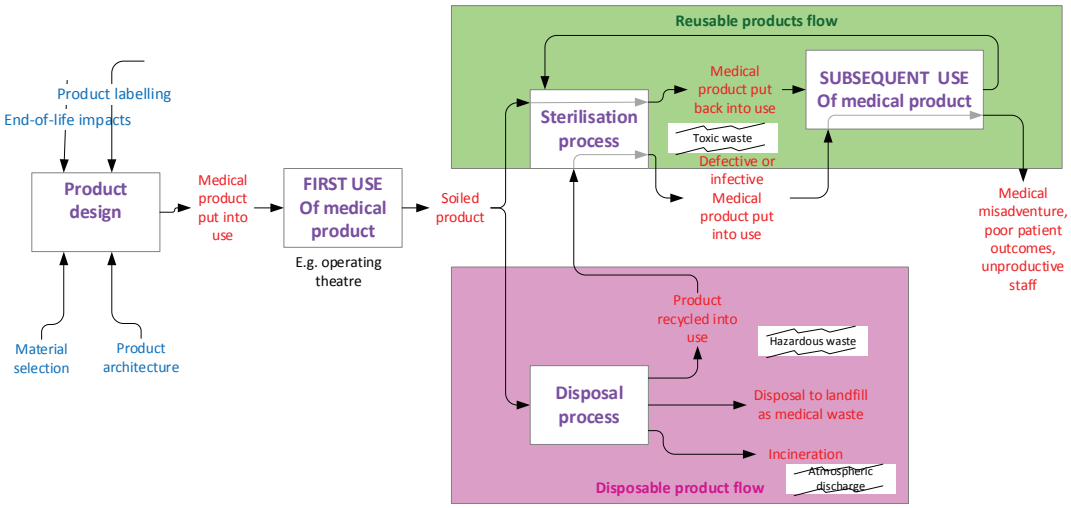

Figure 1: System Life cycle model for medical device usage, including re-use, disposal and hybrid remanufacturing processes.

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