

PATEY PRIZE 1

O1 TEN YEAR FOLLOW UP CASE CONTROL STUDY OF THE EFFECT OF PORTAL VEIN EMBOLIZATION (PVE) ON THE SURVIVAL OF PATIENTS WITH COLORECTAL LIVER METASTASES (CRLM) AND THE INFLUENCE OF HYPOXIA FACTORS ON TUMOUR GROWTH.

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Introduction: PVE facilitates hepatectomy in patients with a small anticipated future liver remnant, but stimulates tumour growth. Hypoxia may mediate this increased tumour growth as Hypoxia-Inducible-Factor-1 α (HIF-1 α) increases angiogenesis, invasion and other Hallmarks of Cancer. This study investigates the relationship of patient survival to expression of HIF-1 α and other hypoxia factors regulated in resected CRLM, in a case control study, comparing patients with and without PVE.

Method: Twenty-six patients who had PVE were compared with 25 controls matched with the number and size of metastases (tumour-burden). Immunostaining was performed on CRLM formalin-fixed-paraffin-embedded sections to compare the expression of hypoxic factors regulated factors, HIF-1 α and CA-9, vascular endothelial growth factor (VEGF) and a blood vessel marker, CD31, between the groups. Disease progression, liver specific recurrence and actuarial survival were recorded.

Result: The clinicopathological characteristics of the cancers were comparable between the groups. The median follow-up was 115 months (range 106-124). Overall, 5 year, local hepatic recurrence-free survival and progression-free periods were poor in those patients undergoing PVE ($p=0.026$, $p=0.060$, $p=0.001$ and $p=0.008$ respectively). The expression of hypoxia markers between the groups was similar.

Conclusion This is the first long-term (>5 year) case matched series on outcome of patients with CRLM following PVE. Whilst, PVE facilitates potentially curative resection of CRLM, prognosis is less than those patients not requiring PVE. Whilst further molecular research is required to investigate the cause of tumour growth and reduced prognosis, the hepatic artery buffer response may have a role in preventing intratumoural hypoxia following PVE.

Take-home message:

Whilst portal vein embolisation (PVE) facilitates potentially curative hepatectomy for colorectal liver metastases, it is associated with poorer prognosis compared to a matched patient group with no PVE. PVE associated increased tumour perfusion may be the cause.

O2 RELATIONSHIP BETWEEN THE ABERDEEN VARICOSE VEIN QUESTIONNAIRE (AVVQ) AND DISEASE SEVERITY

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Introduction: The AVVQ is a patient-completed disease-specific quality of life (QoL) instrument comprising 12 questions and manikin diagram where patients draw their veins. Recent interest has focused on the potential role of the AVVQ to select patients for varicose vein treatment, and whether it can be used without the manikin diagram. We investigated whether individuals with more severe venous disease had worse QoL (higher AVVQ score) and whether any relationship persisted when the manikin diagram was omitted.

Method: Pre-treatment data from a UK multi-centre trial comparing varicose vein treatments (CLASS) were analysed. The relationship between AVVQ (scored with and without the manikin diagram) and disease severity, assessed by Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification and Venous Clinical Severity Score (VCSS), was determined using multiple linear regression models.

Result: 407 participants had uncomplicated (CEAP grade C2) and 338 complicated varicose veins (CEAP C3-6). Those with CEAP C3-6 had higher AVVQ scores compared to those with CEAP C2 when the AVVQ was scored with or without the diagram. CEAP C3-6 was associated with an increase in AVVQ score of 3.94 units with the diagram (95%CI 2.73-5.15, $p<0.001$) and 4.29 units without the diagram (95%CI 2.82-5.75, $p<0.001$). A one point increase in VCSS corresponded to an increase of 1.63 points on AVVQ scored with the diagram (95%CI 1.37-1.88, $p<0.001$) and 2.02 points excluding the diagram (95%CI 1.70-2.35, $p<0.001$).

Conclusion: The AVVQ responsiveness to disease severity supports its use as a patient selection tool; this relationship persists when the AVVQ is used without the diagram.

Take-home message:

The AVVQ could be used without the manikin diagram component to select patients for varicose vein treatment.

O3 METABOLIC RELATIONSHIPS WITHIN THE TUMOUR MICROENVIRONMENT OF PANCREATIC DUCTAL ADENOCARCINOMA - PANCREATIC STELLATE CELLS INDUCE GLYCOLYSIS IN CANCER CELLS

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Introduction: KRAS regulates various metabolic pathways at a transcriptional level. The metabolic relationship between pancreatic ductal adenocarcinoma (PDAC) and pancreatic stellate cells (PSCs) is not well defined. Establishing their impact can help determine potential avenues for targeted therapeutics with respect to either mitochondrial or glycolytic inhibitory strategies.

Method: A transwell system was used in 48hr co-culture of PSCs and 3 PDAC cell lines; Miapaca2, Panc1 and Bxpc3 (KRAS mutant). Seahorse technology was utilized to assess the effect on basal oxygen consumption rate (OCR – an indicator of mitochondrial respiration), glycolytic activity (through the measurement of extracellular acidification rates representing lactic acid production) and ATP production. Comparisons were made with solo controls.

Result: PSCs demonstrated differing metabolic responses when comparing the KRAS WT and mutant PDAC lines. Co-culture of PSCs with Miapaca2, Panc1 and Bxpc3 resulted in percentage changes in basal OCR of +15%, +51.4%, -7% respectively (p=NS), and glycolytic activity +8.9%, -4.7%, -38% (p=NS). Most interestingly, co-culture resulted in a dramatic increase in glycolytic activity in all PDAC lines; Miapaca2 +40.5%, Panc1 +82.8% and Bxpc3 + 112.4% (p<0.05), with a reduction in ATP produced by OXPHOS.

Conclusion: These novel results suggest PSCs induce glycolysis in cancer cells in vitro, mimicking the Warburg Effect, which is typically associated with hypoxia. This does not seem to be dependent on KRAS. Therapeutic approaches towards this metabolic relationship may represent an ideal method of shutting down the protumorigenic relationship between PSCs and PDAC.

Take-home message:

Pancreatic stellate cells (PSCs) induce glycolysis in pancreatic ductal adenocarcinoma (PDAC), regardless of KRAS mutation. This novel finding presents intriguing additional factors regarding the Warburg Effect theory, and suggests anti-glycolytic therapy may be the ideal method to disrupt the protumorigenic relationship between PSCs and PDAC.

O4 EX-VIVO NORMOTHERMIC PERFUSION WITH THE NOBLE GAS ARGON IN AN EXPERIMENTAL MODEL OF KIDNEY TRANSPLANTATION

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Introduction: Noble gases can exert biological actions that may help to reduce transplant related ischaemic injury. The aim of this study was assess the effects of argon administered directly to the kidney during EVNP.

Method: Under Home Office Animals (Scientific Procedures) Act 1986 porcine kidneys were retrieved after 10 minutes of WI. After 17h static cold storage, kidneys underwent 1h of EVNP with a leukocyte depleted blood based solution with either argon (n = 6) [70% argon/25% O₂/5% CO₂], oxygen (n = 5) [95% O₂/5% CO₂] or nitrogen (n = 6) [70% nitrogen/ O₂/5% CO₂]. After EVNP kidneys were reperfused ex-vivo for 3h with oxygenated whole blood to assess renal function and injury.

Result: The argon treated kidneys produced significantly more urine during EVNP compared to the oxygen treated kidneys (argon 278 ± 88 vs oxygen 180 ± 42ml vs nitrogen 199 ± 88ml;P=0.049). During reperfusion levels of oxygen consumption at 1h were significantly higher in the argon kidneys (argon 31.4 ± 8.8 vs oxygen 15.6 ± 12.5 vs nitrogen 32.0 ± 14.8ml/min/g;P=0.036). CrCL and total urine output were also significantly higher [(AUC CrCL, argon 4.5 ± 3.5 vs oxygen 1.4 ± 0.4 vs nitrogen 3.4 ± 1.9ml/min/100g; P=0.010), (total urine output, argon 388 ± 179 vs oxygen 207 ± 44 vs nitrogen 280 ± 103ml;P=0.002)].

Conclusion: Kidneys treated with argon during EVNP had improved renal function and oxygen consumption during reperfusion compared to kidneys treated with oxygen. AUC Area under the curve CrCL Creatinine clearance EVNP Ex-vivo normothermic perfusion WI Warm ischaemia

Take-home message:

The noble gas argon may help to improve early graft function in donation after circulatory death kidneys.

O5 HTATIP2 REGULATES THE IMPAIRED ANGIOGENIC ACTIVITY OBSERVED IN MONOCYTES ISOLATED FROM PATIENTS WITH CRITICAL LIMB ISCHAEMIA

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Introduction: Functional impairment in autologous cells used for angiogenic therapies is thought to contribute to their lack of clinical efficacy. This study aimed to determine the relative angiogenic potency

of a subgroup of monocytes expressing TIE2 (TEMs) obtained from critical limb ischaemia (CLI) patients, and to investigate the mechanisms involved in any impairment.

Method: Circulating TEMs were isolated from CLI patients and age-matched controls by FACS (ethics 10/H0804/67). Angiogenic activity was compared by Matrigel/HUVEC assay and the murine hindlimb ischaemia (HLI) model in accordance with Home Office approval. Differential gene expression was assessed by whole genome microarray and qPCR. The functional significance of differentially expressed genes was determined using siRNA silencing technology and the aforementioned angiogenesis assays.

Result: TEMs from controls promoted greater in vitro tubule formation (area and length), and recovery of blood flow to the ischaemic hindlimb compared with CLI TEMs (both $P < 0.05$). Microarray analysis identified 1098 differentially expressed genes between CLI and control TEMs (fold change > 3 , $P < 0.05$). Thirty-two genes were validated by qPCR, based on their angiogenesis-modulating potential. Only transcription of the human HIV-1 TAT interactive protein-2 (HTATIP2) gene was significantly increased in CLI TEMs. Silencing HTATIP2 expression in TEMs enhanced tubule formation, and reperfusion in the HLI model (both $P < 0.05$).

Conclusion: We have previously identified TEMs as key regulators of revascularisation in the ischaemic limb but the functional impairment observed in CLI would limit their therapeutic use. Ex-vivo modulation of HTATIP2 may offer a strategy for enhancing their angiogenic activity prior to autologous delivery.

Take-home message:

Angiogenic TIE2-expressing monocytes are functionally impaired in critical limb ischemia patients; associated with HTATIP2 overexpression. Modulation of HTATIP2 expression enhances the angiogenic potential of TIE2-expressing monocytes, which may provide a novel target for ex-vivo modulation of cells for autologous injection.

06 THE INFLUENCE OF OBESITY ON MECHANISMS UNDERLYING PERIOPERATIVE INSULIN RESISTANCE

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Introduction: The pathogenesis of perioperative insulin resistance (IR) is poorly understood but may be linked to adaptive changes in gene expression. Body composition may also influence the development of perioperative IR.

Method: Thirty-two patients undergoing elective open abdominal surgery participated in a 2x2 factorial, randomised controlled trial. Sixteen obese (from body mass index and waist circumference) and sixteen non-obese patients were randomised to receive preoperative carbohydrate drinks or placebo. Vastus lateralis (VL) and adipose biopsies were taken pre-, intra- and post-operatively and omental biopsies were taken intra-operatively. TaqMan® Low density Array Micro Fluidic Cards, designed for each tissue were used to assess changes in gene expression. Gene pathway analysis was conducted using Ingenuity Pathway Analysis (IPA).

Result: Fat oxidation gene expression pathways (PPAR α / RXR α) pathway) were elevated in VL samples in obese compared with non-obese patients postoperatively ($p < 0.00001$). The greatest magnitude fold change in this pathway was seen in tyrosine aminotransferase (TAT) (389%) and follistatin-like 1 (FSTL1)(235%). Stearoyl Co A Desaturase in VL increased significantly between the preoperative sample and start of surgery (364%) but decreased during surgery (92%) and between end of surgery and first postoperative day (69%). In omental fat, genes associated with lipid metabolism were elevated postoperatively in obese compared with non-obese patients with no changes observed in pathways involved in carbohydrate metabolism.

Conclusion: This study suggests that adaptive responses in expression of genes involved in lipid rather than carbohydrate metabolism occur in patients undergoing major surgery and that obesity can influence the magnitude and direction of the effect upon metabolic gene expression.

Take-home message:

Obesity can affect perioperative changes in metabolic gene expression.

07 INVESTIGATION OF THE EFFECT OF GENETIC POLYMORPHISMS ON AORTIC GROWTH IN PATIENTS WITH ABDOMINAL AORTIC ANEURYSM (AAA)

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Introduction: Abdominal aortic aneurysm (AAA) is a disease with strong genetic background, based on evidence from epidemiological studies. At least four genome-wide association studies (GWAS) have identified genetic loci associated with AAA-presence and several single nucleotide polymorphisms (SNPs) have been identified through candidate-gene studies. However, there is limited evidence regarding the effect of genetics on AAA-growth.

Method: We identified a population of 389 patients of common geographical origin (mean age: 69 ± 8 years, 88% males) with available AAA sizes over > 1 year and matched them to a control group (age,

sex, smoking-habit) of patients with no AAA. We subsequently analysed nine functional SNPs linked with aortic inflammation and proteolysis (identified through a systematic review of candidate-gene association studies) and 4 polymorphisms previously associated with AAA-presence in the AAA-GWASs available to date.

Result: The rs6511720 low-density lipoprotein receptor (LDLR) SNP and the rs1795061 SNP were associated with both AAA presence [odds ratio (OR): 1.7, $p=0.03$; OR: 1.9, $p<0.001$ - respectively] and change in annual aortic size (OR: 1.2, $p=0.02$; OR: 1.4, $p=0.01$ - respectively, analysis adjusted for age, sex, hypertension, hyperlipidaemia and smoking). Both SNPs had been associated with AAA-presence in previous GWASs. None of the other 11 SNPs analysed were associated with annual aortic growth in this population; even though the SNPs previously identified through GWASs and the rs3091244 C-reactive protein (CRP) SNP were associated with AAA presence independently.

Conclusion : Two SNPs were found to be associated with aortic growth in this population of patients with AAA, which represents a novel finding.

Take-home message:

An association between 2 SNPs, previously associated with AAA presence in large genome-wide association studies, and AAA growth has been documented in this study. This offers pathophysiological and therapeutic insights.