

ORAL PRESENTATIONS 3A

BURNAND AND WILLIAMS PRIZE SESSION

073 A COMPARISON OF METHODS OF BODY COMPOSITION ANALYSIS

N Tewari, S Awad, IA Macdonald, DN Lobo

School of Medicine and School of Life Sciences, University of Nottingham, Queens Medical Centre, Nottingham

Introduction: Body composition is associated with health outcomes and its measurement is increasingly considered in research and clinical practice. However, there is no consensus about the best method of assessing body composition in the clinical situation.

Method: Patients were recruited from two clinical trials investigating metabolic changes associated with major abdominal surgery and neoadjuvant chemotherapy (NAC) for oesophagogastric cancer. Dual X-Ray Absorptiometry (DXA) scans were performed in the week before surgery, and before and after commencement of NAC.

Result of Bioelectrical Impedance Analysis(BIA), performed at the same timepoints, were used in standard equations to calculate fat free mass (FFM). Sliceomatic (Tomovision) analysis of CT scans performed for clinical purposes was used to estimate FFM and fat mass (FM).

Result: DXA, CT and BIA were performed in 47 patients. There was excellent correlation between FM on DXA and CT ($p < 0.0001$, $r^2 = 0.6632$) and FFM on DXA and CT ($p < 0.0001$, $r^2 = 0.7634$). There was significant correlation between FFM on DXA and BIA ($p < 0.0001$, $r^2 = 0.6275$). Correlation between FFM on CT and BIA was also statistically significant ($p < 0.0001$, $r^2 = 0.2742$). On Bland Altman analysis, average bias for FM on DXA and CT was 0.2564, 95% limits of agreement (LOA) -9.451 to 9.964. For FFM on DXA and CT, average bias was -0.1477, LOA -8.621 to 8.325. For FFM on DXA and BIA, average bias was -3.792, LOA -15.52 to 7.936 and FFM on CT and BIA, average bias was -2.661, LOA -22.71 to 17.39. Discussion: DXA is recognised as an accurate method of measuring body composition but it exposes the subject to radiation. Analysis of CT and MRI scans has emerged as a suitable alternative, but these methods are expensive and time consuming to perform and interpret. BIA has been shown in this series to be a useful method to estimate FFM.

Take-home message:

Bioelectrical Impedance Analysis can provide results comparable to DXA and CT in the assessment of body composition.

074 AZD1775 INHIBITS ENDOTHELIAL CELL REMODELING IN COLORECTAL LIVER METASTASES IN VITRO

PJ Webster (1), DA Burke (2), RK Prasad (3), DJ Beech (1)

(1) Faculty of Medicine and Health, University of Leeds, UK (2) The John Goligher Colorectal Unit, St. James's University Hospital, Leeds, UK, (3) Department of Hepatobiliary and Transplant Surgery, St. James's University Hospital, Leeds, UK

Introduction: Colorectal liver metastases are reliant upon the process of angiogenesis for growth and dissemination. We have previously identified the WEE1 protein kinase as a potential anti-angiogenic target. WEE1 regulates Cyclin-Dependent Kinase 1 activity, which has an important role in initiating DNA replication. The aim of this study was to determine if the WEE1 inhibitor, AZD1775, could disrupt endothelial cell remodelling in colorectal liver metastases.

Method: Endothelial cells were obtained from patients undergoing curative liver resection for colorectal liver metastases. Matched normal liver endothelial cells (LECs) and tumour endothelial cells (TECs) were isolated using a CD31-microbead technique. Proliferation was assessed using a WST1 assay and migration was quantified using a scratch wound assay. Flow cytometry was used to assess double-stranded DNA breaks by measuring levels of pH2AX, a specific marker.

Result: AZD1775 inhibited proliferation of TECs with a significantly lower IC50 than in matched LECs ($p = 0.008$). At 1 μ M, AZD1775 significantly inhibited migration of TECs at 24 hours ($p = 0.04$) and caused significantly more double stranded DNA breaks than vehicle control ($p < 0.0001$). Double stranded DNA breaks could be prevented by application of the CDK1 inhibitor R0-3306 (10 μ M, $p < 0.0001$).

Conclusion: WEE1 inhibition with AZD1775 causes double-stranded DNA breaks in tumour endothelial cells isolated from colorectal liver metastases. This results in reduced endothelial cell proliferation and migration, two angiogenic processes necessary for tumour growth. Pre-clinical studies are ongoing to assess the efficacy of AZD1775 against tumour vasculature in vivo.

Take-home message:

AZD1775, a WEE1 inhibitor, causes double-stranded DNA breaks in endothelial cells derived from colorectal liver metastases and inhibits endothelial cell remodelling in vitro.

075 A NOVEL DEMONSTRATION OF THE TRPC1 ION CHANNEL SUBUNIT IN HUMAN ABDOMINAL AORTIC ANEURYSM VASCULAR SMOOTH MUSCLE CELLS

BL Green (1,2), MA Bailey (1,2), KE Porter (1,2), DJA Scott (1,2), DJ Beech (1,2)

(1) School of Medicine, University of Leeds, Leeds, UK, (2) The Leeds Vascular Institute at the Leeds General Infirmary, Great George Street, Leeds, UK

Introduction: Classical transient receptor potential channel (TRPC) 1 is a ubiquitously expressed cationic channel subunit present in vascular smooth muscle cells (VSMC). TRPC1 has been shown to play a role in pathological remodelling of vascular smooth muscle, affecting cell migration and proliferation. We aimed to determine whether or not TRPC1 is present in AAA VSMCs and if so, whether or not it is functionally active.

Method: AAA VSMCs were obtained from patients undergoing open AAA surgery. Cells were studied by intracellular calcium measurement using the ratiometric fluorescence indicator dye, Fura-2 AM: fluorescence measurements were made using the FlexStation device. Cells were activated using the oxidised phospholipid PGPC, in cells pre-incubated with TRPC1 antibodies, antibody-peptide complex, or ethanol control. TRPC1 mRNA expression was studied using quantitative real-time polymerase-chain-reaction on a Lightcycler using SYBR green, normalised to beta actin. Data were compared using the independent samples t-test.

Result: TRPC1 mRNA transcripts were readily detectable from early passage human AAA VSMCs (n=4). PGPC activated calcium influx as compared to ethanol vehicle control ($p < 0.001$), which was strongly inhibited by pre-incubation with TRPC1 specific antibody ($p < 0.01$).

Conclusion: PGPC activates calcium influx in AAA VSMCs and is inhibited by antibody directed to the TRPC1 subunit. As a major component of atherosclerotic plaque, PGPC may therefore play a pathological role in AAA, mediated in part through TRPC1. TRPC1 blockade should be considered a potential area of interest as a modulator of AAA development.

Take-home message:

Calcium influx in human abdominal aortic aneurysm vascular smooth muscle cells is activated by the the oxidised phospholipid PGPC (a major component of atherosclerotic plaque). The response is inhibited by antibody directed at the TRPC1 ion channel subunit thereby suggesting a potential role for TRPC1 blockade in modulating aneurysm development.

O76 HLA-SPECIFIC ALLOANTIBODY DEVELOPMENT CAN BE PREDICTED USING A NOVEL COMPUTATIONAL SCORING SYSTEM THAT QUANTIFIES 3-DIMENSIONAL ELECTROSTATIC POTENTIAL DIFFERENCES BETWEEN DONOR AND RECIPIENT HLA MOLECULES

DH Mallon (1), C Kling (2), JA Bradley (1), CJ Taylor (3), D Kabelitz (2), V Kosmoliaptsis (1)
(1) Department of Surgery, University of Cambridge (2) Institute of Immunology, University of Kiel (3) Tissue Typing Department, Addenbrooke's Hospital, Cambridge

Introduction: HLA matching reduces the risk of alloantibody-mediated rejection, but current matching strategies in kidney transplantation are inadequate. We have created a computational HLA matching algorithm that quantifies surface electrostatic potential differences between donor and recipient HLA (Electrostatic Mismatch Score; EMS-3D) to predict alloantibody responses following transplantation.

Method: We examined 141 patients that underwent lymphocyte immunotherapy (LIT) as treatment for infertility. Patients were injected subcutaneously with partner lymphocytes and serum samples collected before and after LIT to assess sensitisation. Following 4-digit HLA typing and HLA structural modelling, donor-recipient HLA comparisons were performed to determine EMS-3D and assess its ability to predict donor-specific alloantibody (DSA) development and overall sensitisation (calculated Reaction Frequency, cRF, against the UK donor pool) post-LIT.

Results: Donor EMS-3D predicted overall HLA class I and class II sensitisation (cRF > 15%; OR: 5.68 per unit increase, 95% CI: 1.84-17.49, $p = 0.002$) with an ROC area-under-curve score of 0.68 for cRF > 15% ($p < 0.0046$) and 0.71 for cRF > 85% ($p < 0.0001$). Donor HLA with the highest EMS-3D (fourth quartile) were associated with a higher risk of DSA development both for HLA class I (OR: 2.90, 95% CI: 1.62-5.23, $p = 0.031$) and for HLA class II (OR: 16.07, 95% CI: 9.11-142.68, $p < 0.0001$). Notably, physicochemical differences between donor and recipient HLA-DQ were strong predictors of HLA-DQ DSA development (OR: 30.0, 95% CI: 6.33-87.73, $p < 0.0001$). Interpretation: Our study provides further evidence that physicochemical properties of donor HLA are strong predictors of their immunogenic potential. Our HLA matching algorithm may help inform future deceased-donor kidney allocation policy.

Take-home message:

This study provides evidence for the use of a physicochemical scoring system to improve the current matching donors and recipients for kidney transplantation.

O77 BLAST TRAUMA INCREASES MICROVESICLE SHEDDING IN AN IN VIVO MODEL OF THORACIC BLAST TRAUMA

AE Sharrock (1,2,3), A Barnett-Vanes (1,2), R Rickard (3), S Rankin (1,2)

(1) Royal British Legion Centre for Blast Injury Studies, Imperial College (2) National Heart and Lung Institute, Imperial College (3) Academic Department of Military Surgery and Trauma, Royal Centre for Defence Medicine

Introduction: Blast trauma accounts for the majority of combat injuries and is increasingly utilised by civilian fractions and paramilitary groups. Blast trauma is associated with inflammatory dysregulation and coagulopathy, Systemic Inflammatory Response Syndrome and Multi-Organ Failure. Raised cellular microvesicles have been implicated, but not assessed in an in-vivo blast model. The objective was to identify and compare the lineage of microvesicles at pre-defined time points following thoracic blast injury, and to elucidate a mechanism for production.

Method: All animal work was performed with home office approval. Using a bespoke shock tube, anaesthetised rats were exposed to an isolated thoracic 14 bar blast wave or sham intervention. Animals were culled at 1, 3, 6 or 24 hours, five per group. Plasma was centrifuged and washed in PBS and Annexin V binding buffer. Annexin V positive particles between 0.23 – 1.23µm were defined as microvesicles, and CD31, CD61, His48 and CD11b antigens were used to define endothelial, platelet and leukocyte lineage respectively. Wash controls were developed to ensure protocol reliability.

Result: The protocol concentrated microvesicles compared to wash controls (p=0.007). When assessed by time point, more microvesicles were present in the blast than sham group at three hours (p=0.04), with an upward trend at all other time points. Increases were seen across all lineages, lineage ratios remained constant.

Conclusion : Microvesicles are increased following blast trauma, across all lineages. This suggests a possible mechanical cellular activation and microvesicle shedding. Future functional microvesicle assays will clarify their significance in inflammatory dysregulation and coagulopathy in trauma.

Take-home message:

Endothelial, platelet and leukocyte microvesicles are formed following blast injury. They may play a role in the propagation of inflammatory dysregulation and coagulopathy in blast trauma.

078 THE IVICA TRIAL: A RANDOMISED CONTROLLED TRIAL COMPARING THE EFFICACY OF INTRAVENOUS AND ORAL IRON IN THE PREOPERATIVE MANAGEMENT OF COLORECTAL CANCER ANAEMIA.

BD Keeler (1), JA Simpson (1), O Ng (1), H Padmanabhan (2), MJ Brookes (2), AG Acheson (1) and the IVICA trial group.

University of Nottingham

Introduction: Preoperative treatment of anaemia is advocated as part of Patient Blood Management aiming to minimise perioperative allogeneic red-blood transfusion (ARBT) use. The study aimed to compare the efficacy of preoperative intravenous (IVI) and oral iron (OI) in reducing ARBT use in anaemic patients undergoing colorectal cancer (CRC) surgery.

Method: 116 anaemic patients with non-metastatic CRC adenocarcinoma were recruited preoperatively and randomised to receive OI (ferrous sulphate) or IVI(ferric carboxymaltose). Perioperative changes in Haemoglobin(HB) and ARBT were recorded.

Result: Demographics, recruitment HB(P=0.24) and treatment duration (P=0.75) were comparable between groups. However, HB levels were higher at Surgery with IVI (11.9g/dL[11.5-12.3]; OI 11g/dL[10.6-11.4],P<0.01). Median preoperative HB increases attributable to iron were higher with IVI (1.5g/dL[0.9-2.6]; OI 0.5g/dL[-0.1-1.3],P<0.01), causing fewer anaemic IVI patients at surgery (75%vs90%,P<0.05). OI patients received mean 0.63units[0.26-1] from recruitment to day28 postoperatively vs mean 0.47units[0.1-0.84] for IVI. Neither number of patients transfused (P=0.33) nor mean units transfused (P=0.54) differed over this period. When patients with heavy intraoperative losses (>1.5L) were excluded in subgroup analysis, significant differences in mean units transfused were evident up to day7 postoperatively (n=108;OI 0.6u[0.23-0.96];IVI 0.16u[0.01-0.3],P<0.05) whilst significantly less IVI patients were transfused (10vs25%,P<0.05).

Conclusion: IVI appears more efficacious than OI at treating preoperative anaemia in patients undergoing CRC surgery. Although it did not minimise overall ARBT requirement, it may reduce ARBT use in a selected patients during the immediate perioperative period when the implications of ARBT are greatest.

Take-home message:

Intravenous iron is more efficacious than oral iron at treating preoperative anaemia in colorectal cancer patients which translates to a reduction in blood transfusion use in selected patient groups.

079 THE IMPACT OF SARCOPENIA AND MYOSTEATOSIS ON OUTCOMES OF UNRESECTABLE PANCREATIC CANCER AND DISTAL CHOLANGIOCARCINOMA

KE Rollins (1), N Tewari (1), A Ackner (1), A Awwad (1), S Madhusudan (1), IA Macdonald (1), KCH Fearon (2), DN Lobo (1)

(1) Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH (2) Department of Clinical and Surgical Sciences, University of Edinburgh, Royal Infirmary, Edinburgh, EH16 4SA

Introduction: Patients with pancreatic cancer have a poor prognosis and frequently demonstrate features of systemic inflammation. Analysis of body composition from CT scans has been used to study sarcopenia and its association with prognosis cancer. It has also been suggested that myosteatorsis, defined as attenuated mean skeletal muscle Hounsfield units (HU), is associated with reduced survival. This study aimed to assess the association between sarcopenia, myosteatorsis and outcome in unresectable pancreatic cancer.

Method: All patients diagnosed with unresectable pancreatic cancer at a single centre between 2006 and 2013 were considered for inclusion. A total of 228 patients were retrospectively included. Body composition was assessed using CT analysis to calculate skeletal muscle index for sarcopenia and mean skeletal muscle HU for myosteatorsis.

Result: The prevalence of sarcopenia was 60.5% (138/228) and this was not associated with any difference in survival ($p=0.779$), however patients who were overweight/ obese and sarcopenic had a significantly lower survival ($p=0.013$). The prevalence of myosteatosi s was 55.3% (126/228) and this was associated with a significant reduction in survival ($p=0.049$). Univariate Cox regression revealed myosteatosi s but not sarcopenia to be predictive of reduced survival, however this was lost on multivariate testing. Myosteatosi s, but not sarcopenia, was associated with significantly increased systemic inflammation and anaemia.

Conclusion: This is the largest study on the association between body composition and survival in patients with unresectable pancreatic cancer and has shown that the presence of myosteatosi s was associated significantly with the presence of systemic inflammation and reduced survival.

Take-home message:

Myosteatosi s, defined as attenuated mean skeletal muscle Hounsfield units (HU), is associated with significantly elevated levels of systemic inflammation and a significantly lower survival in patients presenting with inoperable pancreatic cancer.

O80 A NOVEL METHOD FOR THE DIAGNOSIS AND GRADING OF INTUSSUSCEPTION USING TRANSVAGINAL ULTRASOUND

AJ Hainsworth, D Solanki, AMP Schizas, AB Williams
Guy's and St Thomas' Hospital

Introduction: Intussusception is the telescoping of the rectal wall which may be associated with defaecatory dysfunction. The advent of new treatments for intussusception, for example ventral mesh rectopexy, demands accurate assessment. Gold standard imaging is defaecatory proctography and MRI but transvaginal ultrasound may provide a useful first line assessment tool. On proctography, intussusception is graded using the Oxford Radiological Classification System. We present a technique for classification using transvaginal ultrasound and correlate ultrasound findings with proctography and treatment.

Method: Images from 393 undergoing transvaginal ultrasound and proctography between 2011 and 2014 were independently and blindly reviewed. Intussusception was graded using the Oxford System on proctography. Intussusception on transvaginal scanning was classified as; -Grade I - II: in folding rectal wall stopped prior to inferior edge of puborectalis (grade I first half of puborectalis, grade II second half), -Grade III - IV: in folding stopped between the inferior edge of puborectalis before the perineal body (grade III onto/ grade IV into anal canal), -Grade V: in folding reached beyond perineal body. Grade III to V were pathological.

Result: There were 142 cases of intussusception on proctography and 99 on ultrasound. Inter - and intra - rater repeatability were good. Positive predictive value was 79%, negative predictive value 72%, specificity 89% and sensitivity 56%. Correlation between ultrasound and proctography was moderate. Patients with intussusception on ultrasound were significantly more likely to require surgery ($p = 0.03$).

Conclusion: Transvaginal ultrasound can be used to detect and grade intussusception such that some patients may avoid defaecatory imaging.

Take-home message:

Transvaginal ultrasound provides an accurate and repeatable alternative to defaecation proctography for the detection and grading of intussusception such that defaecatory imaging may be avoided in some women presenting with pelvic floor defaecatory dysfunction.