RELATIONSHIP BETWEEN BLOOD PRESSURE LEVEL AND HYPERTENSIVE MEDIATED ORGAN DAMAGE

Dellaneira Setjadi, Christian Delles, Gemma Currie, Carlos A Celis-Morales. School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow G12 8TA, UK

It is well-known that blood pressure (BP) level correlates with hypertension-mediated organ damage (HMOD), however, a disproportional degree of organ damage in relation to BP level has been observed clinically. The study aims to quantify the proportion of discrepancy between BP level and HMOD severity including its risk factors.

This cross-sectional study includes 268 participants from the UK Biobank cohort study (49.6% were females, mean age 56 years). The independent variable was BP including systolic BP, diastolic BP and pulse pressure (PP). Arterial stiffness measured by pulse wave velocity (PWV) was the marker used as a proxy of HMOD. To identify outliers for each of these variables a 0.5 standard deviation (SD) above or below the mean was used as cut-off point. The association between BP and HMOD variables were investigated using regression analysis.

Preliminary results using PWV variables showed that 67 and 44 participants were classified as outliers for PWV and BP, respectively. Men were more likely to be outliers than women for PWV while women were more likely to be an outlier for SBP. Participants aged <56 years were also more likely to be outliers for PWV and BP than their older counterparts. No difference on the numbers of outliers were observed across BMI categories.

Analysis using complete variables is necessary to conclude results from this study and its application in clinical practice.

DEVELOPMENT OF A FUNCTIONAL ORGAN-ON-A-CHIP OF HUMAN VASCULAR AGING

Juliane Loges*, Mairi Sandison, Christopher McCormick, Juri Wu. University of Strathclyde, Glasgow, UK

With increasing age, the risk of cardiovascular disease such as stroke and heart attack, increases in humans due to structural and mechanical changes within the cardiovascular system. This is due to many factors that occur in advanced age, such as increased arterial stiffness and intra-plaque and medial arterial calcification. Other diseases such as diabetes and hypo- or hypertension also increase the risk of developing arterial problems. Medial calcification is driven by the aging process, as well as diseases such as diabetes and chronic kidney disease.

During medial calcification smooth muscle cells (SMCs) within the medial layer of the arterial wall undergo processes similar to bone formation, due to continuous calcium phosphate diffusion. With increasing age or due to diseases the inhibitors that avoid an accumulation of those minerals within the blood vessels, become less effective and functional. This then causes phenotypical changes within vascular SMCs (VSCMs) to osteocytic and osteoblastic type cells. However, the exact morphologies are mostly still unknown. The development of an organ-on-a-chip (OOC) model could help to further the understanding of the changes that the cells undergo, as it would provide a functional and easily manipulated in vitro system of medial calcification. Furthermore, it could also provide a possibility to be used as a model for other cardiovascular research interests.

DOES MISUTUGMIN 23 PLAY A ROLE IN DOXORUBICIN-INDUCED CARDIOTOXICITY?

Katie Abraham*, Amy M Dorward, Quentin Hurst, Samantha J Pitt. School of Medicine, University of St. Andrews, St. Andrews, UK

The main non-malignant cause of death in cancer survivors is heart disease caused by side effects from many chemotherapy agents, including anthracycline doxorubicin. Approximately 1-in-10 cancer survivors suffer irreversible heart damage, but the cause remains unknown. We have recently suggested that Misutugmin 23 (MG23) is a Ca2+-leak channel located in sarcoplasmic reticulum (SR) membranes (Reilly-O’Donnell et al., 2017). Leakage of Ca2+ from SR stores is a hallmark of heart failure (Bers, 2014). We hypothesize that doxorubicin modulates MG23 resulting in Ca2+ cycle dysfunction. To study the impact of doxorubicin on intrinsic Ca2+ cycling, cardiomyocytes were isolated from wild type (WT) and MG23 knockout (KO) mice using a Langendorff-free method (Akers-Johnson et al., 2016). Cells were treated with 2.5 μM doxorubicin for 24 hours, cells were loaded with 2 μM Fluo-4 and SR Ca2+ store levels assessed by addition of 10 mM caffeine. Doxorubicin reduced SR Ca2+ store levels in cardiomyocytes isolated from both WT and MG23 KO mice but had a markedly greater effect on store levels in WT cells. To investigate the direct effect of doxorubicin on MG23 channel function we incorporated mouse cardiac SR vesicles into artificial bilayers under voltage-clamp conditions (Pitt et al., 2010). We show that luminal addition of doxorubicin to MG23 increases channel activity. Human model translation was assessed by demonstrating that doxorubicin increased the activity of recombinant human MG23 channels. This work implicates MG23 as a potential new therapeutic target in the treatment of cardiac dysfunction as a side effect of anthracycline chemotherapies.

THE EFFECT OF GLUTAREDOXIN-1 IN WESTERN DIET INDUCED CARDIOVASCULAR PATHOPHYSIOLOGY: AN ASSESSMENT OF SEXUAL DIMORPHISM IN A MOUSE MODEL

Yahika Relan*, Jennifer Kerr, Alison D McNelly, Colin E Murdoch. University of Dundee, Dundee, UK

Western diets, characterised by a high fat/high sucrose (HFHS) content, are associated with increased cardiac oxidative stress and cardiovascular diseases (CVDs). Increased post-translational modifications (oxPTM) like S-glutathionylation are correlated with the aetiology of CVD. Glutaredoxin-1 (Grx1) reverses S-glutathionylation and is overexpressed in CVDs. However, the role of Grx1 in HFHS-induced obesity and hypertension is unknown. This project aims to investigate potential sexual dimorphisms in the effect of HFHS...
diet-induced weight gain and cardiovascular pathophysiology in glutaredoxin-1 (Grx1Tg/+) overexpressing male and female mice.

Grx1Tg/+ (TG) and wild-type (WT) littermates (Female and Male, 8-12 weeks) were exposed to a normal chow (NC) or HFHS diet for 10 weeks. Bodyweights were taken weekly and EchoMRI was conducted before and after diet exposure. After 10 weeks, LV pressure-volume loop and blood pressure were obtained by inserting a catheter into the LV under anaesthesia.

In male and female WT mice, HFHS-diet increased bodyweight over 10-weeks. Interestingly, HFHS induced weight gain was attenuated in TG mice, accompanied with a decrease in % fat mass. HFHS-diet increased diastolic and mean blood pressure (BP). However, no significant increase in BP was observed in TG mice. In female TG mice, HFHS-diet reduced end diastolic volume stroke-volume and cardiac output compared to WT hearts. Heart-rates remained the same between all groups.

Overexpression of Grx1 attenuated weight-gain and % fat mass in male and female TG and hypertension in female TG. Additionally, it induced HFHS-diet induced cardiac remodelling in female TG.

8 EFFECT OF MYELOID PROTEIN TYROSINE PHOSPHATASE 1B (PTP1B) INHIBITION ON DIABETIC WOUND HEALING

Abrar Othman*, Heather M Wilson, Mirela Delibegovic. University of Aberdeen, Aberdeen, UK

Diabetes and its associated vascular complications e.g., cardiovascular disease and chronic wounds is a leading healthcare concern. Protein tyrosine phosphatase 1B (PTP1B) is a key regulator of whole-body glucose and energy metabolism. Our recent research suggests that myeloid-specific PTP1B deletion protects against atherosclerosis. We hypothesised that inhibiting myeloid-specific (macrophage) PTP1B would improve the efficacy of wound healing that is hampered by the diabetic environment.

In vivo, wound healing was assessed under physiological, normoglycaemic conditions in control wildtype (PTP1Bfl/fl) and myeloid-PTP1B deficient (LysM PTP1B-/-) littermate. Experiments were conducted in streptozotocin-induced diabetic mice. Wound healing was quantified over a period of 10 days. Two circular wounds were made horizontally in the dorsal region. The wounds were assessed using tracing and ruler methods.

In vitro, wound healing was assessed using wound healing assays, under hyper-glycaemic conditions. The keratinocyte cell line (HaCaT) was cultured with bone marrow-derived macrophages (BMDM) from diabetic C57Bl6 mice. Wound healing was also assessed in presence/absence of the PTP1B inhibitor, MSI-1436.

Under physiological conditions, there was a significant improvement in wound healing in LysM PTP1B-/- mice 4 days post-surgery. Under diabetic conditions, LysM PTP1B-/- mice had a significantly faster wound closure compared to PTP1Bfl/fl on day 8 post-surgery. Wound healing assays revealed more efficient wound closure in HaCaT cells co-cultured with BMDM from diabetic C57Bl6 mice, in the presence of MSI-1436. Thus, inhibiting myeloid-PTP1B improves wound healing rate under normoglycaemic and hyperglycaemic conditions, suggesting that PTP1B inhibition as a novel therapy for treatment of non-healing wounds in diabetes and CVD.

9 MONOCYTE CHEMOTACTANT PROTEIN-1 AS A BIOMARKER OF VASCULAR DYSFUNCTION IN PATIENTS WITH TYPE 2 DIABETES

William MacDonald*, Francesco Casanova, Kim Gooding, Kuni Aizawa, Angela Shore, Faisal Khan. Division of Systems Medicine, University of Dundee School of Medicine, Dundee, UK; Diabetes and Vascular Medicine Research Centre, University of Exeter Medical School and NIHR Exeter Clinical Research Facility, Exeter, UK

10.1136/heartjnl-SCF-2023.9

Endothelial dysfunction has been shown to be strongly associated with cardiovascular disease (CVD) outcomes. CVD risk in diabetes shows heterogeneity and new biomarkers are required to stratify CVD risk in these patients. This study analysed the association of Monocyte Chemoattractant Protein-1 (MCP-1) with measures of vascular function in 509 patients with type 2 diabetes mellitus (T2DM). Endothelial function was measured using laser Doppler imaging (LDI) and peripheral arteriometry (PAT) (EndoPat). Arterial stiffness was measured using carotid to femoral pulse wave velocity (PWV) (SphygmoCor).

Firstly, the study showed the negative association of MCP-1 with endothelium-dependent vasodilator responses to acetylcholine (R2=0.240, p=5.02*10^-10) as measured by LDI. Secondly, the study showed the negative association of MCP-1 with reactive hyperaemia index (RHI) (R2=0.0716, p=0.0109) and Framingham RHI (R2=0.0987, p=0.0294) as measured by PAT. Thirdly, the study showed the positive association of MCP-1 with PWV (R2=0.387, p=0.0088). Framingham risk factors, diabetes duration, HbA1c and eGFR were controlled for. The study also showed the independent association of MCP-1 with CVD death (odds ratio (OR)=18.2, 95% confidence interval (CI) [1.46 - 631.0], p=0.0487) and all-cause mortality (OR=4.51, 95% CI [1.07 - 21.8], p=0.0462) in a three-year follow-up period. There was no significant improvement to area under receiver operating characteristic curve (AUROC) when MCP-1 was added into risk models.

This study shows MCP-1 to be a good candidate as a biomarker of vascular dysfunction in T2DM. Further research in larger cohorts with longer follow-up periods should be conducted to determine its usefulness in improvement of risk models.

10 GLUTAREDOXIN-1 OVEREXPRESSION INDUCES HYPERTENSIVE PREGNANCY AND MOTHERL CARDIAC FIBROSIS

Jennifer Kerr*, Agathe Lermant, Colin E Murdoch. University of Dundee, Dundee, UK

10.1136/heartjnl-SCF-2023.10

Elevation of oxidative stress is explicitly linked to hypertensive pregnancies with high levels measurable in the maternal circulation. Hypertensive pregnancies lead to life-long risk of cardiac dysfunction, yet the underpinning molecular pathway are unknown. Oxidative stress modify proteins via oxidative post-