RELATIONSHIP BETWEEN BLOOD PRESSURE LEVEL AND HYPERTENSION MEDIATED ORGAN DAMAGE

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10.1136/heartjnl-SCF-2023.4

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

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10.1136/heartjnl-SCF-2023.5

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 osteogenic 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 MITSUGUMIN 23 PLAY A ROLE IN DOXORUBICIN-INDUCED CARDIOTOXICITY?

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10.1136/heartjnl-SCF-2023.6

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 Mitsugumin 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 (Acker-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 the 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

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10.1136/heartjnl-SCF-2023.7

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