Results: Participant demographics (mean age 67±9 years, 92% male) and cardiovascular risk factors were representative of atherosclerotic disease.

45Ga-DOTATATE mean (m) maximum tissue-to-blood ratios (TBRmean) were higher in recently infarcted myocardium defined by clinically adjudicated (treated) culprit coronary arteries, compared to non-infarcted myocardial segments (Figure A-B: median 2.33 [IQR 1.55–2.71] vs. 1.8 [1.32–2.22], p = 0.003). In patients with old MI, 45Ga-DOTATATE TBRmean was also greater in myocardium with impaired contractility assessed by transthoracic echocardiography, compared to regions with preserved function (Figure C: akinetic, median 2.89 [IQR 2.48–3.26] hypokinetic, 2.71 [2.43–3.08] preserved, 1.89 [1.52–2.36], p < 0.0001).

Intriguingly, bone marrow 45Ga-DOTATATE uptake was also highly correlated with both persistent myocardial inflammation detected by 45Ga-DOTATATE (r = 0.63 [95% CI 0.48–0.69], p = 0.0013), and metabolic bone marrow activity measured by 99mTc-FDG indicating increased monocyte mobilisation (r = 0.64 [95% CI 0.079–0.89], p = 0.029).

Conclusion: We found that 45Ga-DOTATATE could identify active inflammation within recently infarcted myocardium, as well as remote myocardial ischemic injury, fuelled by systemic monocyte mobilisation.

Reference

P3.1 VARIATION OF VON WILLEBRAND FACTOR EXPRESSION IN THE ENDOTHELIUM OF HUMAN CORONARY Atherosclerotic plaques: IMPLICATIONS FOR THROMBOSIS

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Rationale: Atherosclerotic plaque rupture is often preceded by high macrophage activity and is complicated by thrombosis: an important mechanism responsible for acute coronary syndrome. Platelet binding to von Willebrand Factor (vWF) is a fundamental mechanism underlying arterial thrombosis. P-selectin and vWF are the principle molecules in Weibel-Palade bodies. Since P-selectin is upregulated during arterial inflammation, this study investigated the changes in vWF expression in various stages of atherogenesis in human tissues.

Hypothesis: Endothelial vWF expression is inversely correlated with sub-endothelial inflammation.

Methodology: Immunohistochemistry double-staining was performed on paraffin-embedded autopsy samples of 17 human atherosclerotic coronary artery sections by direct immunoperoxidase for vWF and macrophages. P-selectin and CD31 markers confirmed intact endothelium. The levels of endothelial and sub-endothelial vWF, and intraluminal CD68+ macrophages were quantified and compared between advanced plaque, active plaque and control regions via image analysis.

Results: Compared to control regions, vWF staining intensity was decreased over active plaque regions, indicated by macrophage concentration and P-selectin expression (n = 9, p < 0.0001). Large, stable plaques (n = 5) characterised by low inflammatory cell count, a necrotic lipid core and fibrosis do not follow this trend: vWF expression between plaque and control regions is uniform. Luminal thrombi were negatively correlated with endothelial vWF expression (n = 3).

Conclusions: Endothelial vWF expression depends on the extent of sub-endothelial inflammation of the atherosclerotic plaque, acting as a marker for plaque thrombogenicity. Additionally, vWF may be a potential therapeutic target in preventing thrombosis formation without plaque rupture.

P3.2 LOCALISED CORONARY ARTERY INFLAMMATORY BIOMARKER EXPRESSION DOES NOT CORRELATE WITH SYSTEMIC ELEVATION OF BIOMARKERS OR hsCRP

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Aim: Recent data have identified residual inflammatory risk as a novel target for therapies designed to modulate risk of future coronary/vascular events. We sought to compare indices of systemic inflammatory activity with local intracoronary inflammation.

Methods: Using a novel dedicated catheter to sample the unceded boundary layer, we collected blood samples simultaneously at discrete locations proximal and distal to atherosclerotic plaques in patients undergoing coronary stenting procedures. Both coronary and systemic samples were analysed for quantification of 90 inflammatory proteins by multiplexed assays, and systemic samples for the presence of hsCRP.

Results: Samples were obtained from 23 patients immediately after balloon dilatation of culprit coronary plaques. Cluster analysis by K-means identified 2 distinct groups with overall low (n = 11 patients) and high (n = 12) coronary inflammation (p < 0.05), despite no differences in patient demographics. However, presence of coronary biomarker gradients were not reflected in peripheral biomarker samples (PDGBF r = 0.09, p = 0.87; MCP1 r = 0.26, p = 0.61; Dkk1 r = 0.15, p = 0.76; IL6 r = 0.44, p = 0.21), except for CCL4 which demonstrated an inverse relationship (CCL4 r = -0.71, p < 0.02). Further, there was no difference in hsCRP levels between these clustered groups (median 2.6 [16.3-9.9mg/L vs. 1.2 [12.2-7.9mgL/L] p = 0.1).

Conclusions: These data explore the relationship between systemic and local inflammation in vascular risk: rather than hsCRP acting as a biomarker for adverse events, it appears that presence of coronary inflammation may be an independent entity. Further studies should address the complex relationship between systemic and coronary inflammation, and their interactions with ‘vulnerable’ plaque phenotypes in modulating patient events.

P3.3 NRFP2-MEDIATED UPREGULATION OF OSGIN1 AND OSGIN2 TRIGGERS CELL DETACHMENT THROUGH DYSREGULATED AUTOPHagy: A POTENTIAL MECHANISM FOR ENDOTHELIAL EROSION OVERLYING STENOtic PLAQUES

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25-30% of acute coronary syndromes are precipitated by endothelial erosion of plaques. Using quantitative imaging, we demonstrate that this frequently occurs proximal to, or at the site of minimal luminal diameter where endothelial cells are exposed to elevated flow. To investigate this, we exposed human coronary artery endothelial cells (HCACs) to Simglin TNFα and aqueous cigarette smoke extract (CSE) observing ~30% cell loss when adapted to elevated shear stress (ESS), with no cell loss observed under oscillatory shear stress. Inclusion of NFκB activators sulphoraphane (2.5μM) or isookaempigenin (10μM) triggered ~80% cell loss at elevated shear stress with TNFα and CSE. implying that hyperactivation of the NFκB system promotes cell detachment. OSGIN1 and OSGIN2 expression were maximally increased under conditions where cells were detaching, and both were upregulated by NFκB activation. Adenosine overexpression of OSGIN1 and 2 in static culture resulted in cell cycle arrest in S-phase (5.5-fold increase, p = 0.003), with a significant increase in the number of multicellular clusters (4.5-fold, p < 0.0001). Immunochemical analysis indicated loss of focal adhesions and stress fibres, dysregulation of autophagy and induction of senescence in HCAEC, with a significant increase in senescence-associated β-galactosidase staining (6.7-fold, p < 0.0001) and P16 expression (3.2-fold, p = 0.035). Importantly, OSGIN1-2 overexpression induced cell detachment (6.8-fold, p < 0.0001), that could be partially rescued by metformin treatment and inhibition of HSP70, essential for chaperone-mediated autophagy. Taken together, hyperactivation of NFκB induced OSGIN1-2, inhibits autophagy, resulting in endothelial cell detachment, potentially contributing to plaque erosion overlying stenotic plaques.

P3.4 FLUID-STRUCTURE INTERACTION MODELLING FOR ANALYSING ADVANCED CORONARY ATHEROSCLEROTIC PLACe FORMATION IN TRANSGenic HYPERLipidaemic MiniNPs

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Acknowledgements: This work is carried out under funding from the British Heart Foundation (P47414). Authors are grateful for the support provided by the British Heart Foundation. Atherosclerotic plaques are the main cause of acute coronary syndromes. Interestingly, plaques tend to develop in arterial regions where shear stress due to blood flow is low and multidirectional. These specific disturbed blood flow profiles have been shown to correlate to regions of advanced atherosclerosis (Samady, Estahñardi et al. 2011). Further, in our previous study, we showed a causal relationship between disturbed blood flow and the development of advanced plaques, including thin cap fibroatheroma, in hypercholesterolemic minipigs (Pedreg, Poulsen et al. 2015). However, all of these investigations neglected the elasticity of the vessel wall (assuming a perfectly rigid wall), which may affect calculation of blood flow derived shear stress. In this study, a fluid-structure interaction model was developed to address these limitations. In this model, we reconstructed the coronary arteries from intravascular optical coherence tomography within hypercholesterolemic pigs. Our model predicted a higher prevalence of disturbed blood flow within atherosclerotic regions of the vessels and greater overlap between, particularly, low shear stress and histologically-defined advanced plaques. We also demonstrate changes in the mechanics (i.e., strain) of the atherosclerotic vessel that may additionally promote plaque progression.