antiplatelet therapy (DAPT) representing a risk factor for thrombosis. Coagulation pathways also play a central role and configuration of the fibrin network is a vital determinant of clot stability and outcome,with dense clots composed of compact thin fibres associated with thrombotic events. However, despite the interwoven nature of platelet activation and the coagulation system, studies relating both aspects of thrombosis in the same population are limited.

Methods Four groups of healthy volunteers (n = 8) received single anti-platelet therapy aspirin (75 mg) or prasugrel (10 mg) or DAPT with aspirin (75 mg) plus prasugrel (10 mg) or aspirin (75mg) plus ticagrelor (90mg) for 7 days. In this study, we characterised the influences of these standard anti-platelet therapies on platelet function using standard tests of platelet activation and aggregation. We then associated platelet reactivity to fibrin clot microstructure which was determined using advanced rheological techniques to analyse the viscoelastic properties of incipient clots; fractal dimension (D_f) and mean relative mass (RM).

Results Aspirin alone caused inhibition of platelet responses to arachidonic acid (AA), but did not reduce ATP release, P-selectin or PAC-1 binding. Aspirin also had no effect upon the measures of clot structure D_f (1.71 ± 0.01 to 1.69 ± 0.01, p = 0.41) or RM (-8 ± 19%, p = 0.47). Prasugrel significantly reduced D_f(1.72 ± 0.02 to 1.67 ± 0.01, p = 0.03) and RM (-40 ± 11%, p = 0.03), as well as caused a significant decrease in ATP release, PAC-1 and p-selectin expression (p < 0.05). Both aspirin plus prasugrel and aspirin plus ticagrelor inhibited platelet responses to all agonists tested and decreased P-selectin expression. Significant platelet inhibition was associated with a reduction in D_f; 1.73 ± 0.02 to 1.68 ± 0.02 (p = 0.03) and 1.72 ± 0.03 to 1.62 ± 0.02 (p = 0.04) by aspirin+prasugel and aspirin+ticagrelor, respectively. This corresponded to reductions in RM both for aspirin plus prasugrel (-35 ± 16% change, p = 0.04) and for aspirin plus ticagrelor (-45 ± 14% change, p = 0.04).

Conclusion We demonstrate that platelets are important determinants of clot microstructure which is modifiable by anti-platelet therapies. These therapies may rely on their abilities to reduce thrombus density to exert their therapeutic effects with increased levels of platelet inhibition associated with the formation of more open, porous fibrin clots. We also suggest that it is activation of $P2Y_{12}$ receptors rather than TX (A_2) receptors that are key to clot formation. We conclude that there lies both diagnostic and therapeutic potential in determining the functional relationship between platelet reactivity, eventual clot quality and clinical outcome and D_f could be a useful novel biomarker in risk stratification and tailored anti-platelet therapies.

187 MITOCHONDRIAL DYSFUNCTION IN THE DIABETIC HEART Â€ " IMBALANCE IN FUSION/FISSION AXIS?

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Background Cardiovascular disease is the leading cause of morbidity and mortality among diabetic patients. Diabetic cardiomyopathy is closely linked to mitochondrial dysfunction, however the pathophysiological mechanisms responsible are not known. Maintenance of mitochondrial function relies on the balance between fusion and fission events. The fusion protein mitofusin-2 (Mfn2) has been implicated in the pathogenesis of diabetes. Alongside fusion, Mfn2 is widely believed to function as a molecular tether, binding mitochondria to the sarcoplasmic reticulum (SR) to form specialised Ca^{2+}microdoomains. Nonetheless, the role of Mfn2 in the heart is poorly characterised. Therefore, the aim of this study was to investigate changes to cardiac mitochondrial protein expression and function in diabetes with a particular focus upon the fusion/fission axis.

Methods and results Protein expression levels were measured in control and streptozotocin-treated (STZ) Wistar rat heart using Western Blot. Mitochondrial OXPHOS function was assessed using enzyme activity assays. Lastly, changes to the mitochondrial proteome were investigated using Mass Spectrometry (MS). Western Blot showed a significant increase in Mfn1 and Mfn2 expression levels in STZ compared to controls with no change to the fission protein Drp1. Enzymatic assays revealed that mitochondrial function was altered in the STZ rat heart compared to control. Lastly, MS identified 1437 proteins, of which there was an upregulation of proteins involved in beta oxidation in the STZ compared to controls. In contrast, there was a downregulation of proteins associated with OXPHOS in the STZ suggesting mitochondrial dysfunction that corroborates the functional data.

Conclusion These data suggest that mitochondrial dysfunction may be linked to an imbalance of the mitochondrial fusion/fission axis in the diabetic heart. Future work will focus on the 3-D reconstruction of the mitochondrial networks using electron microscopy to determine whether changes to mitochondrial function are linked to structural alterations. These studies will enhance our understanding of the pathogenesis of cardiac mitochondrial dysfunction in diabetes, with the hope to elucidate potential targets for therapeutic intervention.

188 CHANGES IN PERIVASCULAR ADIPOSE TISSUE IN AGEING AND ATHEROSCLEROTIC MICE

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Perivascular adipose tissue (PVAT) encases the majority of blood vessels and is an important component of the vasculature. PVAT is an active endocrine organ but until recently was not considered important in the pathogenesis of atherosclerosis. In healthy vessels PVAT exerts an anti-contractile effect which is attenuated in states of metabolic disturbance. The following experiments were conducted to determine the influence of PVAT, age and progression of atherosclerotic disease on isolated arterial reactivity.

Upon weaning, male $ApoE^{-/-}$ or C57/BL6 (control) mice were fed a standard rodent chow diet for a period of eight or twenty-six weeks. Aortic atherosclerotic lesion area was analysed by en face quantification with Oil Red O. Aortic PVAT was collected and weighed. Contractile responses of the thoracic aortae to cumulative doses of phenylephrine ($1 \times 10^{-10-} - 3 \times 10^{-5}$ M) were measured in PVAT intact or PVAT denuded vessels using myography. Adipokine expression from PVAT was examined using an adipokine proteome profiler.