6.2: PREDICTING THE FUNCTIONAL IMPACT OF RESIDUAL AORTIC COARCTATION LESIONS DURING EXERCISE USING ADVANCED COMPUTER MODEL SIMULATIONS

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5.6 INDEPENDENT RELATION BETWEEN ETHNICITY, BASELINE HAEMOSTATIC VARIABLES, ARTERIAL STIFFNESS AND MORTALITY: A 22-YEAR FOLLOW-UP STUDY

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Objectives: To examine the relationship between haemostatic factors, pulse wave velocity (PWV), blood pressure (BP) and mortality in British Europeans, African-Caribbeans (AfC) and Gujarati Indians.

Design and Methods: Prospective cohort study of 331 subjects (40-79 years), followed-up over 21 years for mortality. PWV, Apolipoprotein-A1 (Apo-A1), apolipoprotein-B (Apo-B), factor VIIc (FVIIc), fibrinogen and vWF were measured at baseline in 118 Europeans, 100 AfC and 113 Gujaratis.

Results: 113 (34%) subjects died during a mean of 16.8 years follow-up with 57 cardiovascular deaths. Women had significantly higher, and AfC males the lowest FVIIc and Apo-A1 levels. HDL levels were lowest (F = 3.13; P = 0.04) in Gujarati Indians. Baseline age-sex and ethnicity adjusted FVIIc levels were higher in those who died (133.9 vs. 117.6%; P = 0.03), with similar levels of the other haemostatic factors by mortality status. In similarly adjusted partial correlations, Apo-A1 was inversely related to PWV (p = -0.23, P = 0.04). No independent associations were found between fibrinogen, FVIIc, Apo-B, ApoB/Apo-A1 ratio, vWF and PWV. In Kaplan-Meier curves (Figure 1), those above, compared with those below the median of Apo-A1 levels, had reduced mortality. In Cox regressions, SBP (per 5mmHg) was associated with a 9%, PWV a 20% (per m/s), and FVIIc a 6% (per 10-unit; HR 1.06 (1.01, 1.10, P = 0.016) increased risk of mortality.

Conclusions: The relationship between haemostatic variables with cardiovascular disease is well known, however few studies report their association with arterial stiffness. The results here are consistent with the independent effect of haemostatic variables influencing arterial stiffness and mortality.

Oral Session 6
Young Investigators’ Presentations

6.1 UNSUPERVISED NON-INVASIVE MEASUREMENT OF AORTIC PULSE TRANSIT TIME BY MEANS OF ELECTRICAL IMPEDANCE TOMOGRAPHY

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Objectives: This study provides first experimental evidence on the feasibility of measuring Pulse Transit Time (PTT) values within the aorta by means of non-invasive and non-obtrusive Electrical Impedance Tomography (EIT) technology.

Methods: A wide range of pulse wave velocity scenarios were obtained by administering noradrenaline and nitroglycerine to an anesthetized pig under mechanical ventilation. Two arterial lines were inserted into the ascending and the descending aorta for measuring reference PTT values. EIT images were generated from 32 impedance electrodes placed around the chest at the level of the axilla. Regions of Interest (ROI) such as the descending aorta were automatically identified by a novel time-based processing algorithm as the respective EIT pixels representing these structures [1]. Aortic EIT-PTT values were determined as the delay between the opening of the aortic valve (obtained from arterial line) and the arrival of pressure pulses at the aortic ROI within the EIT plane.

Results: For 9 experimental conditions, with mean BP ranging from 73 to 141 mmHg, strongly significant correlation (r = 0.98, p < 0.00001) between aortic EIT-PTT and arterial line PTT was observed (Figure 1).

Conclusion: EIT is a novel candidate technology for the unsupervised monitoring of arterial stiffness.

Figure 1 Correlation between aortic PTT as measured by arterial lines and EIT technology at different hemodynamic conditions


6.2 PREDICTING THE FUNCTIONAL IMPACT OF RESIDUAL AORTIC COARCTATION LESIONS DURING EXERCISE USING ADVANCED COMPUTER MODEL SIMULATIONS

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Background: Exercise can be used to unmask the functional impact of a residual narrowing and/or stiffening following treatment of aortic coarctation. Measurements of the hemodynamic response during exercise are, however, difficult to perform and not very accurate, as suspension of exercise during imaging can be required or a low temporal resolution might be insufficient at the high heart rates present during exercise. This work aims to predict central aortic hemodynamics during exercise using advanced modeling tools.

Material and methods: The geometry and the flow boundary conditions, used in this model, are obtained from MRI data at rest (Figure 1). As model simulations with rigid walls fail to capture important physiological phenomena such as wave propagation and reflections, the fluid-structure interaction between the blood flow and the deformation of the arterial wall is taken into account.

Results: The numerical model is first calibrated to the resting conditions such that the predicted aortic distortions match the measured values. Predicted velocities throughout the aorta are compared to 4D velocity measurements. Next, exercise conditions are simulated, with blood flows obtained using an MRI-compatible bycicle type ergometer, in which motion is restricted to the lower legs. Model output includes pressure along the aorta and velocity fields during exercise conditions.

Conclusions: Advanced modelling techniques allow to simulate aortic hemodynamics in 3D and are capable to provide complementary data that are difficult to obtain in vivo.
6.3 OXIDATIVE STRESS AND INFLAMMATION: IMPLICATION IN ENDOTHELIAL DYSFUNCTION AND CARDIOVASCULAR AGING ON MURINE MODELS

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The aim of the study was to characterize cardiovascular aging with functional (Doppler) and molecular (RT-qPCR and immunohistochemistry quantifications) approaches using three murine models. Molecular studies on aorta (AO) and mesenteric arteries (MA) were used to explore the role of oxidative stress and inflammation. Time-induced aging model corresponded to 25 months-old C57Bl/6J mice feed with standard diet. Doppler exhibited a concentric left ventricle hypertrophy with a decreased aortic distensibility, and an increased aortic thickening. This model presented both aortic wave reflection characteristics and an oxidative stress and inflammation. In normotensive CT-1-treated rats, the incremental elastic modulus-circumferential wall stress curve was shifted leftward compared to vehicle, indicating increased arterial stiffness. Aortic media thickness was higher (40%) in CT-1-treated rats. Aortic collagen type I (80%), fibronectin (80%), metalloproteinases activities (40%), integrins (70%) and focal adhesion proteins (60%) were also increased in whereas elastin levels were similar to controls. Further, increased aortic wavespeed in CT-1 rats (1678 ± 2 ms⁻¹ compared to 1673 ± 2 ms⁻¹, p < 0.001) was found in parallel with increases in collagen volume fraction (21 %) as compared to 9 % in controls.

6.4 CARDIOTROPHIN-1 INDUCES STRUCTURAL AND MECHANICAL CHANGES IN AORTA

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Aims: Cardiotrophin-1 (CT-1), a cytokine belonging to the interleukin-6 family, exerts proliferative and secretory effects in vascular smooth muscle cells. We investigated the morphological, micromechanical and molecular vascular changes induced by chronic CT-1 administration in rats.

Methods: Recombinant rat CT-1 (20 µg/kg, IP) or vehicle (n = 10/group) was administrated to Wistar rats for six weeks. Vascular structure and function were determined with an echo-tracking device. Aortic extracellular matrix (ECM) protein production and attachments were quantified by immunohistochemistry, RT-PCR and Western blot. Acoustic wavespeed within the aorta was determined using a novel scanning acoustic microscopy (SAM) method at 1 GHz which enables tissues stiffness to be determined with a ~1 µm spatial resolution.

Results: In normotensive CT-1-treated rats, the incremental elastic modulus-circumferential wall stress curve was shifted leftward compared to vehicle, indicating increased arterial stiffness. Aortic media thickness was higher (40%) in CT-1-treated rats. Aortic collagen type I (80%), fibronectin (80%), metalloproteinases activities (40%), integrins (70%) and focal adhesion proteins (60%) were also increased in whereas elastin levels were similar to controls. Further, increased aortic wavespeed in CT-1 rats (1694 ± 2 ms⁻¹ compared to 1673 ± 2 ms⁻¹, p < 0.001) was found in parallel with increases in collagen volume fraction (21 %) as compared to 9 % in controls.

Conclusions: We demonstrate that CT-1 is a key player in arterial remodeling and stiffness by modulating aortic mechanical properties, media thickness, ECM production and attachments. Thus, CT-1 could be a new biotarget to reduce arterial stiffness and decrease ECM deposition in vascular diseases.

6.5 ACUTE β-ADRENERGIC BLOCKADE INCREASES AORTIC WAVE REFLECTION IN YOUNG MEN AND WOMEN: DIFFERING MECHANISMS BETWEEN SEXES

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Acute β-adrenergic blockade increases aortic wave reflection, however, the mechanisms remain unclear. Evidence suggests that β-adrenergic receptor sensitivity in the peripheral vasculature differs between sexes. Therefore, the goal of this study was to examine whether β-adrenergic blockade alters aortic wave reflection and forearm vasconstrictor responsiveness to a similar extent in young men and women. In thirty-one subjects (16M/15F; 26 ± 1 years) non-invasive aortic pressure waveforms were synthesized from high-fidelity radial pressure waveforms via applanation tonometry before and during systemic β-blockade (0.25 mg/kg bolus, followed by 0.004 mg/kg/min continuous infusion of propranolol). Forearm vasoconstrictor responses to exogenous intra-arterial norepinephrine (NE) were also assessed in a subset of subjects (13M/9F). Wave reflection characteristics were analyzed by measuring augmentation index (AIx) and wave reflection amplitude (aortic augmented pressure (AG)) in both sexes. However, the increase in wave reflection tended to be greater (P < 0.05) and P = 0.07 for AG and AIx, respectively) in women following β-blockade. AIx adjusted for HR (AIx@75bpm) increased in women following β-blockade, whereas it was unchanged in men. Moreover, the change (Δ) in AIx was inversely correlated to ΔHR only in men (r = −0.54, P = 0.05). Finally, β-blockade caused an enhanced forearm vasconstrictor response to exogenous NE in women (Figure 2). Our data suggest that: 1) aortic wave reflection is increased to a greater extent in women following systemic β-blockade; and 2) the mechanism for enhanced aortic wave reflection that NADPH oxidase and Thioredoxin1 seem to play a key role in the arterial aging process and might be interesting potential targets for therapeutics assays.