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

L. Taelman, J. Degroote, J. Bols, V. Muthurangu, S. Panzer, A. Swillens, J. Vierendeels, P. Segers

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5.6

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

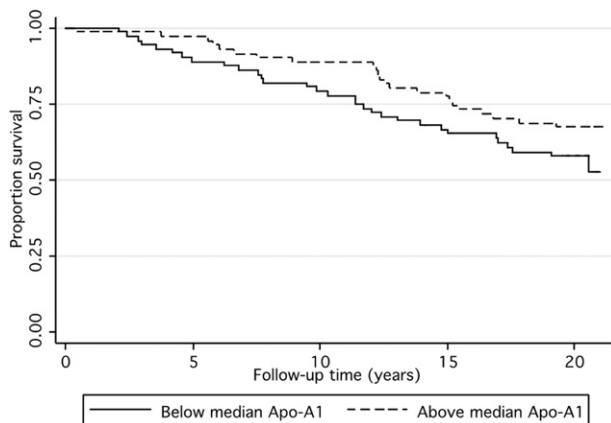
S. G. Anderson¹, A. H. Heald¹, J. K. Cruickshank²¹University of Manchester, Manchester, United Kingdom²King's College London, London, United Kingdom

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 ($\rho = -0.23$, $P = 0.04$). 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

J. Solà¹, A. Adler², A. Santos³, G. Tusman⁴, F. Suárez Sipmann^{3,5}, S. H. Bohm¹¹CSEM – Centre Suisse d'Electronique et de Microtechnique, Neuchâtel, Switzerland²Systems and Computer Engineering, Carleton University, Ottawa, Canada³Department of Critical Care, Fundación Jiménez Díaz-UTE, IIS-FJD, CIBERES, Madrid, Spain⁴Department of Anesthesiology, Hospital privado de Comunidad, Mar del Plata, Argentina⁵Section of Anaesthesiology & Critical Care, Dept of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden

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 noradrenalin 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.

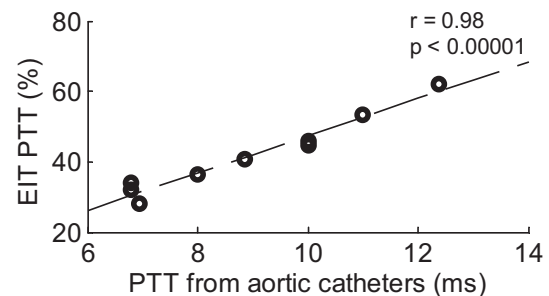


Figure 1 Correlation between aortic PTT as measured by arterial lines and EIT technology at different hemodynamic conditions

[1] Solà, J. et al, *Non-invasive monitoring of central blood pressure by Electrical Impedance Tomography (EIT): first experimental evidence*, Med Biol Eng Comput, Epub ahead of print, 15 Mars 2011.

6.2

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

L. Taelman¹, J. Degroote², J. Bols², V. Muthurangu³, S. Panzer⁴, A. Swillens¹, J. Vierendeels², P. Segers¹¹IBiTech-bioMMeda, Ghent, Belgium²Department of Flow, Heat and Combustion Mechanics, Ghent, Belgium³Centre for cardiovascular MR, UCL Institute of Child Health, London, United Kingdom⁴UZ Gent, Ghent, Belgium

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 distensions 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 bicycle 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.

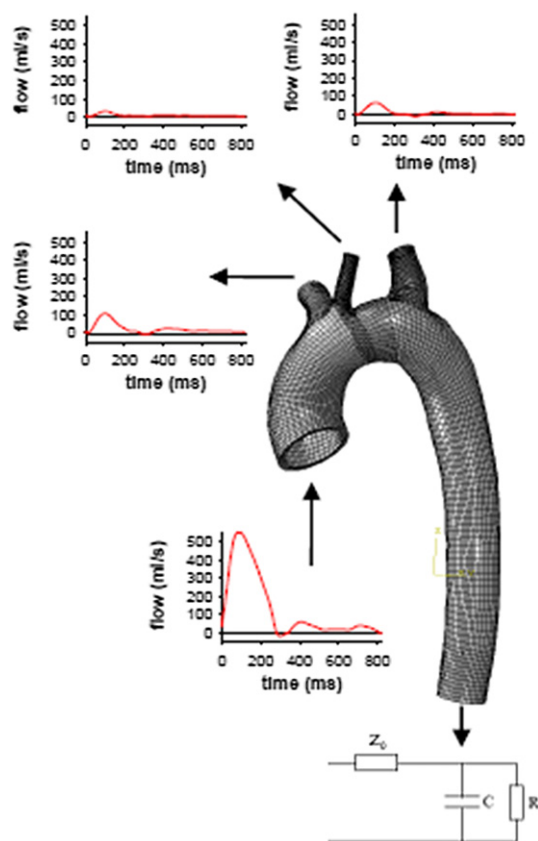


Figure 1 Patient-specific geometry and boundary conditions.

6.3 OXIDATIVE STRESS AND INFLAMMATION: IMPLICATION IN ENDOTHELIAL DYSFUNCTION AND CARDIOVASCULAR AGING ON MURINE MODELS

S. Baron^{1,*}, T. Bedarida^{1,*}, M. M. Strelcyn¹, C. H. Cottart^{1,2}, F. Vibert¹, G. Renault³, B. Saubamea⁴, E. Veissieres⁵, D. Henrion⁵, J. L. Beaudoux^{1,2}, V. Nivet-Antoine^{1,6}

¹Groupe VIVA, EA4466, Université Paris Descartes, Paris, France

²APHP, Hôpital Pitié Salpêtrière-Charles Foix, Service de biochimie-hématologie Charles Foix, Ivry sur seine, France

³PIPA, Institut Cochin, Université Paris Descartes, Paris, France

⁴SCICM, Université Paris Descartes, Paris, France

⁵Laboratoire CNRS- INSERM 771 Faculté de médecine, Angers, France

⁶APHP, Laboratoire de Biochimie, Hôpital Européen Georges Pompidou, Paris, France

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 a decreased Thioredoxin1 expression (AO and MA) and an increased NADPH oxidase (MA) expression. Inflammation markers were increased in MA (IL-1beta in MA and in AO (IL-6, TNF-alpha). Three months with High Fat and Protein Diet (HFPD) at 9 months induce a major hyperlipidemia. This model exhibited a dilated cardiopathy with both a decreased aortic distensibility and an increased aortic thickening. HFPD increased NADPH oxidase, IL1-beta and TNF-alpha expressions and decreased Thioredoxin1 expression (AO and MA). The mixed model corresponded to 25-months old C57Bl/6J mice feed for 3 months with HFPD. They presented a major cardiopathy with a decreased aortic distensibility, and exhibited both a major oxidative stress (increased NADPH oxidase and decreased Thioredoxin1 in AO and MA) and a major endothelial inflammation (increased IL-1beta, IL-6 and TNF-alpha in AO and MA). eNOS gene was not modify in any model. We conclude

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.

6.4 CARDIOTROPHIN-1 INDUCES STRUCTURAL AND MECHANICAL CHANGES IN AORTA

R. Akhtar¹, N. López-Andrés², C. Labat², J. Díez^{3,5}, F. Zannad^{2,4}, X. Zhao¹, B. Derby¹, J. K. Cruickshank⁶, P. Lacolley², P. Rossignol^{2,4}

¹The University of Manchester, Manchester, United Kingdom

²Inserm, Vandoeuvre-lès-Nancy, France

³Division of Cardiovascular Sciences, Centre for Applied Medical Research, Pamplona, Spain

⁴CIC-INSERM CHU de Nancy, Vandoeuvre-lès-Nancy, France

⁵Department of Cardiology, University Clinic, Pamplona, Spain

⁶King's College, London, United Kingdom

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 acoustic wavespeed in CT-1 rats ($1694 \pm 2 \text{ ms}^{-1}$ compared to $1673 \pm 2 \text{ ms}^{-1}$, $p < 0.001$) 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

D. P. Casey, T. B. Curry, M. J. Joyner, N. Charkoudian, J. N. Barnes, E. C. Hart

Mayo Clinic, Rochester, MN, United States of America

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 vasoconstrictor 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 are summarized in Table 1. β-blockade increased aortic augmentation index (Alx) 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 Alx, respectively) in women following β-blockade. Alx adjusted for HR (Alx@75bpm) increased in women following β-blockade, whereas it was unchanged in men. Moreover, the change (Δ) in Alx was inversely associated to Δ HR only in men ($r = -0.54$, $P < 0.05$). Finally, β-blockade caused an enhanced forearm vasoconstrictor 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