AORTA: FROM STRUCTURE TO RUPTURE

UNIVERSITY OF LIVERPOOL

Inaugural meeting of the Liverpool Aortic Biomechanics and Biochemistry (LABB) Research Group.

Hosted By
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Tuesday 17th July 2018

9.00 AM : **5:00** PM

School of Engineering, University of Liverpool

LABB
Liverpool Aortic Biomechanics & Biochemistry Research Group

ABOUT

An interdisciplinary meeting bringing together clinicians, engineers and life scientists to explore state-of-the-art in aortic pathology research. Key topics include:

- Biochemistry and biomechanics of ascending/thoracic aneurysms
- Surgical challenges for thoracic aneurysms
- Behcet's disease
- Novel techniques for vascular research – CT, AFM, Fast Digital Laser Sheet Microscopy and nanoindentation
- Structure and development of the aorta
- Mechanical Circulatory Support

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OUR SPEAKERS

Prof. Rob Moots Institute of Ageing and Chronic Disease, University of Liverpool

Prof. Deborah Henderson Institute of Genetic Medicine, Newcastle University

Prof. Kennedy Cruickshank Cardiovascular Medicine & Diabetes , King's College London and President of the Artery Society.

Dr. Liz Laird Institute of Ageing and Chronic Disease, University of Liverpool

Dr. Phornphop Naiyanetr Department of Biomedical Engineering, Mahidol University, Thailand

Dr. Hannah Davies Institute of Integrative Biology, University of Liverpool

Dr. Bill Chaudhry Institute of Genetic Medicine, Newcastle University

Dr. Ya Hua Chim School of Engineering, University of Liverpool

Dr. Colin Grant Hitachi High-Technologies Europe, Daresbury

Dr. Lucy Walton School of Health Sciences, University of Salford

Mr. Omar Nawaytou Liverpool Heart and Chest Hospital

Programme Booklet

The Aorta: From Structure to Rupture

17th July 2018, Mason Bibby Common Room, School of Engineering, University of Liverpool

Meeting Programme

9-9.30 AM Registration

9.30-9.35 AM *Welcome and Overview* (Dr Riaz Akhtar, University of Liverpool)

9.35-9.45 AM *School of Engineering and Biomedical Engineering* (Professor Ahmed Elsheikh, Dean of School of Engineering, University of Liverpool)

Session 1 – Aortic Aneurysms (Session Chair: Mr Mark Field, Liverpool Heart and Chest Hospital)

9.45-10.10 AM – *Ascending Aortic Aneurysms – A Surgeon's Perspective* (Mr Omar Nawaytou, Liverpool Heart and Chest Hospital)

10.10-10.35 AM – *The role of amyloid formation in thoracic aortic aneurysms* (Dr Hannah Davies, Institute of Integrative Biology, University of Liverpool)

10.35 – 11.00 AM – *Elastin degradation in ascending aortic aneurysms* (Dr Ya Hua Chim, School of Engineering, University of Liverpool)

11.00 – 11.30 AM Coffee Break and Refreshments

Session 2 – Vascular Nanomechanics and Imaging (Session Chair: Dr Riaz Akhtar)

11.30 - 11.55 AM – *The application of micro-CT and nanoindentation to discern the mechanisms of ageing and disease in arteries* (Dr Lucy Walton, Salford University)

11.55 – 12.20 PM – *AFM nanomechanics of porcine tunica adventitia* (Dr Colin Grant, Hitachi High-Technologies Europe, Daresbury)

12.20 – 12.45 PM - *Fast Digital Laser Sheet Microscopy for Vascular Applications* (Dr Bill Chaudhry, Cardiovascular Research Centre, Institute of Genetic Medicine, Institute of Genetic Medicine, Newcastle University)

12.45 – 13.45 Lunch and Poster Viewing

Session 3 – Aortic development, function and failure (Session Chair: Dr Bill Chaudhry)

13.45 – 14.10 PM – *Development of the aorta* (Professor Deborah Henderson, Cardiovascular Research Centre, Institute of Genetic Medicine, Institute of Genetic Medicine, Newcastle University)

14.10 – 14.35 PM – *Why aortic function matters: beyond blood pressure and other risk factors* (Professor Kennedy Cruickshank, King's College London; President of Artery Society).

14.35 – 15.00 PM – *Hemodynamics of Mechanical Circulatory Support* (Dr Phornphop Naiyanetr (Department of Biomedical Engineering, Mahidol University, Thailand)

15.00 – 15.30 PM Coffee Break and Refreshments

Session 4 – Orphan diseases and rare conditions (Session Chair: Prof. Kennedy Cruickshank)

15.30 – 15.55 PM – *Homotrimeric type I collagen mouse models of cardiac-valvular Ehler's Danlos syndrome and osteogenesis imperfecta* (Dr Liz Laird, Institute of Ageing and Chronic Disease, University of Liverpool)

15.55 – 16.20 PM - *Thoracic aortic aneurysms in Behcet's disease* (Professor Rob Moots, Institute of Ageing and Chronic Disease, University of Liverpool)

16.20 - 16.25 PM – *Closing remarks* (Dr Riaz Akhtar, University of Liverpool)

Abstracts

Only the names of the presenting authors have been included in the abstract booklet, not of all the contributing authors.

Ascending Aortic Aneurysms – A Surgeon's Perspective

Mr Omar Nawaytou, Liverpool Heart and Chest Hospital

Thoracic aortic aneurysms are life-threatening conditions. Surgery to replace aneurysmal sections of the aorta carries significant risk to life and therefore is indicated only when size reaches over 5cm. However evidence suggests some people present as emergencies with rupture or dissection when diameters are significantly less than 5cm. Key for the surgeon in the future will be to understand non-size dependent risks factors for an acute event thus allowing earlier surgery. This presentation will discuss aetiology of aortic aneurysms, current guidelines for Surgery, types of operations and finish with a discussion of innovations in non-size dependent variables and how the surgeon may include them in decision making.

The role of amyloid formation in thoracic aortic aneurysms

Dr Hannah Davies, Institute of Integrative Biology, University of Liverpool

The most common form of localised amyloid occurs in the aortic media (aortic medial amyloid; AMA) and is estimated to occur in 97% of Caucasian people above the age of 50. The pathological impact of AMA is unknown, but it is believed that extracellular amyloid accumulation contributes to age-related diminished elasticity of the vessels and that prefibrillar intermediates of medin may underlie the pathogenesis of sporadic thoracic aortic aneurysm. The main constituent of AMA is a 50 amino acid polypeptide medin, thought to be cleaved from milk fat globule protein 8 (MFG-E8). We will present data on the prevalence of AMA in our cohort of aneurysm patients and describe how we can classify sporadic aneurysm patients based on amyloid levels.

Elastin degradation in ascending aortic aneurysms

Dr Ya Hua Chim, School of Engineering, University of Liverpool

Current treatment for ascending aortic aneurysms is dependent on its size and growth rate. A better understanding of the causes of specific aneurysms is needed to develop therapeutic tools and appropriate clinical interventions. In this study, we combined experimental data from micromechanical, biochemical and histological tests, and statistical modelling to distinguish between specific ascending aortic aneurysms; bicuspid aortic valve with associated aneurysm (BAV) and idiopathic degenerative aneurysm (DA).

Aortic biopsies (n=30) were obtained from patients undergoing aneurysmal repair. Oscillatory nanoindentation was applied to the medial layer [1]. The same tissues were digested and quantified for collagen, elastin and glycosaminoglycan (GAG) levels using hydroxyproline, fastin elastin kit and 1-9 dimethylmethylene blue respectively. Elastic fibre numbers and length were measured from

Verhoeff-Van Gieson stained images. All measured data and patient clinical characteristics were analysed using least absolute shrinkage and selection operator (LASSO) regression.

Micromechanical properties of BAV tissue was found to be higher than DA tissue ($p<0.001$). A similar significant trend was also noted for GAG ($p=0.004$) and collagen levels ($p=0.02$). Although elastin levels were not significant, an increase in the number of long fibres was observed in BAV tissue ($p=0.02$). LASSO regression showed that micromechanical and elastin microstructural properties were unique predictors for BAV, whereas age, gender, collagen and aorta size were unique for DA. Our statistical approach is the first to show that specific ascending aortic aneurysms can be distinguished using novel in vitro measurements.

References:
1. Akhtar R., et al., (2018). *J Mater Res,* **33**(08) p873-883.

The application of micro-CT and nanoindentation to discern the mechanisms of ageing and disease in arteries

Dr Lucy Walton, Research Fellow, Diagnostic Imaging, University of Salford

Histological approaches are commonly utilised to describe and quantify alterations to tissue morphology during ageing and disease. The two-dimensional nature of histological approaches limit it's utility in furthering our understanding of the mechanisms of disease. In recent years improvements in CT detector capabilities have opened up new applications for Micro-CT to characterise the 3D structure of small tissue samples and organs. Many diseases are synonymous with alterations in the mechanical properties of tissues; Nanoindentation has emerged as a powerful tool to explore the quasi-static and dynamic properties of biological tissues. This talk describes the complementary application of micro-CT and Nanoindentation to better understand the relationship between tissue structure and function. We demonstrate that Micro-CT can be utilised to differentiate between sub-tissues layers of biological paraffin embedded tissues without staining; it can localise important arterial micro-structural features, for example the elastic lamellae (media) and collagen bundles (adventitia); and quantify the effects of acute (during loading) and long-term (during ageing) increases in blood pressure on arterial structure. Finally, we demonstrate the application of Nanoindentation to identify changes in the micro-stiffness (media and adventitia) and molecular structure of fibrillar collagen in rat arteries during ageing. Future work will include the development of 4D Micro-CT to characterise the real-time relationship between artery micro- structure and function in health and disease.

AFM nanomechanics of porcine tunica adventitia

Dr Colin Grant, Hitachi High-Technologies Europe, Daresbury

Tunica adventitia, the outer layer of blood vessels, is an important structural feature, predominantly consisting of collagen fibrils. This study uses pseudo-static atomic force microscopy (AFM) nanoindentation at physiological conditions to show that the distribution of indentation modulus and viscous creep for the tunica adventitia of porcine aorta and pulmonary artery are distinct. Dynamic nanoindentation demonstrates that the viscous dissipation of the tunica adventitia of the aorta is greater than the pulmonary artery. We suggest that this mechanical property of the aortic adventitia

is functionally advantageous due to the higher blood pressure within this vessel during the cardiac cycle. The effects on pulsatile deformation and dissipative energy losses are discussed.

Fast Digital Laser Sheet Microscopy for Vascular Applications

Dr Bill Chaudhry, Cardiovascular Research Centre, Institute of Genetic Medicine, Newcastle University

Localisation of gene expression is important in vascular biology and sub-cellular resolution over a wide field of view in living tissues is an aspirational goal. The 'hope and hype' of sheet-light microscopy will be discussed and practical details of how we image vascular tissue will be presented.

Development of the aorta

Prof. Deborah Henderson, Cardiovascular Research Centre, Institute of Genetic Medicine, Newcastle University

The aorta is a complex organ that is derived from several different progenitor populations in the early embryo. Whereas the descending aorta is formed from cells that originate in the forming somites, the ascending aorta develops as part of the outflow tract of the heart and has a more complex genesis. In mouse, the cells giving rise to the endocardial and epicardial layers of the distal outflow tract, that will form the arterial trunks, are derived from the second heart field (SHF). Neural crest cells (NCC) that have arisen from the neural tube then migrate to form a continuous layer of smooth muscle cells immediately below the endothelium of the early cardiac outflow tract. SHF-derived cells then add to form the outer layers of the media. As well as this patterning through the thickness of the arterial wall, there is also patterning along its length, with the aortic root being mostly SHF-derived and the aortic arch entirely arising from NCC. These patterns are maintained in the mature adult aorta and may have relevance in the linkage of congenital intracardiac malformations and diseases that affect the aorta, such as dilatation, aneurysm and atherosclerosis.

Why aortic function matters: beyond blood pressure and other risk factors'

Prof. Kennedy Cruickshank, Professor of `Cardiovascular Medicine & Diabetes King's College London;

President of Artery Society, 2016-18.

Arteries are central to larger animal life. Their universal, obvious yet clinically still neglected role is that, large and small, *their intact structure and function* are essential to supply oxygenated blood to every tissue, for (re-) growth over the entire life-course and in every clinical ailment or catastrophe. We now have a variety of non-invasive and ambulatory methods to measure arterial health, some precise but technically time-consuming and expensive, others ambulatory, accurate but still participant-dependent.

Remarkably, central aortic and now carotid status and their progressive stiffening over the life-course as measured by Pulse Wave Velocity (PWV) are more powerful indicators of cardiovascular prognosis and all-cause mortality than blood pressure (BP) and all other known 'standard' risk factors combined. PWV also depends on cardiac, that is ventricular-aortic, 'coupling'. As a direct index of arterial health, PWV is now an 'Intermediary Outcome' not a highly variable risk factor like BP.

This talk outlines the data supporting these points, some of the methods available to measure PWV and 'central' BP. Less understood but also prognostic is Augmentation, whereby forward and returning waveforms combine to 'augment' peripheral pressure/flow waves. Also covered are initial efforts to treat arterial stiffening directly but independently of the ambient BP required for fluid to flow through a tube.

Haemodynamics of Mechanical Circulatory Support

Dr Phornphop Naiyanetr (Department of Biomedical Engineering, Mahidol University, Thailand)

Nowadays, the number of patient with mechanical circulatory support (MCS) is increasing. Continuous-flow Left ventricular assist device (CF-LVAD) is one of the MCS systems that is used for end-stage heart fail patient. CF- LVAD is a device that unloads blood from the left ventricle and pumps blood to the aorta. During CF-LVAD support, the pulsatility of aortic pressure (systolic and diastolic pressures) changes depending on the support ratio. Increasing support ratio reduces an end-diastolic volume and increases the diastolic pressure. In case of partial support with aortic valve opening during the systolic phase, high pulsatility still remains. In case of full support without aortic valve opening, the effect of increasing of support ratio reduces the pulsatility. For long-term full support, reduction of pulsatility affects aortic wall structure by increasing wall stiffness and wall thickness. Therefore, full support may not usable for patients require a bridge to recovery and destination therapy, because the aortic wall structure is changed. In conclusion, high blood flow is still required for heart failure patients but it reduces pulsatility, which affects aortic property. Therefore, a novel control system for reducing the effect of full support should be developed for maintaining aortic property.

Homotrimeric type I collagen mouse models of cardiac-valvular Ehler's Danlos syndrome and osteogenesis imperfecta.

Dr Elizabeth G. Canty-Laird, Institute of Ageing and Chronic Disease, University of Liverpool

Type I collagen is the major structural component of tissues where it exists as heterotypic fibrils with other collagens. In the aorta type I collagen is present in the intimal, medial and adventitial layers but is most abundant in the adventitia. Type I collagen molecules are predominantly $(\alpha1)_2(\alpha2)_1$ heterotrimers derived from the polypeptide gene products of the COL1A1 and COL1A2 genes. However homotrimeric $(\alpha1)_3$ type I collagen has been linked to cardiovascular, musculoskeletal and fibrotic diseases. The 'oim' mouse model of osteogenesis imperfect contains solely homotrimeric type I collagen due to defects in the α2(I) collagen chain and has brittle bones, fragile skin, myxomatous valve disease and decreased strength of the descending thoracic aorta. Furthermore patients with osteogenesis imperfecta have an increased risk of cardiovascular disease. Humans with COL1A2 null mutations have Ehler's Danlos syndrome with aortic and/or mitral valve insufficiency and reports of aortic aneurisms. A true COL1A2 null mouse knockout has been generated as part of the knockout mouse project. Phenotyping data indicates no increased fracture risk but significant left ventricular hypertrophy. Current studies will address the hypothesis that collagen (I) homotrimer causes reduced cardiovascular integrity and that pathological accumulation of collagen (I) homotrimer contributes to cardiovascular disease.

Thoracic aortic aneurysms in Behçet's Syndrome

Professor Rob Moots, Institute of Ageing and Chronic Disease, University of Liverpool

Behçet's Syndrome (BS) is a serious multisystem autoinflammatory condition that is typified by recurrent oral and genital ulcers, often with skin and eye disease, but which can affect any organ from the brain down to the big toe. Whilst very rare in the UK, it is prevalent in the countries of the old "Silk Route", especially Turkey. In order to optimally diagnose and manage BS, three NHS National Centres of excellence were formed in 2012 in London, Birmingham and Liverpool. These Centres take referrals from the UK and abroad.

The full aetiology of BS is yet to be elucidated. There is a weak genetic susceptibility, with GVAS studies highlighting HLA-B51 and ERAP-1, but a large, as yet unknown, environmental component. The key pathophysiological feature of BS is vasculitis. This atypical for most vasculitides as it can not only affect any sized artery, but also veins.

Some patients with BS develop a predominately vascular form of disease, characterised by deep vein thromboses together with aneurysms in the aortic root and large pulmonary arteries. Undetected and untreated, this form of disease is often fatal, with life threatening haemorrhage as aneurysms rupture.