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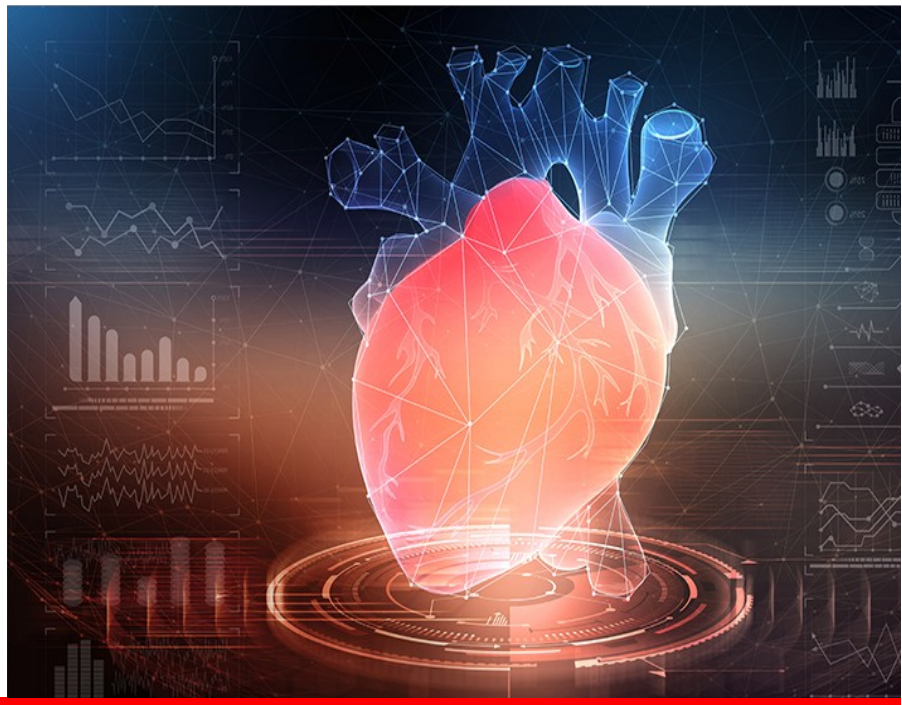
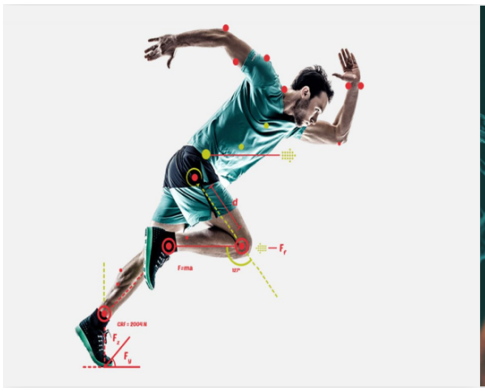


AORTA: FROM STRUCTURE TO RUPTURE 2019

2nd Annual meeting of the Liverpool Aortic Biomechanics and Biochemistry (LABB) Research Group

Programme

25th September 2019



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Programme Overview

Wednesday 25th September 2019

Hub Lounge, Foresight Centre, Brownlow Street, L69 3GL

09.00 - 09.30 Registration

09.30 - 09.35 *Welcome and Overview*
Dr Riaz Akhtar, University of Liverpool

09.35 - 09.45 *Cardiovascular Sciences and Medicine at Liverpool*
Professor Zarko Alfirevic, Pro-Vice- Chancellor for Clinical Research, University of Liverpool

09.45 - 10.00 *A patient perspective on Aortic research*
Gareth Owens, Aortic Dissection Awareness UK & Ireland

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

10.00 - 10.30 ***Inflammation Underlying Aortic Catastrophes***
Keynote Speaker - Professor John Pepper, Royal Brompton Hospital

10.30 - 10.50 *The role of Plasma Membrane Calcium ATPase 4 (PMCA4) as a regulator of pro-inflammatory signalling in human aortic endothelial cells*
Kinza Khan, University of Wolverhampton

10.50 - 11.20 Coffee Break and Refreshments

Session 2 – Aortic Imaging and Modelling (Session Chair: Professor Vanessa Diaz, UCL)

11.20 - 11.40 *Cardiovascular magnetic resonance imaging for diseases of the aorta*
Dr Tim Fairbairn, Liverpool Heart and Chest Hospital

11.40 - 12.00 *4D Flow MRI-based computational analysis of blood flow in patient-specific aortic dissection*
Dr Selene Pirola, Imperial College London

12.00 - 12.20 *Patient-specific modelling for treatment optimization and outcome prediction during aortic valve repair and root remodelling*
Mr Massimo Capoccia, University of Strathclyde and Royal Brompton and Harefield NHS Foundation Trust

12.20 - 13.20 Lunch and Poster Viewing

Session 3 – Novel approaches in aortic disease (Session Chair: Mr Omar Nawaytou, Liverpool Heart and Chest Hospital)

13.20 - 13.50 ***A decade of computational Modelling to Understand the Haemodynamics of Dissected Aortae - What have we learnt and where do we go from here?***
Keynote Speaker – Professor Vanessa Diaz, UCL

13.50 - 14.10 *Patients with mutations in MYLK: From gene structure to aortic rupture in the era of personalised genomic medicine*
Dr Victoria McKay, Liverpool Heart and Chest Hospital

14.10 - 14.30 *A multi-disciplinary approach to investigate underlying pathology in aortopathies*
Dr Jill Madine, University of Liverpool

14.30 - 14.50 *Exploring the utility of I-knife in aortic surgery and research*
Dr Hannah Davies, University of Liverpool

14.50 - 15.30 Coffee Break and Refreshments

Session 4 – Novel approaches in aortic disease (Session Chair: Dr Jill Madine, University of Liverpool)

15.30 - 15.50 *The difference faces of bicuspid aortic valves and their associated aortopathy*
Mr Omar Nawaytou, Liverpool Heart and Chest Hospital

15.50 - 16.10 *The unique nature of Bicuspid Aortic Valve aortopathy – from amyloid to elastin*
Dr Riaz Akhtar, University of Liverpool

16.10 - 16.20 *Closing remarks*
Mr Mark Field, Liverpool Heart and Chest Hospital

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Keynote Speakers

Professor John Pepper

Biography

Professor John Pepper was educated at Cambridge University and Guy's Hospital prior to his postgraduate training in cardiothoracic surgery at the National Heart Hospital, London Chest Hospital and Guy's. He was a consultant cardiothoracic surgeon at London Chest Hospital and St George's Hospital before moving to Royal Brompton Hospital. Professor Pepper is currently the interim director of research at the Trust. In June 2015, Professor Pepper was awarded an Order of the British Empire (OBE) for services to heart and lung surgery, in Her Majesty the Queen's birthday honours. Professor Pepper's clinical expertise includes diseases of the aortic valve and thoracic aorta. His current research activities are focused on the development of an external support, specific to the individual patient with Marfan Syndrome, the investigation of left ventricle remodelling in LVAD patients using micro-RNA technology, and the investigation of genes, networks and pathways in diseases of the thoracic aorta. Professor Pepper has contributed chapters to numerous books and is regularly published in peer-reviewed journals.

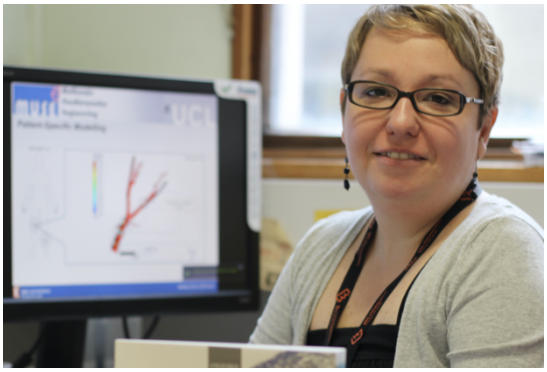
Abstract

Inflammation Underlying Aortic Catastrophes

Understanding and unravelling the pathophysiology of thoracic aortic aneurysm (TAA), a vascular disease with a potentially high mortality rate, is one of the major challenges in vascular biology. The processes leading to the formation of TAA, of unknown cause not due to genetic or inherited conditions, so-called degenerative TAA, are complex. There are promoters and inhibitors of the development of degenerative TAA. Promoters of TAA development include age, hypertension, increased pulse pressure, neuro-humoral factors increasing blood pressure and inflammation, specifically IFN-γ, IL-1β, IL-6, TNF-α and S100 A12; the coagulation system specifically plasmin, platelets, and thrombin as well as matrix metalloproteinases (MMPs). SMAD-2 signalling and specific micro-RNAs modulate TAA development. The major inhibitors or factors opposing TAA development are the constituents of the aortic wall (elastic lamellae, collagen, fibulins, fibronectin, proteoglycans, and vascular smooth muscle cells), which maintain normal aortic dimensions in the face of aortic wall stress, specific tissue MMP inhibitors, plasminogen activator inhibitor-1, protease nexin-1, and Syndecans. Increases in promoters and reductions in inhibitors expand the thoracic aorta leading to TAA formation.

Professor Vanessa Diaz

Biography



Professor Vanessa Diaz obtained her degree in Mechanical Engineering from University Simon Bolivar (Venezuela), where she was awarded her MEng degree with First Class Honours. She finished her PhD in Automatic Control and Industrial Informatics that she obtained with "Les Felicitations du Jury", from Ecole Centrale de Lille, France in 2003, her PhD work focused in lumped parameter models, simulation and optimization of cardiac dynamics. She was a Marie Curie Fellow (Intra-European Fellowship) from 2005 till 2007 in the Academic Unit of Medical Physics at the University of Sheffield. Vanessa was the scientific Coordinator of the "Virtual Physiological Human NoE" (www.vph-noe.eu) as well as the Principal Investigator of the EC funded (FP7) Marie Curie Initial Training Network "MeDDiCA" (www.meddica.eu) and the project "DISCIPULUS" (www.digital-patient.net). She currently holds an EPSRC grant (Personalised Medicine Through Learning in the Model Space) and a new Marie Curie ITN (VPH CaSE). Vanessa was awarded a prestigious Leverhulme Trust Senior Research Fellowship for 2015-2017 to work on the exploration of structural uncertainties in multiscale models using simulation.

Professor Vanessa Diaz leads the Multiscale Cardiovascular Engineering (MUSE) group at UCL in applying mathematical tools and engineering principles to understand cardiovascular pathophysiology, in what is known as 'patient-specific modelling'. Their group is focussed on developing tools and methods for concrete applications of multiscale cardiovascular engineering; trying to incorporate into these patient-specific models information about each individual patient that include imaging and different biomarkers, spanning different biological and timescales. They have pioneered work on the understanding and prediction of patient-specific vascular remodelling and complex aortic diseases, such as aortic dissections.

Abstract

A decade of computational Modelling to Understand the Haemodynamics of Dissected Aortae - What have we learnt and where do we go from here?

Aortic Dissections are amongst the most difficult conditions to treat for vascular surgeons. Each patient has a unique set of characteristics, making predictions, almost impossible even with best medical treatment. This is an area where modelling and simulation can offer much needed help. We are witnessing the dawn of haemodynamics-based predictions, reliant on patient-specific simulations. This area had developed at dizzying speed and tools have matured enough to become reliable and helpful. The question is: where next and how do we get there?

Oral Abstracts

A patient perspective on Aortic research

Gareth Owens[1]

[1]*Aortic Dissection Awareness UK & Ireland*

Gareth Owens is a survivor of aortic dissection and the chair of Aortic Dissection Awareness (UK & Ireland). Gareth will speak about the importance of aortic research from the perspective of the patient.

https://aorticdissectionawareness.org
https://thinkaorta.org

The role of Plasma Membrane Calcium ATPase 4 (PMCA4) as a regulator of pro-inflammatory signalling in human aortic endothelial cells

Kinza Khan[1], Miguel R Campanero[2,3], James M Cotton[4], Juan Miguel Redondo[3,5], Angel L Armesilla[1,3]

[1]*Cardiovascular Molecular Pharmacology Laboratory, School of Pharmacy, Research Institute in Healthcare Science, Faculty of Science and Engineering, University of Wolverhampton, Wolverhampton, UK;* [2]*Department of Cancer Biology, Instituto de Investigaciones Biomedicas Alberto Sols, CSIC-UAM, Madrid, 28029, Spain;* [3]*CIBERCV;* [4]*Department of Cardiology, Heart and Lung Centre, New Cross Hospital, Wolverhampton, UK;* [5]*Gene Regulation in Cardiovascular Remodelling and Inflammation Group, Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain*

Introduction: An Aortic Aneurysm (AA) is a multifactorial degenerative disease, characterised by focal dilatation of the aorta. Aneurysms affecting the abdominal region of the aorta, abdominal aortic aneurysm (AAA), have been linked to increased medial angiogenesis, extracellular matrix degradation, and chronic inflammation. We have recently identified the calcium transporter protein Plasma Membrane Calcium ATPase 4 (PMCA4) as a negative regulator of VEGF-induced angiogenesis. Angiogenesis involves degradation of the ECM, cell migration, and proliferation-processes aberrant in the wall of AAA aneurysm. We are investigating the role of PMCA4 in gene expression regulation in aortic endothelial cells treated with inducers of inflammation.
Results: Stimulation of human primary Aortic Endothelial Cells (AoEC) with the pro-inflammatory cytokineIL1β has revealed a time-and dose-dependent downregulation in PMCA4 expression at the RNA and protein levels. To determine the consequences of reduced PMCA4 expression in the aorta, we have analysed the expression of 84 genes related to ECM biology by gene array screening. si-RNA mediated knockdown of PMCA4in AoEC enhanced the IL1β-induced expression of ADAMTS1, and the basal expression of Selectins L and P. Conversely, ectopic expression of PMCA4 in AoEC by adenoviral infection, led to reduction in the expression of these genes.
Conclusion: AAA current treatment involves surveillance until the risk of rupture outweighs the risk of surgery. Understanding the molecular and cellular mechanisms implicated in aortic dilation and AAA progression will aid the design of efficient therapeutic strategies. Our results demonstrate that an inflammatory environment leads to downregulation ofPMCA4expression in AoEC. Reduction in PMCA4 levels results in increased expression of proteins related to ECM remodelling and cell adhesion in the aortic endothelium, suggesting an important role for PMCA4during the inflammatory processes linked to AAA progression.

Cardiovascular magnetic resonance imaging for diseases of the aorta

Dr Tim Fairbairn[1]

[1]*Liverpool Heart and Chest Hospital, Liverpool, UK*

Cardiovascular magnetic resonance imaging is used for the assessment and management of diseases of the aorta. It's unlimited field of view, lack of ionising radiation and multi-parametric imaging techniques make it an ideal tool for the long-term assessment of aortic disease structure and function. This talk focuses on how CMR can help diagnose, manage and provide prognostic information for clinician and patient alike.

4D Flow MRI-based computational analysis of blood flow in patient-specific aortic dissection

Dr Selene Pirola[1]

[1]*Imperial College London, London, UK*

Computational hemodynamics studies of aortic dissections usually combine patient-specific geometries with idealized or generic boundary conditions (BCs). A comprehensive methodology for patient-specific analysis of flow in type B aortic dissection (TBAD) based on fully patient-specific BCs will be presented. 4D flow magnetic resonance imaging (MRI) and Doppler-wire (DW) pressure measurements were acquired from a TBAD patient, and these data were used to derive boundary conditions for CFD modelling of flow pre-and post-thoracic endovascular repair (TEVAR). Validations of the computational results were performed by comparing predicted flow patterns with 4D flow MRI, as well as pressures with *in vivo* DW measurements. Pre-and post-TEVAR flow patterns were then compared to evaluate changes in hemodynamics after TEVAR. The obtained CFD results were in good qualitative and quantitative agreement with 4D flow MRI and DW measurements. Using the derived BCs the developed model correctly predicted the reduction of true-lumen pressure after TEVAR procedure, demonstrating that pre-TEVAR 4D flow MRI can be used to tune BCs for post-TEVAR hemodynamic analyses. The proposed methodology can also be applied to other TBAD geometries when anatomical images are the only available patient-specific data.

Patient-specific modelling for treatment optimization and outcome prediction during aortic valve repair and root remodelling

Massimo Capoccia[1,2], Soumik Pal[1], Michael Murphy[1], Cesare Quarto[1], Andreas Hoschtitzky[1], George Asimakopoulos[1], John Pepper[1], Ulrich Rosendahl[1]

[1]*Royal Brompton Hospital, London, UK;* [2]*University of Strathclyde, Glasgow, UK*

Aortic valve repair may be a suitable treatment in selected patients where echocardiographic and anatomical assessment remains critical for a successful outcome. The ventricular-aortic junction and the sino-tubular junction play a key role in normal valve function and both of them require attention during aortic valve repair. The choice of the technique remains operator-dependent and related to patient's suitability. We sought to review our experience in terms of choice of technique and attitude towards repair. Between May 2003 and April 2019, 56 patients (age range 18-82 years) underwent aortic valve repair either with commissural re-suspension or more advanced techniques (Yacoub's remodelling or David's procedure). The outcome has been analysed in terms of left ventricular function, left ventricular systolic and diastolic diameters, degree of residual aortic regurgitation and freedom from re-intervention. Our early experience has witnessed a preference of Yacoub's remodelling with a shift towards David's procedure in more recent years. Commissural re-suspension has been used in a limited manner. At follow up, 8 patients developed severe regurgitation requiring replacement; 4 of these patients had a known connective tissue disorder. An additional

patient required replacement in view of endocarditis. At present, 4 patients remain under surveillance in view of moderate aortic regurgitation. Again, two of them have a known connective tissue disorder. The choice of the surgical technique is often based on surgeon's preference and experience based on imaging assessment as part of preoperative planning, which remains of paramount importance. A more dynamic and quantitative assessment based on patient-specific modelling with structural and computational fluid dynamics evaluation may help choose the most suitable technique for each group of patients.

Patients with mutations in MYLK: From gene structure to aortic rupture in the era of personalised genomic medicine

Dr Victoria McKay[1]

[1]*Liverpool Centre for Genomic Medicine, Liverpool, UK*

The MYLK gene encodes the calcium-calmodulin dependent enzyme myosin light chain kinase (MLCK), which phosphorylates the regulatory light chain to initiate contraction in smooth muscle cells. A number of different isoforms of MLCK are produced by differential use of the 31 coding exons of the gene, but only one isoform is expressed in the thoracic aorta. Germline mutations are increasingly being detected in patients with hereditary aortic disease and aortic dissection, as this relatively newly discovered gene is included in more diagnostic gene panel tests. The clinical phenotype confers a high risk of early type A dissection or type B dissection with refractory labile hypertension. The age of onset of and likelihood of patients suffering a serious aortic event differs depending on the individual variant they carry. This is clinically challenging on a number of levels, as dissections in patients who carry pathogenic mutations happen at normal aortic dimensions, making imaging surveillance unreliable and optimal timing of surgical intervention difficult to predict. Understanding the function of this gene and the clinical phenotype in mutation carriers gives further insights into the complex genomic landscape of aortic dissection. It also highlights the importance of understanding genomic results at the variant level in order to apply results accurately to individuals and families in a clinical setting.

References:
Wallace, S.E., et al. *Genet. Med.* 21 (2019): 144–151.
Wang, L., et al. *Am. J. Hum. Genet.* 87 (2010): 701–707.
Watterson, D.M., et al. *J. Cell. Biochem.* 75 (1999): 481– 491.

A multi-disciplinary approach to investigate underlying pathology in aortopathies

Hannah A. Davies[1], Eva Caamaño-Gutiérrez[2], Ya Hua Chim[3], Mark Field[4], Omar Nawaytou[4], Riaz Akhtar[3], Jill Madine[1]

[1]*Institute of Integrative Biology, University of Liverpool, Liverpool, UK;* [2]*Computational Biology Facility, Technology Directorate, University of Liverpool, Liverpool, UK;* [3]*School of Engineering, University of Liverpool, Liverpool, UK;* [4]*Liverpool Heart and Chest Hospital, Liverpool, UK*

We have employed the expertise available within the Liverpool Aortic Biomechanics and Biochemistry (LABB) Research Group to explore the relationship between biochemical properties (collagen, elastin, glycosaminoglycans, matrix metalloproteinases) and micromechanical properties (shear storage modulus, G′ and shear loss modulus, G″) of the aortic wall in aneurysm and dissection patients. We also determined relative levels of aortic medial amyloid-related factors (medin, milk fat globule-EGF factor 8, oligomers and fibrils) to probe the importance of amyloid deposition within the medial layer. Statistical analyses combining all of these data identified key contributing factors and subgroups of patients with distinct characteristics. We now propose mechanisms for pathogenesis in our aortic patient cohorts for further investigation.

Exploring the utility of I-knife in aortic surgery and research

Hannah A Davies[1], Jos Harris[2], Mark Field[3], Omar Nawaytou[3], Jill Madine[1]

[1]Institute of Integrative Biology, University of Liverpool, Liverpool, UK; [2]Centre for proteome research, University of Liverpool, Liverpool, UK; [3]Liverpool Heart and Chest Hospital, Liverpool, UK

Rapid evaporative ionisation mass spectrometry or iknife is an emerging technology that allows rapid characterisation of biological samples with no need for sample preparation. The system comprises an electrosurgical knife coupled to a mass spectrometer, smoke from the vaporised tissue is sucked into the mass spectrometer and provides a rich source of information. Here we explore the potential of using the iknife technology during aortic surgery to provide real-time information to aid decision making. We have studied ex-vivo tissue from different aortopathies; i-knife can successfully distinguish different tissue types. Here we outline our data to date, next stages and clinical potential of this exciting technology.

The difference faces of bicuspid aortic valves and their associated aortopathy

Mr Omar Nawaytou[1]

[1]Liverpool Heart and Chest Hospital, Liverpool, UK

Bicuspid aortic valve disease is the commonest congenital cardiac disease affecting 1-2% of the population. Patients may also present with an associated aortopathy. Up until recently, bicuspid aortic valves and their associated aortopathy were grouped together as a single entity. This presentation will shed the light on the growing body of evidence differentiating different clusters of BAV disease and the clinical implications on valve and aortic repair.

The unique nature of Bicuspid Aortic Valve aortopathy – from amyloid to elastin

Ya Hua Chim[1], Hannah A. Davies[2], David Mason[2], Omar Nawaytou[3], Mark Field[3], Jill Madine[2], Riaz Akhtar[1]

[1]School of Engineering, University of Liverpool, Liverpool, UK; [2]Institute of Integrative Biology, University of Liverpool, Liverpool, UK; [3]Liverpool Heart and Chest Hospital, Liverpool, UK

Bicuspid aortic valve patients (BAV) are associated with increased risk of ascending aortic aneurysms. However, is unclear whether matrix degradation varies in different ascending aneurysm aetiologies. In this study, we combined micromechanical, biochemical and microstructural analysis to determine whether BAV-associated aneurysms (BAV-A) exhibit unique properties as compared to idiopathic degenerative aneurysm (DA) for the same aortic size. Aortic tissue was obtained from patients undergoing aneurysmal repair surgery (BAV-A; n=15 and DA; n=15). Coronary artery by-pass graft punch biopsies served as controls (CABG; n=9). The elastic modulus (E) was measured with nanoindentation for the medial layer. Glycosaminoglycan (GAG), collagen and elastin levels were measured using biochemical assays. Relative levels of aortic medial amyloid-related factors (medin, milk fat globule-EGF factor 8, oligomers and fibrils) were also determined. Verhoeff Van Gieson-stained sections were imaged for elastin microstructural quantification. BAV-A had a higher E relative to control and DA. There was no significance between DA and controls. Collagen level of BAV-A and DA were higher compared to the control. GAG and elastin levels were not significant between the groups. Amyloid was not found in BAV patients suggesting unique patterns of dilation relative to DA. Loss of tissue compliance was not related to elastin levels but to the microstructural arrangement of elastin fibres. Elastin segments were uniform in controls. Aneurysmal tissues had loss of segments close to the intima and adventitia layers. BAV had more elastin segments compacted in the medial layer whereas elastin segments were highly fragmented in DA.

In conclusion, BAV-A has increased stiffness within the aortic wall relative to DA and control tissue, and were protected from amyloid accumulation. The spatial distribution of elastin demonstrated a unique profile of matrix degradation for BAV-A. The findings of this work are important for the development of future clinical treatment of BAV-A treatment.

Poster Abstracts

Amyloid and idiopathic aortic aneurysm

Hannah A. Davies[1], Eva Caamaño-Gutiérrez[2], Ya Hua Chim[3], Mark Field[4], Omar Nawaytou[4], Riaz Akhtar[3], Jill Madine[1]

[1]Institute of Integrative Biology, University of Liverpool, Liverpool, UK; [2]Computational Biology Facility, Technology Directorate, University of Liverpool, Liverpool, UK; [3]School of Engineering, University of Liverpool, Liverpool, UK; [4]Liverpool Heart and Chest Hospital, Liverpool, UK

Objective: To explore the relationship of aortic medial amyloid with biochemical and biomechanical properties of the aortic wall in aneurysm patients.
Methods: Human aortic tissues removed during surgery from tricuspid (idiopathic degenerative aneurysm, DA) and bicuspid valve (BAV) patients were subjected to oscillatory nanoindentation experiments to was used to determine localised mechanical properties of the tissue (G′ and G″). Tissue was then digested or homogenised and biochemical testing carried out to determine amounts of collagen, elastin, matrix metalloproteinase 2 and glycosaminoglycans along with relative levels of aortic medial amyloid-related factors (medin, milk fat globule-EGF factor 8, oligomer and fibrils). Measurements were combined with clinical patient data and statistical analyses of hierarchical clustering, principal component analysis and univariate testing performed.
Results: Statistical analysis of the combined biomechanical and biochemical data showed that we can divide DA patients in our cohort into two groups based on their phenotype. One group shared similar biochemical and biomechanical characteristics with bicuspid valve syndrome patients therefore we termed them bicuspid like phenotype-tricuspid valve patients. The second group had high amyloid oligomer species present with significantly lower shear storage modulus (G′)(p=0.01), indicative of reduced elastic response of the tissue, termed amyloid-rich.
Conclusions: We have identified a group of DA patients where amyloid oligomers are a significant contributing factor through altering biomechanical heterogeneity of the vessel wall, in turn causing aneurysm formation. Amyloid is not associated with BAV patients, suggesting at least two distinct mechanisms for pathogenesis.

Nanomechanical and nanostructural properties of collagen in ascending aortic aneurysm

Ya Hua Chim[1], Hannah A. Davies[2], Mark Field[3], Jill Madine[2], Riaz Akhtar[1]

[1] School of Engineering, University of Liverpool, Liverpool, UK; [2] Institute of Integrative Biology, University of Liverpool, Liverpool, UK; [3] Liverpool Heart and Chest Hospital, Liverpool, UK

Introduction: Degradation of collagen is an important pathway related to aortic aneurysms. However, it is unclear whether collagen properties differ in different aneurysm aetiologies. Here, we measured the nanomechanical properties and characterised collagen fibres in the aortic tissue of two specific groups; bicuspid aortic valve with associated aneurysm (BAV-A) and idiopathic degenerative aneurysm (DA).
Methods: Aortic tissue was retrieved from 14 age-matched patients undergoing either BAV-A or DA aneurysmal repair. Atomic force microscopy (AFM) was used to characterise the collagen fibres within the medial layer; the elastic modulus (*E*) and deformation was obtained. Captured AFM images (n=4 per patient) were used to quantify the collagen fibres; the fibre diameter and collagen d-periodicity was measured.
Results: *E* of BAV-A was found to be significantly higher than DA (p=0.007). Expectedly, deformation was significantly lower in BAV-A relative to DA (p=0.01). DA was found to have larger collagen fibre diameter and d-periodicity compared to BAV-A. When the collagen properties were compared with *E*,

a positive correction was found in both aneurysmal tissues. However, when collagen diameter was correlated with deformation, opposite trends were observed for BAV-A and DA; negative and positive respectively.
Discussion: BAV-A tissue was significantly different to DA tissue, having shorter fibre properties and higher tissue stiffness. Interestingly, depending on the type of aneurysm the collagen fibre diameter correlates differently with its nanomechanical properties. These initial observations provide new insight to ascending aortic aneurysms.

Regional variations of biomechanical properties of the ovine aorta at the macro-and micro-scale correlation with in collagen, elastin and glycosaminoglycan levels

Phakakorn Panpho[1,4], Mark Field[2], Jill Madine[3], Riaz Akhtar[1]

[1]School of Engineering, University of Liverpool, Liverpool, UK; [2]Liverpool Heart and Chest Hospital, Liverpool, UK; [3]Institute of Integrative Biology, University of Liverpool, Liverpool, UK; [4]Faculty of Science and technology, Pibulsongkram Rajabhat University, Phitsanuloke, Thailand

Aortic diseases are a significant cardiovascular health problem and occurs in different ways across the vascular tree. Investigation of the mechanical properties of the aorta is important for better understanding of aortic diseases. While there have been previous studies examining the alterations in the macroscopic biomechanical behaviour and how they correlate well with regional microstructural changes, little is known about how these properties vary across its entire length. Our study presents maps the biomechanical properties (at the macro-scale via tensile testing and micro-scale via oscillatory nanoindentation and biochemical properties (Collagen, Elastin and GAG) along its entire length of the ovine aorta. Three ovine aortas were used for nanoindentation testing. For nanoindentation, the entire aorta was split into nine transverse sections. The aorta was divided into sections separated by 2 cm in length from the aortic root to the celiac artery region. Each of these sections were used to create three 5-millimeter circle biopsy punches for nanoindentation (a total of 81 biopsies). 16 oscillatory indentations were applied to the surface of the intimal and adventitia layer. Subsequently, the same samples were used to determine elastin, collagen and glycosaminoglycan (GAG) levels using established biochemical assays. Overall, our study found that there is a significant increase in macroscopic and micromechanical properties from the ascending aorta to the abdominal aorta. There was a significant correlation between an increase in G' ($P<0.0001$) and collagen ($P=0.001$) with distance from the aortic root whilst elastin ($P=0.001$) and GAG ($P=0.01$) levels were significantly decreased.

Biomechanics and biochemistry of the intimal flap in chronic dissection

Phakakorn Panpho[1,5], Ya Hua Chim[1], Hannah devies[2], Ying Yang[3], Mark Field[4], Jill Madine[2], Riaz Akhtar[1]

[1]School of Engineering, University of Liverpool, Liverpool, UK; [2]Institute of Integrative Biology, University of Liverpool, Liverpool, UK; [3]Institute for Science and technology in Medicine, Keele University, Keele, UK; [4]Liverpool Heart and Chest Hospital, Liverpool, UK; [5]Faculty of Science and technology, Pibulsongkram Rajabhat University, Phitsanuloke, Thailand

Background: Aortic dissection is a devastating condition, beginning with a tear through from intima to the medial layer, leading to splitting of aortic layers and creating the false and true lumen with a septum (or flap). The behaviour of the dissection flap is critical in determining surgical treatment and patient care. Understanding dissection flap architecture with time is a key as properties change it may affect the feasibility and success of stent graft interventions [1]. However, little is known about the properties of the dissection flap. Aim: To determine the time-dependent (creep) biomechanical behaviour and biochemical properties of the dissection flap.

Methods: 13 descending thoracic aorta samples were obtained from patients (mean age=53.0±13.5 years, ranges between 39-72 years old) undergoing elective surgery for chronic dissected aneurysms. Creep was measured using a non-destructive ball indentation technique [2, 3] utilising a stainless-steel ball over 5 hours. Images were obtained using a long focal distance objective microscope. Remaining tissues were used to determine elastin and glycosaminoglycan (GAG) levels.
Results: The elastic modulus (tissue stiffness) was 61.4± 13.6 kPa, 55.1 ± 9.5 kPa and 36.9±9.5for the flap, true and false aortic wall respectively. Over 5 hours, the central deformation of the flap tissue was found to be 0.55± 0.09mm as compared to 0.63± 0.04mm for the true aortic wall and 1.05±0.38 mm for false aortic wall (P=0.0024). Collagen levels were 43.0± 9.5 μg/mg for the flap and 84.6± 19.1 μg/mg for the false lumen (P=0.007). No significant in elastin levels, they were 98.1± 38.3 μg/mg for the flap and 74.2± 15.3 μg/mg for the false lumen. The GAG levels were 4.1 ± 0.6μg/mg for the flap 3.0±0.5 (p=0.05) for the true and 2.1±0.5 μg/mg (p=0.003) false lumen. When comparing the interval index of the dissection event to operation with central deformation, it was found that central deformation increased with the interval index.
Conclusion: The dissection flap exhibits reduced time-dependent deformation and has higher levels of elastin and GAG relative to the aortic wall. These findings may help develop bespoke surgical treatments based on the unique biomechanical and biochemical properties that have been identified.

References:
[1] Peterss, Sven, et al. *J. American college of Cardiology.* 68.10 (2016): 1054-1065.
[2] Weli, H. K., et al. *J. Obstetrics & Gynecology and Reproductive Biology* 214 (2017): 78-85.
[3] Ahearne, Mark, et al. *Journal of The Royal Society Interface* 2.5 (2005): 455-463.

Debunking the aortic myth: can fluid and material biomechanics allow us to predict acute aortic syndrome?

Xiao Yun Xu[1], Selene Pirola[1], Mohammad Yousuf Salmasi[2], Omar A. Jarral[2], Sumesh Sasidharan[3], Jennifer Frattolin[3], Jan-Lukas Robertus[4], James Moore Jr[3], John Pepper[4], Aung Oo[5], Thanos Athanasiou[2]

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Background: The most devastating complication of thoracic aortic aneurysmal disease (TAA) is acute aortic dissection. Current guidelines stratify the risk of AD based on diameter alone, despite evidence that AD often occurs below treatment thresholds. In order to move beyond diameter alone, our research group has developed a preliminary risk rupture prediction model based on image-based patient-specific computational fluid-dynamics (CFD) simulations which are guided by biomechanical testing of aortic specimens from each patient. We believe that this original approach may pave the way to predicting acute aortic syndrome.
Methods: Patients undergoing elective surgery for proximal aortic aneurysm at four different London centres (Harefield, Brompton, Barts, Hammersmith) were recruited. Redo surgery, bicuspid valves and connective tissue diseases were excluded. Patients underwent pre-operative 4D-flow MRI scans, which used to extract patient-specific geometries of the thoracic aorta (Mimics software). Blood flow parameters were measured using both computational fluid dynamics and directly from 4D-flow images. The explanted aneurysmal tissue was subjected to regional thickness measurement as well as uniaxial failure (longitudinal and circumferential directions) and delamination testing. Tests were conducted in a temperature-controlled aqueous environment, and verified using motion tracking technology. Tissue also was analysed histologically for aortic wall degradation in correlation with regions of interest from the biomechanical analysis.

Notes