The Aorta: From Structure to Rupture (2022)

Abstract Booklet

Friday 24th June 2022

Mason Bibby Common Room, 1st Floor, Harrison Hughes Building, School of Engineering

Organised by the Liverpool Aortic Biomechanics and Biochemistry (LABB) Research Group, University of Liverpool

Invited Speakers

Professor Gregory Lip

University of Liverpool

Biography

Professor Lip, MD, is Price-Evans Chair of Cardiovascular Medicine, at the University of Liverpool, UK – and Director of the Liverpool Centre for Cardiovascular Science at the University of Liverpool and Liverpool Heart & Chest Hospital. He is also Distinguished Professor at Aalborg University, Denmark; and Adjunct Professor at Seoul National University and Yonsei University, Seoul, Korea. Half of his time is spent as a clinical cardiologist, including outpatient clinics (leading large atrial fibrillation and hypertension specialist services) and acute cardiology.

Professor Lip has had a major interest into the epidemiology of atrial fibrillation (AF), as well as the pathophysiology of thromboembolism in this arrhythmia. Furthermore, he has been researching stroke and bleeding risk factors, and improvements in clinical risk stratification. The CHA2DS2-VASc and HAS-BLED scores - for assessing stroke and bleeding risk, respectively – were first proposed and independently validated following his research, and are now incorporated into international guidelines. His current group's research interests are broad, ranging from epidemiology to pathophysiology, translational research, clinical risk assessment and trajectories of risk, patient management pathways, and applied health research.

Professor John Elefteriades

Yale School of Medicine

Biography

Dr. John Elefteriades is the William W.L. Glenn Professor of Cardiothoracic Surgery and former Chief of Cardiothoracic Surgery at Yale University and Yale New-Haven Hospital. He has been among the most clinically active academic surgeons in the country.

He has performed all aspects of adult cardiac and thoracic surgery. He is a recognized authority in interventions for the failing left ventricle, including coronary artery bypass grafting, left ventricular aneurysmectomy, and artificial heart implantation. Dr. Elefteriades directs the Aortic Institute at Yale, one of the nation's largest facilities for treatment of the dilated thoracic aorta. He conducts laboratory research in new techniques of heart transplantation. Among his research projects, he is working to identify the genetic mutations responsible for thoracic aortic aneurysms.

Abstract (Session 1, Talk 2)

What to do with Variants of Unknown Significance (VUS) in Aortic Disease?

The advent of affordable Whole Exome Sequencing (WES) is revolutionizing aortic care. When a disease-causing mutation is found, we can apply a size criterion for intervention which is tailored to that particular mutation—a “bespoke” criterion, so to speak—permitting more precise, disease-specific decisions.

However, more often than not, WES identifies only a “Variant of Unknown Significance” (VUS)—meaning, a suspicious genetic “variant”—rather than a true “mutation” known to cause aortic disease. The American College of Medical Genetics and Genomics (ACMGG) has instituted onerous criteria that must be met for a variant to be classified as disease-causing. The ultimate proof of disease-causing status is for the phenotype (aneurysm disease) to correlate with the genotype (variant) over decades of observation of multiple generations.

This creates a naturel tension between the geneticist, who wishes to be scientifically totally accurate before calling a “variant” a “disease-causing mutation”. The surgeon, on the other hand, is charged with keeping the patient alive; she cannot wait for generations to indicate phenotype/genotype correspondence. The patient could easily be lost during that time.

Accordingly, methods have been established to grade the likelihood that a VUS is truly disease-causing: (1) Rarity of the gene in the general population. If the gene is common, it cannot be the cause of a relatively uncommon disease (thoracic aortic aneurysm). (2) Impact of the variant on “reading” of the genetic code. An allelic change that terminates or disrupts reading of the remainder of the gene is likely to be disease causing. (3) Preservation in phylogeny. A variant in an allele that is preserved deep down in the phylogenetic tree is likely to be disease causing. Assessment along these criteria can establish a variant as

"disease-causing" or "likely disease-causing"—enabling surgical treatment long before generations of observation could confirm phenotype/genotype correspondence.

We will discuss these complexities in interpretation of VUS in aortic disease.

We will also present our up-to-the minute work in modeling aortic VUS in zebrafish—a technique that promises to provide another discriminatory tool for clinical assessment of VUS in patient care.

Catherine Fowler & Richard Bonella

The Aortic Dissection Charitable Trust (TADCT)

Biography

Catherine Fowler

A relentless campaigner to improve diagnosis for aortic dissection following the loss of her father to an undiagnosed aortic dissection in 2015. Has appeared on national radio, television and at medical conferences throughout the UK, Ireland and Europe. Co-creator and former lead of a highly successful national campaign, which has been a catalyst for change in first responder and emergency medicine.

Richard Bonella

Richard is a survivor of type-A aortic dissection and has since worked closely with Catherine and the Aortic Dissection Charitable Trust, creating resources for the research advisory group. The TADCT talk will be given by both Catherin and Richard and will concern the work that this charity undertakes.

Abstract (Session 2, Talk 1)

"The Aortic Dissection Charitable Trust; Driving Research Together"

The Aortic Dissection Charitable Trust (TADCT) is the UK's first charity dedicated to aortic dissection. One of our charitable aims is the promotion of research into aortic dissection. TADCT launched in March 2021 and six months later we launched our Research Advisory Group (RAG)

The RAG is made up of 4 researchers and 4 aortic dissection survivors and relatives. It is supported by a research panel of over 250 dissection survivors, relatives and healthcare professionals.

Through the RAG the charity supports research proposals from endorsement through to providing patient and public members of research steering groups. In addition we have just closed applications for our first round of research grants.

Beyond this direct involvement in research we have been able to influence the national agenda for research. NIHR grant 21/585 Early Endovascular Repair in Type B Aortic Dissection was commissioned directly as a result of the influence on one of our trustees. And we expect further national research funding to become available as a result of lobbying by TADCT.

Dr Alexander Fletcher

University of Glasgow

Biography

Dr Fletcher is a Clinical Lecturer at the University of Glasgow. Currently a paediatric trainee, he is following an academic career in congenital heart disease. Research focus is using advanced imaging techniques to better understand mechanisms of disease in congenital heart disease, and translating these into usable clinical tools to improve the care these patients receive.

In 2018, Dr Fletcher was awarded a BHF clinical research training fellowship to investigate the role of microcalcification in identifying patients with high-risk thoracic aortopathy as part of a PhD at the University of Edinburgh. He set up and ran the AoRTAS clinical imaging study, as well as publishing in Circulation, European Heart Journal: Cardiovascular imaging, Journal of American College of Cardiology: cardiovascular imaging and Journal of Nuclear Cardiology, and won the Madeleine Steel young investigator award at British Congenital Cardiology Association national conference in 2021. Back in clinical training with dedicated research time, he continues to actively engage with projects related to thoracic aortopathy as well as other forms of congenital heart disease'

Abstract (Session 2, Talk 2)

"Microcalcification in Thoracic Aortopathy: a window into disease severity"

Objective: Patients with thoracic aortopathy are at increased risk of catastrophic aortic dissection, carrying with it substantial mortality and morbidity. Although granular medial calcinosis (medial microcalcification) has been associated with thoracic aortopathy, its relationship to disease severity has yet to be established.

Approach and Results: One hundred and one thoracic aortic specimens were collected from 57 patients with thoracic aortopathy and 18 control subjects. Standardized histopathological scores, immunohistochemistry and nanoindentation (tissue elastic modulus) were compared to the extent of microcalcification on von Kossa histology and 18F-sodium fluoride autoradiography.

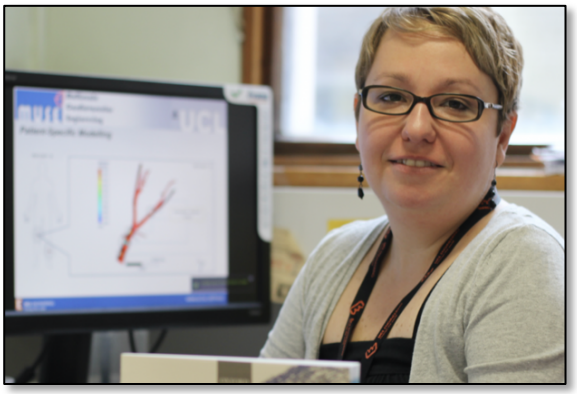
Microcalcification content was higher in thoracic aortopathy samples with mild (n=28; 6.17 [2.71 to 10.39], p≤0.00010) or moderate histopathological degeneration (n=30; 3.74 [0.87, to 11.80], p<0.042) compared with control samples (n=18, 0.79 [0.36 to 1.90]). Alkaline phosphatase (n=26, p=0.0019) and osteopontin (n=26, p=0.0045) staining were increased in tissue with early aortopathy. Increasingly severe histopathological degeneration was related to reduced microcalcification (n=82, Spearman's rho -0.51, p<0.0001), a process closely linked with elastin loss (n=82; Spearman's rho = -0.43, p<0.0001) and lower tissue elastic modulus (n=28; Spearman's rho = 0.43, p=0.026). 18F-Sodium fluoride autoradiography demonstrated very good correlation with histologically quantified microcalcification (n=66; r=0.76, p<0.001), and identified areas of focal weakness in vivo.

Conclusions: Medial microcalcification is a marker of aortopathy, although progression to severe aortopathy is associated with loss of both elastin fibers and microcalcification. 18F-Sodium fluoride positron emission tomography quantifies medial microcalcification and is a feasible non-invasive imaging modality for identifying aortic wall disruption with major translational promise.

Professor Vanessa Diaz

University College London

Biography



Professor Vanessa Diaz obtained her degree in Mechanical Engineering from University Simon Bolivar (Venezuela). 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. 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 and a new Marie Curie ITN (VPH CaSE).

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'.

Abstract (Session 3, Talk 1) – This oral presentation will be given virtually

"An Engineered-Power Vision to Enable Precision Vascular Surgery"

In this talk, we present a unique translational platform to enable precision vascular surgery (*VIRTUOSO*), combining state of the art *in vivo* imaging, *in silico* (simulation) tools and *in vitro* testing, in order to accurately quantify the haemodynamics of complex vascular pathologies, thereby informing individual treatment planning.
To demonstrate the potential of this technology -which is entirely generalisable to other (cardio) vascular pathologies-, we will use a complex and highly patient specific condition, chronic Type-B aortic dissection as an exemplar.
We will show how we use clinical data to build advanced patient-specific computational models of the pathology as well as 3D printed phantoms for experimental testing and validation on a unique and personalisable physical platform for haemodynamic testing, overcoming thus major obstacles for clinical and industrial translation.

Professor Xiao Yun Xu

Imperial College London

Biography

Xiao Yun Xu is a Professor of Biofluid Mechanics in the Department of Chemical Engineering at Imperial College London. She joined Imperial College in 1998 as a Lecturer, and became a full Professor in 2009. She received her BSc and MSc degrees in Thermo-Fluids Engineering from Dalian University of Technology in China, and her PhD in Mechanical Engineering from the City University, London. Her research interests include biomedical engineering and bioprocessing. She has established and led her research group to the cutting edge of multiscale and multi-physics modelling of transport processes in biological systems, with applications ranging from evaluations of endovascular interventional procedures for the treatment of aortic diseases to understanding of drug transport in solid tumours and thrombolytic therapies.

Abstract (Session 3, Talk 4)

"A virtual stent-graft deployment framework for application in aortic dissection"

Thoracic endovascular aortic repair (TEVAR) has become a standard treatment option for complicated type B aortic dissection (TBAD), but the stent-graft (SG) configuration after implantation and biomechanical interactions between the SG and local aorta are not available to clinicians when making pre-surgical decisions. It would be highly desirable to obtain such information via personalized computational simulation. To this end, we have developed a virtual SG deployment simulation framework for application in aortic dissection [1-3].

Our finite element model incorporates patient-specific anatomical information, details of SG design and hyperelastic behaviour of the aortic wall. Parametric models have been developed for a variety of SG products and finite element simulations are performed using Abaqus Explicit. The simulated post-TEVAR SG configurations have been validated against post-TEVAR CT scans, demonstrating good agreement in terms of local open area and stent strut position [2]. Moreover, virtual trials have been performed on patient-specific TBAD geometry with different SG products, as well as varying SG lengths and landing positions [3]. Our simulation results are promising and demonstrate the potential of using the virtual SG deployment model as a pre-surgical planning tool to help select the most appropriate SG product and size for TBAD patients.

<u>References</u>

[1] Yuan X, Kan X, Xu XY, Nienaber C. Finite element modelling to predict procedural success of TEVAR in type A aortic dissection. JTCVS Techniques 2020, doi:10.1016/j.xjtc.2020.10.006.

[2] Kan X, Ma T, Lin J, Wang L, Dong Z, Xu XY. Patient-specific simulation of stent-graft deployment in type B aortic dissection: model development and validation. Biomechanics and Modeling in Mechanobiology, 2021, doi: 10.1007/s10237-021-01504-x.

[3] Kan X, Ma T, Dong Z, Xu XY. Patient-specific virtual stent-graft deployment for type B aortic dissection: A pilot study of the effect of stent-graft length. Frontiers in Physiology 2021; doi: 10.3389/fphys.2021.718140.

Professor Kennedy J Cruickshank

Kings College London

Biography

Professor of Cardiovascular Medicine & Diabetes at King's College & consultant physician at St Thomas' & Guy's Hospitals, London since 2011, and previously in Manchester, UK. He was born & raised in Jamaica, with two 1y Lecturer & Senior Lecturer periods back in the University of the West Indies in Jamaica then Barbados.

After a Physiology BSc during medical school at Birmingham University, UK, clinical research there after MRCP, immunological work at Hammersmith/RPMS then epidemiological research training at the London School of Tropical Medicine, a Wellcome fellowship with Professor George Miller at the MRC Unit and Clinical Research Centre, Northwick Park, N-W London. That included work on HTLV-1 and spastic paraparesis between Caribbean migrants in London and family members in Jamaica, with 14 papers including a 35-pager in Brain 1989. His work on arterial function started then, later showing that arterial stiffness as pulse wave velocity is a more powerful index of prognosis than, and independent of, blood pressure (Circulation 2002).

Abstract (Session 4, Talk 1) – This oral presentation will be given virtually

"Arterial Stiffening measured as Pulse Wave Velocity and Patient Outcomes – State of the Art"

Arterial function measured non-invasively has become a powerful tool for direct measurement of general cardio-vascular risk, primarily as aortic or local carotid Pulse Wave Velocity (PWV). As an index of medial stiffening, PWV estimates cumulative replacement of aortic/ arterial wall elastin by collagen. Given excellent short-term repeatability, PWV's potential and the hypothesis for it is to replace measures of highly variable blood pressure (BP) in routine clinical practice. Several methods, some more demanding, measure PWV well – from original Doppler devices via the poorly-named carotid-femoral (cf)PWV by tonometry or ultrasound to cardiovascular MR imaging. Observational data now from over 90 studies conclusively show that aortic (a)PWV is the strongest clinical indicator of general prognosis (= patient outcome), independent of and usually displacing ambient BP (eg: 1, PMC4401072). Similarly, local carotid (c)PWV predicts brain outcomes better than and independently of ambient BP, whether stroke, cognitive decline or overt dementia [PMID: 2. 35168368; 3. 24583306; 4. PMC9108697].

The first randomised clinical trial (RCT), 'Sparte', testing the hypothesis above, showed encouraging results on slowing the usual rise of PWV over 4 years and improving outcomes [PMC8415523]. Many more, and innovative, RCTs are needed to show its transition from a risk index to a routine clinical measure by nurses, GPs and vascular physicians - and patients.

Reference examples:

1.Ben Shlomo Y et al, JACC 2014; 2 Vasan RS et al, Framingham, Hypertension 2022; 3.Van Sloten T et al, JACC 2014; 4. Li W et al, China w baPWV: Front CardioVasc Med 2022. 5. Laurent S et al; 'Sparte' trial; Hypertension 2021.

Abstract Booklet

Oral Presentations

"Exploring the relationship between neutrophils and aortic medial amyloid"

Session 2, Talk 3

Sarah Shirley [1,3,4], Helen L. Wright [2], David Wilkinson [2] and Jillian Madine [3,4]

[1] Liverpool Heart and Chest Hospital NHS Trust, Liverpool, UK [2] Institute of Life Course and Medical Sciences, Faculty of Health and Life Sciences, University of Liverpool, UK [3] Institute of Systems, Molecular and Integrative Biology, Faculty of Health and Life Sciences, University of Liverpool, UK [4] Liverpool Centre for Cardiovascular Science, Liverpool, UK

Misfolded proteins can aggregate to form insoluble amyloid fibrils and are associated with several diseases. Aortic medial amyloid accumulates in the elastic laminae as we age. Medin, the main protein component of aortic medial amyloid is asserted to be a cleavage product of milk fat globule-epidermal growth factor 8 (MFGE8). However, medin formation is not fully understood, nor is the pathological impact of the accumulation of amyloid protein within the aortic wall. In contrast, inflammation is increasingly believed to be important in the pathogenesis of aortic disease, particularly aortic dissection. Neutrophils, the first responders of the inflammatory response, are found within the aortic wall following dissection. Furthermore, preliminary investigations indicated that factors related to neutrophil biology and amyloid proteins may be associated. Therefore, we aimed to explore the relationship between MFGE8 cleavage, medin aggregation and neutrophils. Neutrophils isolated from healthy human controls (n=3) were stimulated with GM-CSF, fMLP and cytochalasin B to induce degranulation forming a neutrophil degranulation product (NDP). MFGE8 was incubated in the presence of the NDP and MFGE8 degradation products were assessed via gel electrophoresis. Additionally, medin monomers and fibrils were incubated with the NDP and the effect on aggregation/dis-aggregation was assessed using Thioflavin T (ThT) fluorescence and electron microscopy to evaluate and quantify fibril presence and morphology. Following incubation with NDP, MFGE8 showed time-dependent degradation. Incubation of medin monomers with the NDP prevented fibril formation. Interestingly, incubation of pre-formed medin fibrils with NDP for 48h induced re-modelling of the fibrils. These findings suggest a factor within the NDP may influence MFGE8 cleavage and alter medin aggregation. Work is underway to elucidate the mechanisms underlying this relationship.

"Reduced Micromechanical Stiffness of Large Diameter Abdominal Aortic Aneurysm (AAA) Wall Tissue"

Session 2, Talk 4

M. Hossack[1, 2, 3], R. Fisher[1], F. Torella[1], J. Madine[4], R. Akhtar[2, 3]

[1] Liverpool Vascular and Endovascular Service, Royal Liverpool Hospital, Liverpool, L7 8XP. [2] Department of Mechanical, Materials and Aerospace Engineering, School of Engineering, University of Liverpool, Liverpool, L69 3GH. [3] Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool, L69 7TX. [4] Institute of Systems, Molecular and Integrative Biology, University of Liverpool, L69 7BE.

Introduction: Use of a maximum diameter threshold as the sole indicator for aneurysm repair risks rupture during surveillance in higher-risk cases, and unnecessary repair in others. Efforts have been made to improve and personalise risk prediction. Here, we utilise nanoindentation, a high-resolution technique capable of measuring the material properties of vascular tissue non-destructively at an appropriate length-scale in order to characterise the micromechanical properties of aneurysmal aortic tissues with the aim of identifying high-risk cases and directing specific management.

Methods: Full thickness anterior aortic wall tissue samples were harvested from 16 patients undergoing repair of degenerative AAA. We probed the micromechanical properties using nanoindentation with a 100 μm flat punch tip, determining the shear storage modulus (G′) and loss modulus (G''). We performed 4-5 indentations in axial orientation on cross-sectional wall samples in 3 layers (inner, middle, outer) where possible. At least 4 samples were tested from each patient. In total, there were 102 samples (1269 indentations). We stratified micromechanical findings according to maximum transverse diameter (MTD), established through interrogation of pre-operative contrast-enhanced computerised tomography scans.

Results & Discussion: Aortic wall tissue demonstrated a pattern of significantly reducing stiffness from the inner to middle (median 31.5 kPa vs 24.4 kPa, $P<0.05$) and middle to outer layers (24.4 kPa vs 13.1 kPa, $P<0.05$). Wall stiffness increased as MTD increased from 50-59mm to 60-69mm (median 20.7 kPa vs 29.5 kPa, $P<0.05$). At 70-79mm, wall stiffness reduced (median 22 kPa, NS), and reduced further as MTD exceeded 80mm (median 19.6 kPa, $P<0.05$). The mechanical properties of vascular tissues depend largely on the extracellular matrix proteins elastin and collagen. AAA is characterised by elastolysis and a compensatory increase in collagen concentration to maintain vessel integrity. A reduced shear storage modulus observed in larger diameter aneurysms may indicate a failure in the compensatory collagen network, predisposing these aneurysms to rupture.

Conclusion: This micromechanical approach has demonstrated that at higher MTD, AAA wall becomes less stiff. This may indicate a failure of the compensatory collagen network resulting in a higher risk of rupture at larger diameters. Further studies are needed to correlate aortic micro-stiffness with vessel wall biochemistry, histology and clinical presentation, in order to identify individuals with high risk AAA.

“The haemodynamic impact of segmental arteries in type-b aortic dissection: a patient-specific study informed by 4D flow MRI”

Session 3, Talk 2

This oral presentation will be given virtually

Catriona Stokes [1], Fabian Haupt [2], Daniel Becker [3], Vivek Muthurangu [4], Hendrik Tengg von-Kobligk [2], Stavroula Balabani [1], Vanessa Diaz- Zuccarini [1]

[1] Department of Mechanical Engineering, University College London, United Kingdom; [2] Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, University of Bern, Switzerland [3] Clinic of Vascular Surgery, Inselspital, University of Bern, Switzerland [4] Centre for Translational Cardiovascular Imaging, University College London, United Kingdom

Segmental arteries (SAs) branch from the posterior descending aorta. Although small, about 1.5mm in diameter (1), 4D Flow MRI (4DMR) data indicates that they may accept up to 10% of cardiac output (2). Typically neglected in aortic flow simulations, it is not yet understood how the inclusion of SAs affects clinically relevant haemodynamic metrics such as Wall Shear Stress (WSS) and False Lumen (FL) pressure in the case of Aortic Dissection (AD). This understanding is critical if simulations are to be used in a clinical context. Our work demonstrates the very first in-silico assessment of a patient-specific human aorta with all pairs of SAs, along with patient-specific boundary conditions informed by 4DMR. It is the first study of this kind in an AD patient.

In two equivalent patient-specific simulations with and without SAs, the inclusion of the SAs reduced (FL) pressure by 1.5 mmHg and led to elevations of instantaneous WSS in regions surrounding each segmental bifurcation. When the SAs were included, their associated flow loss meant that WSS was also reduced in the abdominal aortic branches.

Our results demonstrate notable differences in pressure and WSS distributions when SAs are included, which may impact the clinical conclusions made from simulations. Considering these results, segmental flow loss should be considered in future haemodynamic studies of the aorta, particularly in AD patients where metrics such as FL pressure are of clinical importance.

References

[1] Jacques et. al., Ann Thorac Surg (1993) 56:1078-81

[2] Stokes et. al., J. Biomech (2021) Vol. 129; 110793

“Compliant Pre/Post-Op Patient-Specific CFD Simulations Informed by Routine TBAD Clinical Data”

Session 3, Talk 3

This oral presentation will be given virtually

Louis Girardin [1], Prof.Vanessa Diaz [1], Prof Stavroula Balabani [1], Prof Aung OO [2]

[1] University College London, [2] Barts Hospital

This study presents a compliant patient-specific Type-B Aortic Dissection (TBAD) follow-up method accounting for wall movement in a complex Aortic Dissection using non-invasive pre-and post-surgery clinical data. It is a new application of the Moving Boundary Method (MBM) [1] by considering a graft in the post-op simulation.

The dataset was provided by the Aortovascular surgery department at St. Bartholomew’s Hospital (London, UK). Non-invasive brachial pressure measurements, heart rate, one plane of 2D flow MR and Cine MR were acquired pre-surgery: CT scans were acquired for the post-op simulations.

Segmentation was performed on CT scans using Scan IP (Synopsis Simpleware). Brachial blood pressure measurements and one plane of 2D flow MRI informed the three-element Windkessel outlet boundary conditions; the 2D flow MR was used to get the inlet velocity profile. Cine MRIs were used to implement the MBM. Transient CFD simulations were performed using ANSYS-CFX (ANSYS Inc.)

Simulations were validated against the flow MR plane for the velocity; the targeted outlets’ flow split was obtained. Inlet systolic and diastolic pressures were obtained within 5% of brachial measurements. The MBM was successfully implemented using two different bodies (aorta, graft) with different stiffness.

This work states a new application of the MBM for compliant TBAD study. Future work includes the comparison of the in-silico calculations with patient-specific in-vitro measurements obtained in state-ofthe-art hemodynamic emulator and used for virtual prototyping.

This work is supported by the BHF Grant (VIRTUOSO) (NH/20/1/34705) as well as the Department of Mechanical Engineering UCL.

References

[1] M. Bonfanti et al.,2017.

“Vascular dysfunction in hard to manage hypertension”

Session 4, Talk 2

Reem Alsharari [1,2], G Neil Thomas [1], Gregory Y. H. Lip [2], Alena Shantsila [2]

[1] University of Birmingham [2] Liverpool Centre for Cardiovascular Science, University of Liverpool

Background: Hard to manage forms of hypertension, resistant hypertension (RH) and malignant hypertension (MHT) remain a clinical challenge with poor prognosis. Their mechanisms are poorly understood. Abnormal vascular function may play a role, but scare evidence exist. The study aims to address this gap in knowledge.

Methods: We have compared three groups of participants, matched by age and body surface area: 23 had RH (age 57±11 years), 18 MHT patients (age 54±13 years), and 23 normotensive controls (NC) (age 50±5 years). Non-invasive assessment of carotid-femoral pulse wave velocity (cf-PWV) and augmentation index (AIx) was done using Vicorder device. Endothelial function was assessed by brachial artery flow mediated dilatation (FMD) using a real-time ultrasonographic edge detection technique.

Results: Office and central blood pressures were elevated in MHT and RH groups ($p<0.05$ vs. NC). cfPWV was increased in MHT and RH compared to NC ($p<0.05$); but no difference observed in AIx between the groups ($p=0.20$). FMD was markedly imparted in the hypertensive groups (RH: 5.45±2.56% and MHT:5.97±2.58% vs. NC: 9.96±2.59%, all $p<0.001$). There was no difference in FMD between MHT and RH ($p=0.8$). MHT and RH patients use similar antihypertensives, except more diuretics in RH (100% vs. 67% in MHT). On linear regression, independent predictors of high PWV, were advanced age, increased office systolic blood pressure and longer history of hypertension ($p<0.02$).

Conclusions: Patients with RH and MHT have impaired endothelial function and increased arterial stiffness. These abnormalities may both contributed to pathophysiology and poor outcome in RH and MHT.

"The PMCA4 calcium transporter and endothelial activation"

Session 4, Talk 3

Kinza Khan [1] Juan Miguel Redondo[2][3] James M Cotton [4] 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] Gene Regulation in Cardiovascular Remodelling and Inflammation Group, Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain [3] Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain [4] Department of Cardiology, Heart and Lung Centre, New Cross Hospital, Wolverhampton, UK

Aims: The inflammatory response relies on the well-coordinated trafficking of leukocytes across the endothelium to sites of tissue injury. Proinflammatory cytokines reorganise the endothelial cell surface to capture circulating leukocytes. The selectin family of cell adhesion molecules mediate the initial adhesive interactions while members of the Ig superfamily such as VCAM-1 mediate firm adhesion and subsequent trans-endothelial migration. Immune cell infiltration is often involved in the initiation and progression of vascular diseases, including abdominal aortic aneurysms. Thus, there is a requirement to resolve endothelial cell inflammation.

Emerging evidence suggests that the PMCA4 Ca2+ transporter regulates signal transduction in the endothelium. Here, we investigate the calcium pump in inflammation of the aortic endothelium and characterise its role in leukocyte adhesion and trafficking.

Methods and Results: IL-1β downregulates the expression of PMCA4 in Aortic Endothelial Cells (hAoEC). The effect of PMCA4 downregulation in IL-1β-mediated gene expression in hAoEC was evaluated through RNA-sequencing and a PCR-based gene array. siRNA-mediated PMCA4 knockdown induced Selectin P (SELP) and SELL expression while enhancing the IL-1 -induced metalloproteinases ADAMTS-1 and -4. Ingenuity pathway analysis (IPA) revealed a role in immune cell trafficking with a propensity to develop aneurysms. Consistent with the IPA, a significant decrease in PMCA4 mRNA expression was determined in abdominal aortic lesions from hypercholesterolaemic angiotensin II infused ApoEdeficient mice.

Conclusion: The downregulation of PMCA4 is associated with a state of endothelial activation, indicated by the induction of cell adhesion molecules. Our findings suggest that PMCA4 is involved in the process of leukocyte adhesion and diapedesis.

Poster Presentations

P1: "Diagnostic and prognostic biomarkers for abdominal aortic aneurysm – a scoping review"

Esther Omotoso [1] and Handy Hamdallah [2]

[1] Royal Preston Hospital, Lancashire Teaching Hospitals NHS Trust [2] Chester Medical School, University of Chester

Background: There are different imaging methods used in diagnosing and monitoring AAA; these methods are not always feasible due to differences in patients' features and the inability of these methods to determine the risk of rupture of AAA.

Aim: To identify diagnostic or prognostic biomarkers for AAA, identify the gap in each selected outcome, and the influence of each gap on using biomarkers for diagnosing or determining the prognosis of AAA.

Method: PubMed and CINACL were searched to retrieve relevant articles with open access. The outcomes reviewed were study design, gender, and the common biomarkers mentioned in the selected articles.

Results: 14 articles were included in this review. 9 studies used case-control study; 10 studies included both men and women in the study population, and about 52 biomarkers were identified for the diagnosis or prognosis of AAA. Only MMP9 and MPO were common in 3 different studies. The 3 studies demonstrated a significant increase in the level of MMP9 in patients with AAA while only one study reported area under the curve (AUC), sensitivity, and specificity of 0.69, 50% and 88%, respectively. The level of MPO was shown to be significantly higher in AAA patients compared to non-AAA patients with a study demonstrating AUC of 0.816 ($r = 0.391$; $p = 0.013$), and another study demonstrating diagnostic potential for AAA with AUC of 0.64 (95% CI: 0.58-0.71; $p<0.001$) and prognostic value for AAA with AUC of 0.71 (95% CI: 0.61-0.81; $p<0.001$), sensitivity of 80% and specificity of 59%.

Conclusion: To determine the diagnostic and prognostic biomarkers for AAA, case-control and prospective cohort studies should be used. Although AAA is more common in men, there has been a similar increase in the incidence of AAA in both genders and the rate of mortality and hospital admissions is higher in women than men. The AUC, sensitivity and specificity reported are inadequate to use either MMP9 or MPO as a diagnostic or prognostic marker for AAA. These gaps have made it impossible to use a specific biomarker to diagnose and determine the prognosis of AAA.

P2: "Arterial stiffness and atrial fibrillation: shared mechanisms, clinical implications and therapeutic options"

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Arterial stiffness (AS) and atrial fibrillation (AF) share commonalities in molecular and pathophysiological mechanisms and numerous studies have analyzed their reciprocal influence. The gold standard for AS diagnosis is represented by aortic pulse wave velocity, whose measurement can be affected by arrhythmias characterized by irregularities in heart rhythm, such as AF. Growing evidence show that patients with AS are at high risk of AF development. Moreover, the subset of AF patients with AS seems to be more symptomatic and rhythm control strategies are less effective in this population. Reducing AS through de-stiffening interventions may be beneficial for patients with AF and can be a new appealing target for the holistic approach of AF management.

In this review we discuss the association between AS and AF, with particular interest in shared mechanisms, clinical implications and therapeutic options.

P3: "Thoracic Aortic Aneurysm and Atrial Fibrillation: Clinical associations with the risk of stroke from a global federated health network analysis"

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Background: An association with aortic aneurysm has been reported among patients with atrial fibrillation (AF). The aims of this study were to investigate the prevalence of thoracic aorta aneurysm (TAA) among patients with AF and to assess whether the co-presence of TAA is associated with a higher risk of adverse clinical outcomes. Methods and Results: Using TriNetX, a global federated health research network of anonymised electronic medical records, all adult patients with AF, were categorised into two groups based on the presence of AF and TAA or AF alone. Between 1 January 2017 and 1 January 2019, 874,212 people aged ≥18 years with AF were identified. Of these 17,806 (2.04%) had a TAA. After propensity score matching (PSM), 17,805 patients were included in each of the two cohorts. During the 3 years of follow-up, 3,079 (17.3%) AF patients with TAA and 2,772 (15.6%) patients with AF alone, developed an ischemic stroke or transient ischaemic attack (TIA). The risk of ischemic stroke/TIA was significantly higher in patients with AF and TAA (HR 1.09, 95% CI 1.04- 1.15; log-rank p-value <0.001).

The risk of major bleeding was higher in patients with AF and TAA (OR 1.07, 95% CI 1.01-1.14), but not significant in time-dependent analysis (HR 1.04, 95% CI 0.98-1.10; log-rank p-value = 0.187), Conclusion: This retrospective analysis reports a clinical concomitance of the two medical conditions, and shows in a PSM analysis an increased risk of ischemic events in patients affected by TAA and AF compared to AF alone.

P4: "Vascular dysfunction in hard to manage hypertension"

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Background: Hard to manage forms of hypertension, resistant hypertension (RH) and malignant hypertension (MHT) remain a clinical challenge with poor prognosis. Their mechanisms are poorly understood. Abnormal vascular function may play a role, but scare evidence exist. The study aims to address this gap in knowledge.

Methods: We have compared three groups of participants, matched by age and body surface area: 23 had RH (age 57±11 years), 18 MHT patients (age 54±13 years), and 23 normotensive controls (NC) (age 50±5 years). Non-invasive assessment of carotid-femoral pulse wave velocity (cf-PWV) and augmentation index (AIx) was done using Vicorder device. Endothelial function was assessed by brachial artery flow mediated dilatation (FMD) using a real-time ultrasonographic edge detection technique.

Results: Office and central blood pressures were elevated in MHT and RH groups ($p<0.05$ vs. NC). cfPWV was increased in MHT and RH compared to NC ($p<0.05$) but no difference observed in AIx between the groups ($p=0.20$). FMD was markedly imparted in the hypertensive groups (RH: 5.45±2.56% and MHT:5.97±2.58% vs. NC: 9.96±2.59%, all $p<0.01$) There was no difference in FMD between MHT and RH ($p=0.8$). MHT and RH patients use similar antihypertensives, except more diuretics in RH (100% vs. 67% in MHT). On linear regression, independent predictors of high PWV, were advanced age, increased office systolic blood pressure and longer history of hypertension ($p<0.02$).

Conclusions: Patients with RH and MHT have impaired endothelial function and increased arterial stiffness. These abnormalities may both contributed to pathophysiology and poor outcome in RH and MHT.

P5: "Patient-specific modelling of a complicated type-B aortic dissection; a proof-of-concept study on pre/postoperative cases of an AD patient"

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Aortic Dissection (AD) is a complicated vascular wall dysfunction [1] in the biggest arterial vessel inside the body. As a result, the main lumen is resected along the intimal layer, and it splits the main conduit of aorta into the true and false lumens. In contrast with type-A AD, which requires an emergency measure, type-B dissection usually affects the descending aorta and gives more time to plan for the treatment. Computational modelling of haemodynamic parameters in AD is one of the innovative approaches to propose optimised solutions by improving the treatment outcome and reducing associated costs and number of interventions. In this study a complicated case of type-B AD patient is simulated pre- and post-operatively. Engraftments at the ascending aorta, descending aorta and aortic arch aneurysm are the major features of the pre-operative case, which was subsequently treated through another engraftment at the descending thoracic aorta. The current in-silico modelling aims to address the following goals: (i) a proof-of-concept study for evaluating the developed pipeline for the personalised medicine, (ii) demonstrating haemodynamic changes because of stent engraftment, and finally (iii) proposing the best treatment method through virtual surgery of diseased aorta.

References

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