Aorta: Structure to Rupture (2024)

Abstract Booklet

Thursday 20th June 2024

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

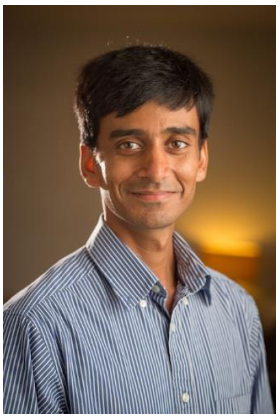
Organised by the Liverpool Aortic Biomechanics and Biochemistry (LABB) Research Group, University of Liverpool

Invited speakers

Dr. Ankush Aggarwal

University of Glasgow

Biography



Dr.Ankush Aggarwal is a Senior Lecturer in Engineering and a member of the Glasgow Computational Engineering Centre (GCEC) at the University of Glasgow. He works in the area of computational biomechanics with application to cardiovascular healthcare. He started his college education at the Indian Institute of Technology, Kharagpur and studied Aerospace Engineering. From there, he moved to the University of California, Los Angeles and obtained a PhD in Mechanical Engineering with a minor in Applied Mathematics. Afterwards, he worked as a postdoctoral fellow at the Center for Cardiovascular Simulation (CCS), part of ICES, at the University of Texas at Austin. Before joining University of Glasgow, he was a National Research Network Fellow at the Zienkiewicz Centre for Computational Engineering (ZCCE), Swansea University for three years.

Abstract (Session 1, Talk 1)

Biomechanical Analysis of Aortic Roots: Differences Between Tricuspid and Bicuspid Aortic Valve Patients

Aortic root connects the left ventricle to the ascending aorta and houses the aortic valve (AV) ensuring one- direction flow of blood during systole. The AV is normally composed of three leaflets, known as tricuspid aortic valve (TAV), but 1-2% of the population is born with only two leaflets, known as bicuspid aortic valve (BAV). The patients with BAV are considered at high risk of developing aneurysms and eventually dissection. The biomechanics of aortic root tissues are hypothesized to play an important role in the disease development. In this study, we use in-vivo echocardiographic images from TAV and BAV patients to analyze the differences in the biomechanics of aortic root tissues.

3D transesophageal echocardiographic (TEE) images of the aortic root were retrospectively acquired from 16 patients with the approval of the Institutional Review Board at the University of Pennsylvania. The images were segmented, registered, and converted into a medial model as presented in a previous study [1]. The medial models were remeshed with an quadrilateral elements. Two methods were used for the biomechanical analysis: 1) patient-specific 3D inverse finite element (FE) modeling, and 2) population-level Bayesian inference based on radius variations.

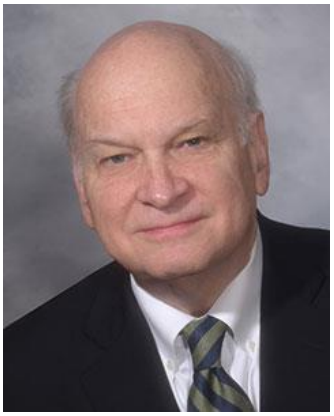
Higher regional strains were found in patients with BAV, which could be related to their higher risk of developing aneurysms. Similarly, higher stresses were found in patients with BAV. However, somewhat surprisingly, the differences in the biomechanical properties of the aortic tissue were not found to be statistically different. The results suggest the inherent biomechanical differences might be caused by geometry, rather than the tissue. The geometrical differences include more prominent sinuses in TAV patients and lower tissue thickness in BAV patients.

This study provides valuable information regarding in-vivo biomechanical properties of aortic roots and related differences between TAV and BAV patients. The findings suggest that even before the aneurysms develop, the BAV patients experience higher strains and stresses in their roots, which could be related to the higher risk of aneurysm development.

Professor Duke Cameron

The Johns Hopkins Hospital, Baltimore, USA

Biography



Duke Cameron, M.D. is a cardiothoracic surgeon in Baltimore, MD. He is a professor of surgery at the Johns Hopkins School of Medicine. Dr. Cameron is world-renowned for his expertise in the surgical repair of the aorta. He is internationally recognized for his contributions to cardiac surgery, particularly aortic surgery for Marfan syndrome, Loeys-Dietz syndrome and other connective tissue disorders. He also specializes in mitral valve repair and adult congenital heart disease. His multiple academic contributions span the breadth of pediatric and adult cardiac surgery. Dr. Cameron is a graduate of Harvard College and Yale Medical School. He completed his general surgery training at Yale-New Haven Hospital and his cardiothoracic fellowship training at the Johns Hopkins Hospital. After his training, he remained on the faculty at Johns Hopkins. Dr. Cameron most recently served on staff at Massachusetts General Hospital before returning to Johns Hopkins.

Abstract (Session 2, Talk 2)

Loeys-Dietz syndrome: What have we learned in 20 years?

Loeys-Dietz syndrome is an inherited connective tissue disorder with an aortopathy that predisposes to aortic dissection and rupture at an earlier age and smaller diameter than other connective tissue disorders. It was first described by the geneticists Bart Loeys and Hal Dietz at Johns Hopkins Hospital in 2005, after a serendipidous coincidence of several young patients seen in clinic to rule out Marfan syndrome. Three distinctive features (bifid uvula, hypertelorism, and proximal aortic aneurysm with tortuosity) were recognized, as well as autosomal dominant inheritance and other features often seen in Marfan syndrome. The initial paper suggested that mutations in the receptor for the cytokine transforming growth factor beta (TGF-b) were responsible for the important features of the syndrome. Two clinical subtypes were identified; type I had prominent craniofacial features such as cleft palate/craniosynostosis and/or hypertelorism while type II did not, but had skin and ocular characteristics (bluish whites of the eyes and thin bluish skin) similar to Ehlers-Danlos syndrome. Currently, 6 subtypes types have been identified, with some resulting from SMAD mutations rather than TGF-b receptor mutations. Early clinical recognition of affected individuals is facilitated by family history and a characteristic phenotype. Confirmation of the diagnosis is possible with genetic testing. Angiotensin receptor blockers (ARBs) and beta blockers form the basis of medical therapy, and early surgical replacement of the aortic root and proximal aorta are key to preventing aortic catastrophe. A high rate of reoperations and distal aortic and aortic branch complications characterize the long-term results. Lessons learned in the last two decades include: a high degree of heterogeneity in severity of aortic disease that was not appreciated in the early experience, extraordinary virulence of some specific mutations, the success of aortic valve sparing procedures, and the need for meticulous lifetime surveillance for late vascular complications.

Catherine Fowler

The Aortic Dissection Charitable Trust (TADCT)

Biography

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.

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.
Catherine Fowler will give an overview of The Aortic Dissection Charitable Trust's support for research. Kirsty and Valerie will describe how their lived experience supports front line research.

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 3, Talk 1)

Identifying high risk thoracic aortopathy in bicuspid aortic valve: the AoRTAS study

In patients with bicuspid aortic valve, the majority of aortic dissections occur below aortic diameter thresholds that trigger prophylactic surgical repair. There is therefore an urgent unmet need to develop novel methods for better risk stratification. In thoracic aortopathy, vascular smooth muscle cell stress and extracellular matrix remodelling results in microscopic calcification deposition on elastin fibres which later disappears with loss of elastic fibres. We aimed to establish whether positron emission tomography (PET) using [18]F-sodium fluoride – a radiotracer than binds to vascular microscopic calcification - could detect high-risk patients who may benefit from early surgery.

In a prospective cohort imaging study, patients across Scotland diagnosed with bicuspid aortic valve and age- and sex-matched control volunteers underwent baseline hybrid PET-CT (Biograph mCT, Siemens) followed immediately by PET-MRI (3.0T Biograph mMR, Siemens) after injection of 250 MBq [18]F-sodium fluoride. Baseline maximum ascending aortic microcalcification activity was measured as maximum standardised uptake value. Ascending aortic diameter was quantified at the level of the right pulmonary artery. In patients, a repeat PET-MRI was performed at 12-24 months. Annualised change in ascending aortic diameter was calculated. Annualised change in maximum aortic microcalcification activity was calculated and stratified into tertiles. Representative ascending aortic wall histological samples were stained for microcalcification (von Kossa) and elastin (elastin van Gieson).

Seventy-five patients with bicuspid aortic valve (52.5±7.5 years, 24% female) and 18 control subjects (50.6±6.2 years, 27% female) were recruited. [18F]sodium fluoride uptake higher in

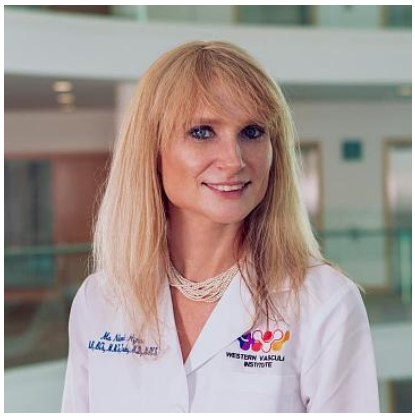
those with bicuspid aortic valve (maximum standardized uptake value 1.81 [1.55 to 1.99] versus 1.45 [1.39 to 1.59]; Wilcoxon p=0.00088). In patients, baseline [18F]sodium fluoride uptake was weakly and inversely related to aortic diameter (R2=-0.068, p=0.024). Those with a loss of aortic microcalcification activity (tertile 1) experienced the greatest change in diameter (0.52±0.51 mm/m²/year) compared to those with static (tertile 2, 0.21±0.21 mm/m²/year) or increasing activity (tertile 3, 0.25±0.42 mm/m²/year; p=0.034).

18F-Sodium fluoride PET can detect and track microscopic calcium deposition within the aortic wall of patients with bicuspid aortic valve. Late loss of aortic microcalcification activity over time is a concerning feature and appears to identify those at greatest risk of disease progression.

Dr Niamh Hynes

University of Galway

Biography



Ms Niamh Hynes is a director and co-founder of the Western Vascular Institute (WVI). Ms Niamh Hynes is a Vascular & Endovascular Surgical Registrar at the Galway Clinic and has over 12 years experience in Vascular clinical practice. Ms. Hynes is a Clinical Lecturer in Endovascular Surgery at the National University of Ireland Galway (NUIG), teaching undergraduate students and co-supervising PhD researchers in Bio-engineering. Additionally, Ms Hynes trains future specialists on clinical and academic aspects of surgery in the MMSc Endovascular Clinical Fellowship. In terms of clinical research has an H index of 21, Citations 1649, i10 index 42 due to 100 Peer-reviewed scientific papers (7 first author, 32 senior author), 9 book chapters, 165 abstract publications., 88 first author oral presentations at international conferences, 22 first author oral presentations at national conferences and 111 first author poster presentations. Ms Hynes has received 18 international awards. Ms Hynes spent 4 years in full time research at NUI Galway, 2 years undertaking a Masters of Medical Science (MMSc) and 2 years for my MD higher degree, at REMEDI. She completed her MD higher degree on microarray analysis of in-stent restenosis in Metabolic Syndrome, having established a dedicated and unique endovascular carotid stenting model in the Zucker rat.

Abstract (Session 4, Talk 1)

The Dynamic Aortic Environment: Challenges for Current Therapies and Future Perspectives

The aorta, previously known as the body's largest artery, has recently been designated an organ in transatlantic EACTS/STS Guidelines. The aorta’s function is just as vital as the heart’s: it transports oxygen-rich blood to the entire body regulates blood pressure and blood flow velocities, and produces hormones. A disease of the aorta is life-threatening and is the third leading cardiovascular (CV) cause of death worldwide, yet it is the only CV disease in which survival rates have not improved in >40 years. Globally, aortic deaths increased 82.1% from 1990 to 2019 (172,426 patients), with a projected 42% increase to 244,685 by 2030, despite less invasive endovascular therapies and annual growth in aortic repairs. The estimated yearly burden to Europe from aortic disease treatment and surveillance exceeds €7.5 billion.

Current therapies erroneously consider aortic disease a morphological problem and replace or exclude the aorta with inert, non-compliant grafts and endografts with no viscoelastic properties or pulsatile function. They fail to support the haemodynamic and biomechanical contribution a healthy aorta plays in left ventricular function and downstream circulation. The therapies we use, both open and endovascular, contribute to further aortic disease, cardiac ischaemia and heart failure. Reintervention and ongoing risk of cardiovascular death mean that aortic patients need to undergo life-long surveillance.

I will present an overview of our aortic research with the ultimate goal of building novel aortic therapies. Our multidisciplinary group of aortic surgeons, bioengineers, biomedical scientists,

mathematicians, and materials experts work hand in glove with industry partners to investigate various aspects of the aortic disease process, from gene expression to biomechanics and functional imaging, with the ultimate goal of disease characterisation, advanced diagnostics and novel therapies. When treated early, the aorta can heal if biomechanical support is given. We are investigating this process at a fundamental cellular and tissue level and will present results on a variation in cellular composition relative to anatomical location and gender. We have also built inverse Fluid-Structure Interaction models using dynamic MRI-informed patient-specific boundary conditions to simulate aortic device deployment. Finally, using cloud-based solutions, we are building machine learning surrogate models to emulate computational processes but with enhanced speed.

Abstract Booklet

Oral Presentations

Establishing a zebrafish model of arterial valve development

Session 1, Talk 2

Christopher J Derrick[1], Lorraine Eley[1], Ahlam Alqahtani[1], Deborah J Henderson[1], Bill Chaudhry[1].

1. Biosciences Institute, Newcastle University, UK

Bicuspid Aortic Valve (BAV) is the most common congenital heart defect, affecting at least 2% of the population and is strongly associated with aortopathies. The embryonic origins of BAV remain poorly understood, limiting the identification of assays for validating patient variants and ultimately causative genes for BAV. We have previously shown in both human and mouse that the left and right leaflets of the arterial valves arise from the outflow tract cushions, with interstitial cells originating from neural crest cells and endocardial-to-mesenchymal transition (EndoMT). In contrast, an EndoMT-independent mechanism of direct differentiation by cardiac progenitors from the second heart field (SHF) forms the anterior and non-coronary leaflets. Defects in either of these developmental mechanisms can result in BAV.

The zebrafish model has been invaluable for investigating cardiac development, demonstrating a high level of conservation of both process and gene regulatory networks. Zebrafish are becoming widely used for human variant testing, yet their naturally bicuspid arterial valve had suggested they were not suitable for understanding human arterial valve development. Here, we set out to investigate to what extent the processes involved in arterial valve and wall development are conserved in zebrafish and ultimately, whether functional testing of BAV variants could be carried out in zebrafish.

Using a combination of live imaging, immunohistochemistry and Cre-mediated lineage tracing, we show that the zebrafish arterial valve primordia develop directly from undifferentiated SHF progenitors with no contribution from EndoMT or neural crest, in keeping with the human and mouse anterior and non-coronary leaflets. Moreover, once formed, these primordia share common subsequent developmental events with all three mammalian arterial valve leaflets. Furthermore, we also show that the contributions from SHF and neural crest cells to the arterial wall of the zebrafish outflow tract are broadly conserved with our previous descriptions in mouse.

Our work highlights a conserved ancestral mechanism of arterial leaflet formation from the SHF, confirming the utility of zebrafish for understanding the development of specific BAV subtypes and aortopathies, as well as offering the potential for high-throughput variant testing.

Viscoelastic characterisation of porcine aorta at the macro and micro-length scale

Session 1, Talk 3

Aadarsh Mishra[1]. Riaz Akhtar[2]. Robin O. Cleveland[3]
1. University of Oxford, 2. University of Liverpool, 3. University of Oxford

The aorta is the largest artery in the human body and plays a crucial role in the circulatory system by distributing freshly oxygenated blood to all tissues and organs throughout the body. The viscoelastic properties of the aorta can alter with cardiovascular disease such as hypertension. Understanding the viscoelastic properties of the aorta will be useful in deploying non-invasive tools to diagnose cardiovascular disease such as dynamic micro-elastography.

Porcine aorta was acquired from an abattoir and tested within 12 hours of slaughter (n=15). The aorta tissue was dissected perpendicular to its longitudinal axis and disc shaped samples (25 mm in diameter and ~1.5 mm thick) were extracted for the macro-length scale testing and rectangular samples (~4-5 mm width, ~7-10mm length and ~2-3 mm height) were extracted for the micro-length scale testing. Viscoelastic testing was performed across the distal descending, proximal descending, mid descending, ascending and abdominal regions. For macro-length scale testing, a stress-controlled rheometer (Physica MCR 301) was used and for micro-length scale testing, a nano indenter (G200 with a DCM-II head, Keysight Technologies, Chandler, Arizona) was used. Dynamic oscillatory shear tests at the macro-length scale were conducted for frequencies from 0.1 Hz to 4.9 Hz, and the shear strain amplitudes varied from 0.01 % to 10%. At the micro-length scale, the frequency varied from 10 Hz to 110 Hz.

At the macro-length scale, a linear viscoelastic behaviour was observed for all the aorta samples from 0.01% to 0.1% shear strain. Dynamic shear measurements at 0.1 Hz and 0.1% shear strain resulted in the storage modulus G'=3.1 kPa and loss modulus G" = 0.9 kPa for distal descending region, G'=3.5 kPa and G" = 0.4 kPa for proximal descending region, G'=2.7 kPa and G"=0.8 kPa for mid descending region, G'=1.0 kPa and G"= 0.3 kPa for ascending region and G'=5.0 kPa and G"= 1.0 kPa for abdominal region. There was power law increase in the storage modulus and loss modulus values until a frequency of 4.9 Hz above which the inertial effects were observed. At the micro-length scale, the storage modulus and loss modulus values at 10 Hz were: G'=50.7 kPa and G"= 14.5 kPa for distal descending region, G'=33.5 kPa and G"= 6.4 kPa for proximal descending region, G'=37.1 kPa and G"= 6.8 kPa for mid descending region, G'=12.0 kPa and G"= 3.8 kPa for ascending region and G'=55.3 kPa and G"= 10.2 kPa for abdominal region. The storage modulus obtained at the micro-length scale using nanoindentation tests is 10 to 16 times higher than measured at the macro-length scale. This is potentially due to the role of the microstructural components such as elastin and collagen dominating at the micro-level.

The viscoelastic properties of aorta were measured at both the macro-length scale and micro-length scale across different regions. At both the length scales, the stiffness values were highest for the abdominal region followed by distal descending, mid descending, proximal descending, and ascending regions. The viscoelastic data obtained from our study will be helpful in understanding the aorta's ability to withstand mechanical loads and strains.

Bicuspid Aortic Valve Aortopathy – Feedback and Recommendations from the Liverpool multidisciplinary workshop

Session 2, Talk 2

Riaz Akhtar[1]

1.University of Liverpool

The University of Liverpool in partnership with The Aortic Dissection Charitable Trust ran a 'Multidisciplinary Approaches to Navigating BAV Aortopathy' in May 2024 bringing together a diverse group including a patient, scientists and clinicians to discuss the challenges and state-of-the-art in bicuspid aortic valve aortopathy. This talk will provide an overview of the event and key recommendations and challenges that arose from the workshop.

Unravelling the Circadian Connection: BMAL1 Alterations in Aortic aneurysms and Insights into Cardiovascular Health

Session 2, Talk 3

Bojin Marinov[1],Rama Iljaz[1], Vanja Pekovic-Vaughan[1], Jill Madine[1], Riaz Akhtar[1]

1.University of Liverpool

Understanding the intricate molecular mechanisms that govern vascular health is crucial to reducing cardiovascular mortality and morbidity. Emerging data has shown that many indices of human cardiovascular function are regulated by the innate circadian rhythm, and disruption of cardiovascular clocks in preclinical models can lead to adverse cardiovascular effects. Morning hours are the period of the day characterized by the highest incidence of major cardiovascular events including myocardial infarction, sudden death or aortic aneurysms. Here we focused on how a circadian marker Bmal1, is altered in thoracic aortic aneurysms (TAAs). This study aimed to compare samples from patients who have genetic predisposition for developing TAA, patients with bicuspid aortic valve (BAV) syndrome and Marfan syndrome with patients who have had a sporadic aortic aneurysm also termed idiopathic or degenerative (DA) aortic aneurysm. Bicuspid aortic valve is characterised by two cusps instead of the regular three which changes the hydrodynamic properties of the aorta thus predisposing for the formation of AA. Marfan syndrome patients have a rare genetic mutation on the FBN-1 gene which results in abnormal fibrillin production. Sections obtained from control (n=6), bicuspid aortic valve patients (n=5), Marfan syndrome patients (n=4) and DA patients (n=5) were immunohistochemically stained using Bmal1 primary antibody. Our data to date revealed significantly increased Bmal1 in inner (23% increase ($p<0.05$)) and outer regions (17% increase ($p<0.05$)) of the DA tissue compared to control tissue. The BAV patient cohort had very little increase of Bmal1 compared to control in all layers observed (mean % increase vs control 4.75% ($p<0.05$)). Marfan patient's cohort exhibited a 9.41% ($p<0.05$) increase in the inner layer and 7.6% ($p<0.05$) increase in Bmal1 compared to control samples. Bmal1 is known to activate the NF-κB signaling pathway, which upregulates the expression of MMP9 known for its role in the degradation of collagen and elastin. Our data suggests that BAV patient's aortic aneurysm tissue is more closely related to non-pathogenic tissue than DA tissue. Further investigations into this pathway may assist understanding of the pathogenesis of thoracic aortic aneurysms.

Exploring the relationship between aortic amyloid and other risk factors associated with aortic pathologies

Session 3, Talk 2

"Alana Maerivoet[1], Rebecca Price[1], Ya Hua Chim[1], Martin Hossack[1], Riaz Akhtar[1], Jill Madine[1]

1.University of Liverpool

Aortic aneurysms and atherosclerosis are often debated to be associated given they share common risk factors which contribute to their development including smoking, age and obesity together with similar pathological characteristics such as inflammation and apoptosis. However, diabetes, a major risk factor for coronary and peripheral artery disease including atherosclerosis is a protective factor against the development of aortic aneurysm. Amyloid deposition within the aortic wall has also been proposed to contribute towards development of aortic aneurysm but to date there have been no studies that have linked amyloid deposition and these other cardiovascular risk factors. Here, we explore the link between diabetes, atherosclerosis and diabetes in patients with aneurysms.

Aortic tissues were collected from patients undergoing surgical intervention for aneurysm (abdominal, n=40 and thoracic, n=12). The presence of amyloid within the aortic wall was determined using dot blots with oligomer and fibril specific antibodies and was compared to patients with high and low atherosclerosis, and those with and without diabetes. We also compare the elastic modulus of tissue from the same patients determined using nanoindentation.

Patients with histologically confirmed atherosclerosis had higher amyloid oligomer:fibril ratios than those without evidence of atherosclerosis. Additionally, these patients had a higher tissue elastic modulus.

Diabetic patients with thoracic aortic aneurysm also had a higher oligomer:fibril ratio than non-diabetics, whilst those with abdominal aortic aneurysms had higher fibril levels in diabetic patients.

Endothelial dysfunction, inflammation, and oxidative stress are hallmarks of diabetes and atherosclerosis. The main protein component of aortic amyloid, medin has also been shown to increase these parameters, further enhancing the potential association of amyloid, diabetes and atherosclerosis.

We hypothesise that presence of amyloid in our diabetic aneurysm patients could present a potential mechanism overcoming the usual protective role of diabetes against aortic aneurysm. Further work is underway to aim to explore this hypothesis and the chicken-egg dilemma surrounding these relationships.

The genetic contribution to variation in aortic distensibility

Session 3, Talk 2

Mehak Chopra[1,2], Niamh Hynes[1], Cathal Seoighe[1,2]

1. University of Galway, Ireland

2. The SFI Centre for Research Training in Genomics Data Science, Ireland

Aorta, the largest artery, carries oxygen-rich blood from the heart to the circulatory system. Older age, hypertension, hyperlipidemia, and other external factors like smoking can cause the aorta to stiffen, potentially leading to a loss in aortic distensibility. Aortic distensibility is a direct measure of aortic stiffness that can be accurately obtained from cardiovascular magnetic resonance imaging. Distensibility can predict adverse cardiovascular events and shed light on the relationships between imaging phenotypes and aortic disorders. In this study, we have focused on the elastic property of the aorta known as distensibility and have performed an analysis of genomic loci that are associated with aortic distensibility in GWA studies. Relating these data to gene expression data from GTEx, we have tried to uncover genetic variation in the cellular composition of the aorta, i.e., inferred using gene expression deconvolution), which may help to explain some of the genetic components of variation in aortic distensibility.

To find the aortic distensibility, an existing deep learning convolutional neural network was applied on 62,497 CMRI from the UKBB. Following quality checks, GWAS was carried out on the aortic distensibility of 56,765 participants. To examine the cellular mechanism and age-related shifts in cellular proportions, we utilized CIBERSORTx deconvolution on aortic gene expression data from 432 GTEx participants. Further, to assess the influence of genetics on distensibility, we built a polygenic score (PGS) using a training dataset. This PGS was then tested on a separate dataset to see how well it predicted actual distensibility measurements. In the future, the project will consider the healthy and diseased ascending aortic tissue, including variability in its cellular composition and cell-type specific gene expression in the healthy and diseased states.

To the best of our knowledge, this is one of the largest studies conducted until now utilising UKBB data, that helped us to identify the SNPs associated with the distensibility. To assess the influence of genetics on distensibility, we built a PGS using a training dataset. This PGS was then tested on a separate dataset to see how well it predicted actual distensibility measurements. While we hoped to find a strong correlation, the PGS did not significantly predict distensibility in the test group. The deconvolution approach on GTEx samples allowed us to uncover the changes in cellular composition with age in aortic samples. We investigated how genetic variants might influence the composition of cell types within aortic tissues. This could potentially explain some of the genetic influence on aortic distensibility. However, due to limited statistical power, the specific genetic variants did not survive the correction for multiple testing. Interestingly, we observed sex differences in cellular proportions within the GTEx data. Overall, the proportion of Vascular Smooth muscle cells II was found more in males compared to females. Additionally, one SNP remained significant after correction in the female participants. This suggests sex-specific genetic effects on aortic cell composition, potentially impacting the aortic distensibility. Further research is needed to explore these sex-specific variants and their role in aortic health. "

Neutrophil activation in Acute Type A Aortic Dissection

Session 4, Talk 2

Sarah Shirley [1], Helen Wright [2], Jillian Madine [3]
1.University of Liverpool

Acute type A aortic dissection (ATAAD) is a life-threatening condition in which the aortic wall separates, allowing blood to flow between the layers. Increased systemic inflammatory markers have been shown to be associated with poorer clinical outcomes. Neutrophils are the most numerous immune cells and are rapidly deployed to a site of infection or injury. This presentation will highlight results from a series of experiments performed to investigate neutrophil biology in ATAAD.

Human aortic tissue samples (ATAAD, aneurysm and healthy control, [n = 5 of each]) were probed for neutrophil markers including myeloperoxidase, interleukin-8, citrullinated histone 3 and matrix metalloproteinases-7, -8 and -9 (MMP). Additionally, serum samples from ATAAD (n =10), chronic dissection (n = 9), aneurysm (n = 12) and healthy control (n = 9) individuals were evaluated by ELISA for neutrophil extracellular trap debris. Finally, neutrophils isolated from peripheral whole blood (ATAAD and healthy controls, [n = 3 of each]) were primed and stimulated to produce an oxidative burst. This was measured by fluorescence over time.

Significantly higher levels of citrullinated histone 3 levels were detected in ATAAD tissue than in aneurysm tissue samples ($p=0.002$). While levels of other markers including myeloperoxidase, interleukin-8, and MMP-7, -8 and -9 were not significantly different, ATAAD samples showed a trend towards higher and more variable levels. Citrullinated histone 3 is a potential marker for the presence of NETs. Therefore, serum levels of NET debris was assessed by a modified ELISA. Similarly, significantly higher levels of NET DNA were detected in serum from ATAAD patients compared to healthy controls (2721ng/ml ± 1222 versus 1352 ng/ml ± 869.4, $p=0.0095$). While NET DNA levels detected in serum from chronic dissection and aneurysm patients fell between ATAAD and healthy controls at 2074 ng/ml ± 786.9 and 1896 ng/ml ± 590.0 respectively. Finally, preliminary data indicate that neutrophils isolated from ATAAD patients produce different patterns of oxidative burst than those from healthy controls.

Taken together the data presented here indicate that neutrophils from ATAAD patients exhibit an activated phenotype. Elevated numbers of activated neutrophils may result in different healing of the aortic wall following surgical intervention. Further investigations are needed to fully elucidate the importance of neutrophil activation postoperative healing.

Biomechanics-based Virtual Stent-graft Deployment Tools for Thoracic Endovascular Aortic Repair of Aortic Dissection

Session 4, Talk 4

Xiaoxin Kan [1,2], Xiaolang Jiang [1], Xiao Yun Xu [2],. Zhihui Dong [1]

1.Fudan University, China, 2.Imperial College London

Although thoracic aortic endovascular repair (TEVAR) has shown its advances in treating of complicated type B aortic dissection patients, complications still occur after TEVAR. Local biomechanical interactions between the implanted stent-graft (SG) and local aortic wall can play a significant role in determining the outcome of TEVAR. Different SGs may cause different biomechanical responses in the treated aorta, but such information is not known to the clinicians at the pre-procedural planning stage. By adopting patient-specific virtual stent-graft deployment simulation framework, it is possible to analyse and compare the biomechanical impact of different SGs on the local aorta for individual patients.

A 66-year-old male type B aortic dissection patient is recruited in this study who successfully underwent a TEVAR treatment with the short version of SG1 product (SG1-S). Unfortunately, after three months of TEVAR, a stent-graft-induced new entry tear (SINE) was found at the distal end of the SG landing zone on the intimal flap. Based the pre-TEVAR CTA scan, the patient-specific aortic dissection model was created and pre-stressed. Parametric models of three commercial SG products (SG1, SG2 and SG3) were built with two different lengths (S/L) for each design. Six simulations were performed by virtually deploying each SG model into the patient-specific aortic dissection model.

The virtual SG deployment model has been quantitatively validated on this patient by comparing the predicted SG configuration for SG1-S with the SG configuration reconstructed from the post-TEVAR CTA scan [5]. For each stent strut, longitudinal position mean deviation was 1.62 ± 1.10 mm, while the transverse spatial deviation was measured at 3.53 ± 2.09 mm and difference in SG opening diameter was -7.01 ± 9.00 %.

SG1-S produced the highest peak of maximum principal stress among the three short SGs with a value of 378.86 kPa, at where the SINE was found in clinical follow-up. SG3 produced best showed conformability by following the local tortuosity of the true lumen among the three designs. SG3-L can produce the most uniform true lumen expansion and reduce the peak stress in the distal landing zone by 78 % compared to SG1-short.

By incorporating different material properties, stent strut shapes and assembly approach, various market leading commercial SGs can be modelled in detail and virtually deployed in patient-specific TBAD geometry via our simulation framework. A quantitative evaluation of the morphological and biomechanical changes induced by different SGs can be performed by analysing the results of virtual SG deployment simulations. For this individual patient, SG3-L would be the most suitable device. For the first time, the virtual SG deployment framework has demonstrated its potential to serve as a pre-procedural planning tool for TEVAR.