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Review article

Microstructure-based engineering of soft biological materials

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ABSTRACT

Aortic disease (AoD) is a leading cause of mortality in developed countries. Two of the most common forms of AoD are aneurysm (widening) and dissection (tear in inner wall). Aneurysm and dissection often associate with bicuspid aortic valve (BAV) instead of the normal tricuspid aortic valve, and BAV aneurysms of ascending thoracic aorta have the tendency to bulge asymmetrically towards the greater curvature of aorta. Multiphoton microscopy can help us image collagen and elastin fibres, which are considered as main load-bearing constituents of the aortic wall, in order to investigate potential role of fibre microstructure in ascending thoracic aortic aneurysm or dissection. Regional differences in fibre microstructure may be driven by distinct mechanisms of vascular remodelling, and, combined with mechanical tests, could improve our understanding of the biomechanical mechanisms of aortic aneurysm and dissection potential. Should we wish to investigate the effect of microstructure in soft tissue formation and organ development, we would have to consider a rapidly growing process. In that process, the cells are the main load-bearing components, which cooperate to produce tissue-level forces that shape tissue formation. Our understanding of this phenomenon, called mechanotransduction, has advanced significantly over the past years, to the point where it is now clear that nearly every biological process is modulated by how these forces are decoded intracellularly. It is therefore important to create our own fluorescently-labeled matrix that could integrate into the tissue and enable tracking of these forces in-vivo. A new 3D optical nanomechanical biosensor (NMBS) based on fluorescent fibronectin fibres was developed based on integrated photolithography and micro-contact printing technology. NMBS was successfully validated under uniaxial tensile test of biologically relevant materials for microscopic vs. macroscopic mechanical strains. In the future, biomimetic 3D scaffolds could be fabricated by assembly of 2D fibre constructs based on the NMBS technology, in order to analyse the effect of selected set of load-bearing microstructural components on both mechanical and functional response of soft biological materials.

Key words: *Aortic aneurysm, Biosensor, Cell, Fibre microstructure, Soft tissue formation;*

1. INTRODUCTION

Aortic disease is currently a large health concern because it is both common and can lead to fatal outcomes [1]. These consist of a variety of conditions targeting the aorta, with the most common forms being aneurysm [2, 3], dissection [4, 5], occlusion owing to atherosclerosis [6, 7] and a general stiffening of the normally elastic aorta that is thought to be a natural consequence of ageing [8-12]. There are many co-morbid abnormalities that can lead to or be associated with one or more of these conditions, including hypertension [13-15], genetic mutations (such

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as Marfan syndrome [16, 17]), developmental defects (such as bicuspid aortic valve (BAV) [18-20]), connective tissue disorders (such as Ehler-Danlos disorder [21, 22], scleroderma [23, 24], osteogenesis imperfecta [25, 26], polycystic kidney disease [27, 28] and Turner syndrome [29, 30]), as well as injury. All aortic diseases are associated with microstructural changes, either to the content or architecture of the connective fibres elastin or collagen.

2. ANEURYSM AND DISSECTION OFTEN ASSOCIATE WITH BICUSPID AORTIC VALVE

Bicuspid aortic valve is the most common congenital heart defect, arising in 1% to 2% of the general population, and along with predisposing to valvular dysfunction the defect is frequently associated with the development of ascending aortopathy and aneurysm [18-20, 31-33]. Patients with BAV uniformly have a large-diameter ascending thoracic aorta (ATA), indicative of the aortopathy, compared with age- and sex-matched controls (CTRL) [34]. Consequently, patients with BAV are at significant risk of aortic dissection [33, 35-37]. There is a bimodal age distribution among ascending thoracic aortic aneurysms (ATAAs), with patients with BAV presenting an average of 10 to 15 years earlier than the degenerative ATAAs that form in patients with tricuspid aortic valve (TAV) [32]. Furthermore, many BAV-associated ATAAs tend to dilate asymmetrically toward the greater curvature of the ascending aorta (extending from the right and noncoronary sinuses) compared with a more symmetric dilatation pattern that occurs in patients with TAV [38-41].].

3. COLLAGEN AND ELASTIN FIBRES: MAIN LOAD-BEARING CONSTITUENTS OF THE AORTIC WALL

The aorta, the blood vessel responsible for delivering blood from the heart to the systemic circulation, normally possesses a high degree of elasticity, which aids in the propulsion of blood downstream to the systemic vasculature [1, 42], and a microstructure that supports this function [43, 44]. It is the connective fibres within this microstructure, elastin and collagen, which impart the elastic properties and strength of the aorta, respectively. Often, it is alteration of the quantity and/or architecture of these fibres that leads to the mechanical, and hence functional, changes associated with aortic disease [10, 15, 45-53]. For example, structural alterations in the walls of large arteries with progressing age cause a decrease in the total arterial compliance [10, 11, 54-57], which in turn leads to both a decreased distal blood flow and an increase in aortic pulse pressure [42]. This increased pulse pressure has been shown to be the strongest predictor of cardiovascular mortality, because it increases the mechanical load on the left ventricle [58].

4. MULTIPHOTON MICROSCOPY IMAGING ANALYSIS

Use of multi-photon microscopy [59-61] allows for imaging of collagen and elastin fibres in fresh tissue specimens without the need for pre-processing (staining) the tissue. The technique is based on wavelength analysis of the excitation light coming from auto-fluorescence of elastin fibres (wavelength: 525 ± 25 nm), and birefringence and periodicity in the molecule of collagen (2nd harmonic, wavelength: 400 ± 50 nm). Multi-photon microscopy can image deep (>100μm), because long wavelength photons penetrate better into biological specimens. The excitation is limited to the focal plane and for this reason there is no need for pinhole. Therefore, it is not a light rejection technique and allows more emitted photons to be detected. On the contrary, one-photon microscopy does not image deep (<100 μm) because it uses short wavelength light. Also, one-photon microscopy is a light rejection technique because the light must go back through a pinhole.

Imaging could be performed using an Olympus multiphoton microscope (Model FV10, Olympus, Center Valley, Pa) to visualize elastin and collagen fibre architecture in 18 locations of the ATAA wall, namely 3 radial (RAD) locations and three circumferential (Θ) regions in both longitudinal-radial (Z-RAD) and Θ-RAD planes for all specimens [31, 60, 61]. During imaging, the Z-RAD or Θ-RAD planes of the samples could face the microscope lens to allow for visualization of RAD-oriented collagen and elastin fibres. Elastin and collagen fibres could be automatically detected according to intrinsic fluorescence and 2nd harmonic generation, respectively. After acquiring images with multiphoton microscopy, the percent of fibres (elastin and collagen) oriented in the RAD direction, the average amplitude of angular undulation and the orientation index of the fibres could be quantified using an image-based analysis tool. A custom automated image-based analysis tool developed in MATLAB (MathWorks, Inc, Natick, Mass) based on image background removal [62] and on fibre detection algorithm [63] could be used to process the multiphoton images, in order to reveal the collagen and elastin fibre architecture in both Z-RAD and Θ-RAD planes of BAV-ATAA and TAV-ATAA in 3 RAD-locations within the aortic wall thickness.

5. REGIONAL DIFFERENCES IN FIBRE MICROSTRUCTURE: ASSOCIATIONS WITH BIOMECHANICAL MECHANISMS OF AORTIC ANEURYSM AND DISSECTION POTENTIAL

Reduced undulation of fibres about Θ-axis in inner wall layers of BAV-ATAA relative to TAV-ATAA may compromise the ability of inner wall layers of BAV-ATAA to resist to RAD loads and predispose to inner wall micro-tears in BAV-ATAA [64]. Increased undulation of elastin fibres about the Θ-axis and increased amount of RAD-oriented elastin and collagen fibre components in the outer wall layers of BAV-ATAA

compared to non-aneurysmal CTRL-ATA is compatible with increased tensile stretch at the inflection point of Θ-strips of outer wall half of BAV-ATAA when compared with CTRL-ATA, since more undulated fibres permit increased stretch before all fibres become engaged (straightened) [10]. It can be suggested that fibre micro-architecture differs in the various tissue planes among patients grouped by valve phenotype, and could explain observed differences in biomechanical properties in BAV-ATAA vs. TAV-ATAA [65, 66]. The discrepancy in fibre micro-architecture with fibres in inner layers being more stretched and with disrupted RAD-oriented components than fibres in outer layers may contribute to distinct mechanisms mediating development, progression and vascular remodeling associated with aneurysms arising in TAV vs. BAV patients.

ATAAs arising in patients with BAV versus TAV involve distinct mechanisms of extracellular matrix (ECM) remodeling indicative of differing vessel wall strength and dissection potential that are likely due to microarchitectural changes among collagen and elastin fibres [31]. Distinctions noted in ECM microarchitecture may form the basis of differing aneurysm geometries and aortic wall integrities in ATAAs arising in these two different valve morphologies. The finding of less RAD-oriented elastin fibres in region N (with respect to noncoronary sinus) and region R (with respect to right coronary sinus) of BAV-ATAA may directly correlate with earlier finding of decreased delamination strength (an ex-vivo measure of aortic dissection potential) in BAV-ATAA compared with TAV-ATAA [65], and may explain the asymmetric dilatation pattern commonly seen in patients with BAV-ATAA compared with those with TAV-ATAA. The region-specific architectural profile in BAV-ATAA may be driven by distinct mechanisms of vascular remodeling that are a consequence of valve morphotype-specific hemodynamic stresses/forces (e.g., blood flow-induced shear stress acting on the luminal surface) and contribute to an asymmetric dilatation pattern and/or convey a different regional propensity for delamination. When combined with additional region-specific (across the wall circumference and thickness) delamination or tensile biomechanical testing, our understanding of the biomechanical mechanisms of aortic aneurysm and dissection potential could be improved. There is a hope that a patient-specific simulation tool could be developed for enabling the prediction of aortic remodeling and disease progression. Such a tool could improve risk assessment for aortic catastrophe and direct therapy for patients with ATAA.

Decrease of elastin percentage distal to the suprarenal aorta within the arterial wall may suggest that beyond the suprarenal aorta, which is an arterial region with different predisposition to aneurysmal disease, arterial elastance is reduced [42, 67]. Future analysis could extend employing both second harmonic generation imaging analysis and uni-axial extension tests [64, 65] to investigate associations between the nondiseased/healthy aortic tissue microstructure and aortic tissue biomechanical properties, respectively [68]. This could provide insight into structure-associated biomechanical mechanisms of aortic aneurysm potential, and whether anatomic location influences arterial function as well as the effects of transluminal pressures and mechanical load on arterial wall connective tissue proteins. Future mechanical test information about the compliance of the aortic wall would also help draw conclusions about effect of mechanical properties on dedicated endovascular devices.

6 TRACKING CELL-GENERATED MICROSCOPIC STRAINS

Cell-generated mechanical forces transmitted via cell-cell and cell-ECM interactions are integral to a wide range of processes, from cell migration [69-74] and contractility [75] to tissue morphogenesis [76-82] and regeneration [83-86]. Our understanding of this phenomenon, called mechanotransduction, has advanced significantly over the past years, to the point where it is now clear that nearly every biological process is modulated by how these forces are decoded intracellularly. In most cases the underlying mechanobiology is not well understood, in part because direct measurement of forces in living tissue during dynamic processes has proved difficult, as well as forces generated on the cellular scale combine to drive macroscale tissue formation [87, 88]. A comprehensive approach to tissue engineering would entail a combination of advanced in-silico and ex-vivo mechanotransduction assays to identify the magnitude of loads and strains that cells, or cell-seeded scaffolds are exposed to in a clinical scenario. This would facilitate the evaluation of bio-realistic loads in a bioreactor/3D cell culture, as to their effect on proliferation and differentiation. How these loads are transduced into cellular structures could be evaluated either through advanced numerical techniques or nanomechanical biosensors. There is a need to develop both in-vitro and in-vivo measurement tool, for cellular and tissue-level mechanical forces in 3D, that can span multiple length scales to enable force tracking, while minimally perturbing the biology of interest.

A fibronectin (FN) based nanomechanical biosensor (NMBS) can be developed to provide the capability to quantify the location, direction, and magnitude of strain on a 3D surface over time, from subcellular to tissue length scales [83]. The NMBS can be fabricated using an adaptation of surface-initiated assembly (SIA), which is a technique to microcontact print ECM proteins onto a thermo-responsive poly(N-isopropylacrylamide) (PIPAAm) surface and then release the ECM proteins (e.g., FN, laminin, collagen type IV, and fibrinogen) as an assembled, insoluble network with defined geometry [89]. Briefly, the NMBS can be designed in CAD (for example line width and spacing of 2 μm × 2 μm, 20 μm × 20 μm, 10 μm × 100 μm, and 100 μm × 100 μm to measure strain from the subcellular to multicellular length scales), transferred to a transparency photomask, and used to photolithographically pattern a photoresist-coated glass wafer. A polydimethylsiloxane (PDMS) elastomer stamp can be formed by casting on the patterned wafer and then

inked with fluorescently-labeled FN. The PDMS stamp can then be used to microcontact print the FN onto a PIPAAm-coated glass coverslip and then removed to leave the NMBS on the PIPAAm surface. The NMBS can then be transferred to another surface, including tensile test strips, by adding room temperature water to dissolve the PIPAAm. The thickness of the dry NMBS is in the order of ~4 nm.

To validate and benchmark the NMBS as a microscopic strain sensor, controlled mechanical testing can be performed while visualizing microscopic deformations through fluorescence microscopy [83]. For example, a PDMS "dog bone" shaped tensile test strip can be designed and molded and NMBS with 10 μm wide lines and 100 μm spacing can be transferred across the gauge length. The test strip can then be mounted in a custom-designed uniaxial testing system that enables simultaneous microscopic imaging of the NMBS and macroscopic imaging of the PDMS. Elongation of the PDMS test strip can be measured by an increased distance between fiducial marks (small black dots on the PDMS in the gauge length). Time-lapse fluorescence imaging of the NMBS can provide tracking of both tensile and compressive strain at the microscopic scale based on mesh deformation. Quantification of strain can be performed using custom MATLAB software by converting the NMBS fluorescence image into global map of tensile and compressive strains with respect to undeformed reference length of NMBS mesh segments. To validate the accuracy of the NMBS strain mapping during uniaxial tensile testing, the average tensile and compressive strain observed via fluorescence microscopy can be correlated to the measured macroscopic distances between fiducial marks on the surface of the PDMS test strip. The overall width and thickness of the test strip can also be measured throughout tensile testing. Agreement between microscopic and macroscopic strains can establish that the NMBS accurately tracks strain of PDMS and indicate that PDMS behaves as an isotropic incompressible material in agreement with literature [90]. The validation experiment can be repeated by using the NMBS to track strain of a fibrin tensile test strip as a model of a biologically-derived compressible hydrogel. Agreement between microscopic and macroscopic strains can establish that the NMBS accurately tracks strain of fibrin and indicate that fibrin behaves as an anisotropic compressible material in agreement with literature [91].

In the future, biomimetic 3D scaffolds could be fabricated by assembly of 2D fibre constructs based on the NMBS technology, in order to analyse the effect of selected set of load-bearing microstructural components on both mechanical and functional response of soft biological materials. NMBS tracking with more sophisticated point-cloud analysis would allow for a more detailed analysis of the strains and a better understanding of the stresses driving processes such as developmental morphogenesis and disease progression [83].

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NOTE

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