CARDIAC BIOENGINEERING

More people worldwide pass away from cardiovascular disease (CVD) than from any other disease. The cardiovascular system is an incredibly complex organ system made up of the heart and blood vessels, which represent many connected, constantly moving tissue components. Heart attack, heart failure, valve failure, arrhythmia, stroke, and cardiomyopathies are only a few of the many illnesses that make up cardiovascular disease (CVD). Although there are numerous risk factors for CVD, age-related artery hardening (arteriosclerosis) and plaque accumulation inside the arteries (atherosclerosis) are understood to be the fundamental causes. Unfortunately, the methods used for CVD diagnosis, follow-up, and management are largely insufficient. The field is still hindered by the sizeable amount of data required for more effective prevention, risk stratification, or care, as well as the complex interrelationships of numerous different factors determining the ultimate fate of a given pathology, despite the paradigmatic shift from an experienced-based approach to an evidence-based approach in clinical care. It is crucial that we continue to create new technologies and better understanding in order to combat what is one of the leading causes of death in the world due to its rapid increase. This is due to the significant biological and physiological complexity as well as the variety of comorbidities that contribute to the aetiology and progression of CVD.

Since its debut, APL Bioengineering has focused on seeking submissions for special issues and collections that attempt to draw attention to pressing medical and health issues and show how bioengineering breakthroughs are addressing these difficulties. In this Editorial, we highlight the recent publications in APL Bioengineering that contribute to a better understanding of human cardiovascular function and dysfunction, the effects of ageing on the operation of this complex system, how we can mimic aspects of human biology and pathology with in vitro cardiac tissue models, and how drug and therapeutic discovery with new human cell-based drug screening platforms will enable us to address heart, and more broadly, cardiovascular issues. Leading bioengineering experts in the fields of cardiac modelling, cardiac physiology and biology, animal models of heart disease, and cardiac tissue models have contributed to this collection, which spans a wide range of topics.

Three modelling papers from the "Bioengineering of the Heart" collection provide fresh insight into right heart remodelling after pulmonary arterial hypertension, the application of artificial intelligence (AI) to more accurately map myocardial electrical activity, and the combination of clinical data to more accurately simulate large artery flow. Two papers describing cutting-edge animal models that offer fresh insights into the pathology of early dissecting abdominal aortic aneurysm formation in apolipoprotein E-deficient mice and into cardiomyocyte (CM) remodelling with age by examining explanted Drosophila hearts complement these modelling papers. Six papers, including a brief review and perspective, are also included in the collection, along with a number of original research articles that describe novel cell-based microfluidic platforms to more accurately model ischemia-reperfusion injury (IRI) following coronary intervention using induced myocardial infarction (IMI). These papers provide comprehensive state-of-the-art positions on how close we are to simulating human heart tissue and function in order to unravel disease mechanisms using ex vivo models.

Cardiac Function Modelling for Improved Treatment and Prevention

In the past few decades, cardiac modelling has developed quickly, offering increasingly realistic and representative virtual phantoms to study heart illnesses and associated treatments. The era of "patient specific" modelling, which combines imaging with clinical data of physical, mechanical, chemical, and electrical cues, enables the creation of customised, realistic morphological models. The two goals are to obtain personalised medicine paradigm indications for the diagnosis and treatment of the unique patient and to provide virtual patient populations for in silico studies. The prediction of tissue remodelling, the real-time accurate mapping of 4D physio-pathological variables from direct measurements, and the realisation of ever more trustworthy and realistic models are only a few of the technical hurdles in this scenario.

A novel structurally based constitutive model for the myocardium of the right ventricular free wall is presented by Avazmohammadi and colleagues. Their goal is to look at how pulmonary arterial hypertension affects the transmural remodelling of the right ventricular myocardium. Indeed, with a mortality rate of 37.2% at 3 years after diagnosis, right ventricular failure is a significant cause of death for individuals with pulmonary arterial hypertension. The separation of the tissue-level impacts of the mechanical and structural adaptations of myo- and collagen fibres, as well as their interactions, is made possible by their method. Their long-term objective is to investigate the potential existence of a "no return" point along the progression of hypertrophy and remodelling, beyond which the adaptive mechanisms fail to restore the wall stress value, as well as the inclusion of sophisticated and validated models of tissue remodelling in patient specific organ-level simulations for the best diagnosis, new research suggests.

In order to accurately diagnose various cardiac arrhythmias, such as premature ventricular contractions, ventricular tachycardia, atrial flutter, and atrial fibrillation, Rajagopal and colleagues present a new model for computing electrocardiogram (ECG) mapping based on a polynomial neural network. Conventional ECG recordings can pick up arrhythmia symptoms, but interpretation and location of, say, atrial fibrillation sources require extensive clinical knowledge. In this situation, anatomical x-ray computed tomography and non-invasive multi-lead body-surface ECG can be used to provide complete 3D reconstructions of heart electrical activity. In contrast to current mapping techniques, the authors of the research suggest an approach that can offer improved spatiotemporal resolution and reconstruction accuracy. Their goal is to give doctors a solid and trustworthy time-resolved 3D cardiac map of a patient before surgery so they can better understand where the patient's atrial fibrillation or premature ventricle contractions are coming from, assess whether an ablation procedure would be a good course of action, and track the patient's electrophysiology over time and while engaging in regular exercise.

Pirola and colleagues look into the validity of existing methods for simulating blood flow in the ascending aorta in the presence of aberrant fluid dynamics, such as those caused by a mechanical or stenotic aortic valve. Although it is widely acknowledged that hemodynamics plays a crucial role in vascular health, accurate in vivo quantification of important hemodynamic parameters like wall shear stresses is still not feasible. Image-based computational fluid dynamics (CFD) is the only method available for studying aortic hemodynamics. In this beautiful paper, the authors show how adding an artificial boundary constraint can result in approximations that are too close to the truth and unrealistic outcomes across the board. They compare the effects of the flat profile, a 1D through-plane velocity obtained using the phase-contrast magnetic resonance imaging technique, and the full 3D phase-contrast magnetic resonance imaging-derived velocity profiles acquired at the valve outlet on the ascending aorta fluid dynamics in particular. Results by Pirola et al. demonstrate unequivocally that when the wrong boundary condition is selected, peak and mean velocities at the proximal end of the ascending aorta can be understated by as much as 41% when the secondary flow components were disregarded.

Engineering Cardiovascular Disease in Animal Models

In order to obtain pertinent and distinctive information to guide disease onset and tissue remodelling, an appropriate design approach can be very successful in animal model research. Animal models provide a very efficient way to quickly get comprehensive data on a variety of diseases that are challenging to obtain even through big patient cohorts and clinical research. The findings, while not directly applicable to humans, are crucial for understanding the underlying causes of diseases and how they spread in order to better understand these conditions and find new therapeutic targets.

Using apolipoprotein E-deficient mice, Phillips and colleagues explored the early pathophysiology of dissecting abdominal aortic aneurysm formation at various stages by continuously administering angiotensin II. This research offers a significant advance because many patients with dissecting abdominal aortic aneurysms have aneurysms with diameters smaller than 5 cm, excluding them from surgical repair. In light of this, knowing how early abdominal aortic aneurysms form and develop should help identify high-risk patients who would benefit from treating smaller aneurysms. In their research, the scientists used a daily ultrasound screening method to detect the development of abdominal aortic aneurysms and aortic dissections. This method was supplemented by the gathering of RNA sequencing data, gene expression analysis, histology, and immunohistochemistry. In order to gain new insight into the biomechanical, microstructural, and inflammatory changes occurring in mice with and without aortic dissection, Phillips et al. assessed extracellular matrix remodelling and inflammatory cell infiltration within 24 hours of aortic dissection or at 10 days after angiotensin II infusion.

The extracellular matrix and intracellular components of the heart undergo substantial remodelling throughout life, which reduces contractile compliance and elasticity. The thickening of the left ventricular wall, an increase in systolic pressure, and reduced myocardial function are all related occurrences. Sessions and colleagues looked into how the upregulation of cardiac vinculin might function as a compensatory mechanism during ageing. They discovered a compensatory mechanism in which vinculin-mediated cytoskeletal reinforcement enhances force production and myofibril resistance balances age-related increases in heart wall strain. The scientists demonstrated that cardiac Vinculin overexpression with ageing is a conserved process in non-human monkey, rat, and fly models, independent of cardiovascular illness, using a multi-model approach. They specifically took beating hearts from Drosophila melanogaster, a fruit fly, and looked at them to statistically explain the alterations in myofiber architecture. They showed that over-expression of the fly heart-specific vinculin enhances contractility, maintaining cardiac respiration with ageing or under mechanical stress. Additionally, they saw that organismal fitness rose with age, in part because glucose was oxidised by aerobic means more effectively. Overall, the ability of cardiac tissue cells to withstand mitochondrial stress and sustain rhythmic contraction may be underpinned by cytoskeletal strengthening. These findings offer important new insight into heart ageing and potential targets for future therapies because they are the first to show that cardiac-restricted cytoskeletal remodelling causes a systemic metabolic response.

Bioengineered Heart In-Vitro Models

A review and a viewpoint open the collection of works on in vitro created heart tissue models. Callaghan et al.'s thorough and thorough review evaluates our capacity to model cardiac complexity, providing a suitable biological and regulatory framework for bioengineers interested in contributing their knowledge to numerous aspects of cardiac bioengineering, drug toxicity, and therapeutic drug discovery, as well as outlining the status (and restrictions) of current physiological measurement modalities and techniques that can be used by biologists. They give a current assessment of the significant improvements and opportunities brought about by contemporary experimental methodologies and strategies, discussing novel single and multicellular models and their efficacy and utility, the significance of simulating physiological states and cues (extracellular, intracellular, mechanical, and electrical), disease models and their viability, and the relevance of tissue engineered constructs and their capacity to model physiological states. Importantly, they emphasise that even though the development of new biomimetic models and improved functional assays represent important steps towards advancing our fundamental knowledge through translational research and are essential elements of the workflow to better pharmaceutical testing and clinical outcomes, they suggest that these are only the beginning of what may be feasible, which is an exciting proposition for the field.

The development of hPSC-CM (and cardiac tissue) is the subject of the Perspective paper by Mills and Hudson7, which focuses on what has been accomplished and what needs to be done. hPSC-CMs have been successfully employed to study hypertrophy, electrophysiology, medication toxicity and discovery, and basic biology thanks to decades of research that resulted in their creation. Since adult human heart maturity has not yet been attained and the molecular pathways of cardiac maturation are still unknown, applicability and translatability are, nevertheless, still limited. The authors provide an overview of the most suitable characterization tests and maturation biomarkers as well as a review of the most promising methods for driving hPSC-CM maturation. Particular focus is placed on the recent successes brought about by the addition of multicellularity, mechanical stress, and pacing; metabolism is also introduced as a key factor in maturation. In order to better understand the still poorly understood maturation process of the heart, as well as to produce better in vitro models for many bioengineering and therapeutic discovery applications, better methodologies to produce fully mature "adult" hPSC-CMs are clearly illustrated by the authors in this perspective's conclusion.

Cardiomyocytes (CMs) produced from induced pluripotent stem cells were used in a unique in vitro model of ischemia-reperfusion injury (IRI) that was described by Hidalgo et al. This study demonstrates the value of employing metabolically matured human iPSC-derived cardiomyocytes (taking only 8 days in their medium), as well as past shortcomings in our mimicking of crucial physiological state changes that occur in vivo following an ischemia attack. While all prior ischemia models remove glucose from the media during the ischemic episode, they demonstrate that, in contrast, in order to mimic the known transient changes in the interstitial tissue microenvironment during an IRI event in vivo, glucose (which mimics glycogen stores in resident CMs) must be available (to prevent the onset of cardio-protective autophagy) and the pH must be lowered during the ischemic episode (to pH 6.2) to recreate local acidification. They reproduce the observed in vivo levels of CM death (60%) following an ischemic-reoxygenation episode in vitro using this model. By testing their model against known pharmacological post-conditioning (PPC) medication candidates, they are able to validate that the observed reduction in reperfusion-induced CM cell death was consistent with the results of clinical trials. This straightforward but beautiful in vitro human iPSC model presents a novel method for investigating IRI and validating and screening human-specific PPC medication candidates.

In a microbioreactor that combines biochemical, mechanical, and electrical stimuli—key cardio-physiological signals that influence heart cell fate and maturation—Visone et al. established a unique and simple in vitro cardiac tissue model. They replicated parts of the intricate electro-mechanical environment of the heart by giving "in-device" created 3D cardiac microtissues a homogeneous electric field and cyclic uniaxial strains. The utility of this novel platform and the significance of multiplexing the pertinent stimuli ex vivo to mimic in vivo tissue states were confirmed by the controlled application of both a low voltage electric field and mechanical stretch (10% strain), which led to significant improvements in cardiac tissue maturity and function. Human cardiac cell types, including iPSC-derived tissues, can be easily exploited thanks to the flexibility of the developed microfluidic platform, which allows for the introduction of any cell type (singly or in combination) and soluble factors within input streams. This makes it possible to screen therapeutics on truly functional 3D cardiac microtissues.

Gonzalez Rodriguez et al. described a prospective treatment approach to valvular heart disease, primarily fibrotic aortic valve stenosis (FAVS), another developing cardiovascular (cardiac-specific) condition, in accordance with our more numerical publications in this collection. Without new treatments, it is expected that the prevalence of valvular heart disease (VHD) would double by 2050 due to an ageing population (much like heart failure). The only method of treatment now available is valve replacement surgery. Gonzalez Rodriguez et al.'s contribution described a hydrogel-based 3D culture method for the carefully regulated distribution of FGF-2 and TGF-B, two of the well-known major effectors of cellular transformation and fibrotic matrix deposition, to valvular interstitial cells (VICs). These cells maintain the extracellular matrix in heart valve leaflets, just like numerous fibroblast populations in the heart, but they also act as wound-healing cells in the event of injury. This study emphasises the significance of physiologically relevant 3D microenvironments in enabling maintenance of a quiescent VIC phenotype prior to exposure to cytokines (that transform them into myofibroblasts), the observation of matrix contraction (or absence thereof), and the use of peptide-functionalized, matrix metalloproteinase (MMP)-degradable poly(ethylene glycol) (PEG) hydrogels that recapitulated key biochemical and biomechanical valve leaflet micro An important validation of the potential of this in vitro model for rapid translation to therapeutic screening approaches and also to further understand the initiation phases of this and other fibrosis-related diseases was provided by comparisons between the responses of VICs encapsulated in these hydrogels and VICs in porcine aortic valve explants. These findings support similar impacts of exogenously delivered factors in explanted tissues.

Menon et al. described a unique microdevice to study vascular inflammation and leukocyte-endothelial interactions in 3D artery stenosis while staying with dysregulated (chronic) inflammation and wound healing. Understanding atherosclerosis, a major contributor to CVDs such acute myocardial infarction (heart attack), is directly impacted by this approach. Because of the buildup of cholesterol-containing low-density lipoproteins in the sub-endothelial space in these areas, this illness primarily damages vascular bifurcation. By enabling tunable 3D constrictions within their cell-laden vessel-like channel to mimic the impacts of stenotic plaque inclusions and the resulting changes in hemodynamics, stresses at cell surfaces, and cell adhesion under flow of multiple (sequentially exposed and relevant to disease progression, i.e., leukocytes) cell types, these authors present a novel, pneumatically actuated 3D stenosis blood vessel model that addresses prior deficiencies of other models. Validation of inflammatory cytokines and whole healthy blood/liquid biopsies (with or without these cytokines)-induced endothelial dysfunction and inflammation-induced cell attachment within the device proved the device's usefulness and demonstrated its significant potential for implementation in high throughput screening assays for drug discovery and Point-of-Care (POC) testing of patients to stratify atherosclerosis susceptibility.

The Bioengineering of the Heart collection offers three different and complimentary methods for modelling cardiac disease, each of which offers a particular perspective on heart function and repair. This collection of papers by experts in the field of bioengineering serves as a convincing example of how the right combination of an engineering mindset and a thorough understanding of biology and physiology can offer previously unheard-of design and technological opportunities to assess cardiac function and disease and find novel therapeutic pathways to achieve functional repair of the cardiovascular system.

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