Special Issue on human heart failure

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Received: 24 December 2014 / Accepted: 24 December 2014 / Published online: 27 January 2015
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This Special Issue of *Biophysical Reviews* focusses on human heart failure. The reviews discussed below are the result of a satellite meeting of the 18th International Biophysics Congress held on Heron Island, Queensland, Australia in August 2014. At this satellite meeting, scientists active in clinical and basic research were brought together in a setting of relative isolation: a tiny coral island on the Great Barrier Reef (Fig. 1). The meeting was designed to integrate researchers at the whole-organ, cellular and molecular levels. These delegates had either worked with samples from the Sydney Heart Bank or intended to do so—but few had actually met. The discussions were lively, and the resulting reviews provide new and interesting insights into why human hearts fail.

The Sydney Heart Bank

In 1989, the Sydney Heart Bank (SHB) was started with the cooperation of the Late Dr Victor Chang, Australia's pioneering heart transplant surgeon. The SHB was developed with the goal of facilitating human-based research by collecting tissue from heart transplant recipients within approximately 40 min of the loss of coronary blood flow. These high-quality samples were collected from a wide range of end-stage heart failure patients who underwent orthotopic heart transplantation. Accordingly, the SHB provides samples that exhibit little or no degradation of RNAs and proteins. Apart from amassing more than 25,000 explanted myocardial and vascular samples from heart transplants patients, the SHB also collects healthy hearts from brain-dead organ donors that were not required for transplantation (e.g. when tissue-type could

not be match to patients in the heart transplant list). Our healthy human donor hearts aged from a few months through to 65 years provide a benchmark against which the failing hearts are assessed. Today, the Bank has broadened its focus to also collecting biopsies and cardiomyectomies, as well as samples acquired from other heart banks and individual researchers. The SHB currently has a collection of 160 failing hearts from patients with dilated cardiomyopathy, 110 with ischaemic heart disease, 25 with hypertrophic cardiomyopathy (HCM), and the remainder from a wide range of other, often rare congenital conditions. All reviews in this Special Issue summarise experiments reported elsewhere, and all were carried out with the appropriate institutional human and/or animal ethics committee approval.

A common approach to understanding the mechanisms by which human hearts fail is to create animal models of the human disease phenotypes. For example, mice can be genetically modified to recreate the phenotype of human disease-causing mutations, enabling researchers to map the downstream consequences of these mutations and identify their corresponding altered proteins. Despite the value of these models in acting as guides to understanding human disease, a significant fraction of the findings in mice do not translate to humans. *Li et al.* in *The future of research into human heart failure and the safety of drug-based therapies* discuss this issue in the Special Issue.

The reviews included in this Special Issue are briefly summarised below.

Altered sarcomere function leads to heart failure

McNamara et al. in *The Role of Super-Relaxed Myosin in Skeletal and Cardiac Muscle* review the importance of super relaxed (SRX) myosin in the heart and skeletal muscle. Myosin heads in this state have a lower ATP turnover via their

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Fig. 1 *Top* Delegates from Australia, France, Japan, UK, and USA attending the Heron Island Meeting. Most of the 30 delegates have contributed to this Special Issue. *Bottom* A panorama of the Heron Island resort on the Great Barrier Reef. This was the venue of a satellite meeting of the International Union for Pure & Applied Biophysics Congress held in Brisbane, Australia in August 2014

highly ordered interaction with the thick filament surface. The SRX state was previously identified in cardiac, fast and slow skeletal muscle. McNamara et al. discusses the potential for SRX myosin heads to be called upon when there is a demand for increased power at times of stress, such as hypoxia and ischemia, thereby operating as a “reserve”. SRX in cardiac muscle provides a potential target for novel therapies.

Kagemoto et al. in *SPontaneous Oscillatory Contraction (SPOC) in Human Cardiomyocytes* describe a relatively new state of cardiac muscle that auto-oscillates under conditions that exist between relaxation and contraction. SPOCs can occur in the presence or absence of physiological levels of free Ca^{2+} , elevated $\text{MgADP} + \text{Pi}$ and low levels of MgATP . These conditions drive an oscillating waveform of rapid lengthening and relatively slow shortening. SPOCs create visible waves of contraction and relaxation, termed the SPOC waves. The mechanism whereby SPOCs are created and synchronized across cardiomyocytes is discussed in detail.

Pleuss et al. in *Adaptations of cytoarchitecture in human dilated cardiomyopathy* report sarcomeric dysfunction, previously described in mouse models, where the structure of the intercalated disc is altered. These authors also discuss switching of myomesin to the more extensible EH-myomesin isoform in patients with dilated cardiomyopathy. These structural changes were verified in human samples from the SHB and probably contribute to the dysfunction seen in some forms of dilated cardiomyopathy.

Biesiadecki et al. went to great lengths to provide a systematic overview of cardiac muscle relaxation in their review titled *Tri-modal Regulation of Cardiac Muscle Relaxation: Intracellular Calcium Decline, Thin Filament Deactivation, and Cross-bridge Cycling Kinetics*. These authors describe factors that influence the decline in the rates of Ca^{2+} transients, thin filament deactivation and cross-bridge cycling and how these physiological factors interact to modulate cardiac relaxation. Although it was not incorporated into this Special Issue, we highly recommend this review (see Biophysical Reviews 6(3-4): 373-290).

Channels and receptors essential for maintaining cardiac contractile function

Walweel et al. in *Mechanisms of SR Calcium Release in Healthy and Failing Human Hearts* explore how cardiac contraction and rhythm is maintained by intracellular calcium ion (Ca^{2+}) fluxes. Ca^{2+} is an essential mediator of cardiac contraction, and altered Ca^{2+} handling is commonly associated with heart failure. Electrical excitation of the surface membrane activates voltage-dependent L-type Ca^{2+} channels to open and allows Ca^{2+} to enter the cytoplasm. The resulting transient increase in cytoplasmic Ca^{2+} concentration activates Ca^{2+} release channels located at specialized sites in the

sarcoplasmic reticulum (SR), which is the main intracellular Ca^{2+} store.

Balycheva *et al.* in *Microdomain-specific Localization of Functional Ion Channels in Cardiomyocytes: An Emerging Concept of Local Regulation and Remodeling* review the topography of ion channels and regulatory receptors along the sarcolemma in living cardiomyocytes. These ion channels and regulatory receptors form interacting networks that couple with macromolecular signaling complexes. Disruption of these pathways contributes to heart failure, arrhythmias and sudden cardiac death.

Ablorh *et al.* in *Phospholamban Phosphorylation, Mutation, and Structural Dynamics: A Biophysical Approach to understanding and Treating Cardiomyopathy* focus on the development of new biochemical and spectroscopic techniques for investigating the structural dynamics of phospholamban (PLB) and the SR/endoplasmic reticulum (ER) Ca^{2+} ATPase (SERCA). Unphosphorylated PLB inhibits SERCA Ca^{2+} transport into the SR, thereby slowing relaxation. The structural states of SERCA-PLB complexes and PLB expression and phosphorylation states in cells and tissues can be quantitatively measured using site-directed labelling, high-resolution spectroscopy and multidimensional immunofluorescence. These powerful tools can analyse and diagnose specific disorders using human tissue samples from the SHB.

Molecular mechanisms in cardiovascular physiology

Foster *et al.* in *G Protein-coupled Receptors in Cardiac Biology: Old and New Receptors* provide a contemporary review of G protein-coupled receptors (GPCRs) and how their complex signalling maintains cardiovascular physiology and contributes to disease. They also provide insights into “orphan” GPCRs, e.g. odorant and taste receptors, and their role in healthy human hearts. These GPCRs probably contribute to the cellular responses in both the healthy and disease state and offer exciting opportunities to therapeutically modulate heart function.

Song *et al.* in their review *LRG1: A New Player in Cardiac Remodeling and Heart Failure* suggest an alternative therapeutic target, leucine-rich alpha-2 glycoprotein 1 (LRG1), for the treatment of heart failure. LRG1 promotes blood vessel formation by regulating context-dependent endothelial transforming growth factor β (TGF β) signaling. TGF β is normally associated with heart development and as such broad-spectrum inhibition of TGF β signalling is commonly associated with fibrosis, aberrant angiogenesis and accelerated progression into heart failure, all of which are unwanted side effects. LRG1 promises to avoid these risks.

Robertson *et al.* in *Molecular Mechanisms of Inherited Thoracic Aortic Disease—From Gene Variant to Surgical Aneurysm* focussed on the mechanisms involved in the formation of aneurysms of the thoracic aorta, with special attention paid to genes that are the clinically silent precursors of acute aortic dissection or confer an increased risk of its occurrence. These mechanisms involve several gene mutations in key structural and regulatory proteins within the aortic wall that predispose patients to thoracic aneurysms. Despite the variation in the proteins affected by these mutations, there is a unifying pathological end-point of degeneration in the media layer of the aortic wall.

Interventional medicine

Wu *et al.* in *Surgery for Hypertrophic Cardiomyopathy* describes a surgical intervention for hypertrophic cardiomyopathy patients that commonly present with a thickened interventricular septum (IVS) and leads to obstruction of the outflow tract of the left ventricle (LV). The surgical goal for patients with moderate to severe LV outflow tract obstruction is surgical myectomy. This technique excises a portion of the hypertrophied IVS to relieve the obstruction. Septal myectomy patients have a low early mortality of <2 %, a long-term survival that matches the general population and durable relief of symptoms.

Ge *et al.* in *Cardiac Stem Cells: Translation to Human Studies* follow up on their recent *Nature* paper on stem cells in the adult mammalian heart as a potential therapy for human heart failure. The authors address the gaps in our understanding of the origins, function and relationships between the different progenitor cell families, many of which are heterogeneous populations with overlapping definitions.

Bioinformatics

Djordjevic *et al.* in *Decoding the Complex Genetic Causes of Heart Diseases Using Systems Biology* summarize state-of-the-art genomic and bioinformatics techniques that will be used to accelerate the pace of disease gene discovery in heart diseases. The authors also provide an interactive web resource (CardiacCode) for systems biology analysis of mammalian heart development and diseases (<http://cardiaccode.victorchang.edu.au/>). CardiacCode features a data set of over 700 manually-curated genetic or molecular perturbation data sets. These authors discuss how whole-genome, exome and transcriptome sequencing can be processed to greatly accelerate the discovery of the complex genetic causes of congenital heart diseases.

December, 2014.