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EDITORIAL

Mechanics and energetics in cardiac arrhythmias and heart failure

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J. JEREMY RICE. 1965–2018

Remembering Jeremy Rice, a wonderful colleague gone too soon

Before discussing the 2018 meeting content, we wish to commemorate Dr J. Jeremy Rice, who died tragically during the conference. Jeremy was an outstanding scientist (member of the Faculty of 1000) whose work on quantitative exploration of cardiac and neuronal electrophysiology, heart mechanics, and electro-mechanical coupling, published in more than 75 papers, has lasting impact on our field. His true impact is much deeper than the published papers for the hundreds of scientists who knew him.

Despite his many accolades, Jeremy was down to earth, modest, and generous in his enthusiastic collaborative and open approach to science. He trained at Johns Hopkins University, was a Principal Researcher at IBM Healthcare & Life Sciences for nearly two decades, and held adjunct faculty posts at Johns Hopkins and Loyola Universities. He loved trains, zydeco music, and dancing with his wife, Laura.

Unbeknownst to many of us, Jeremy had long suffered from severe depression. As highlighted in the accompanying Editorial by Dr Astrid Müller (2020), mental health issues in academics are more common than one might realize, affecting roughly a third of trainees, postdocs and senior scientists at some time. These sobering statistics remind us that, as we sit in the next conference and look to the person on our right and left, one of us three is likely to suffer from this illness at some point (we fondly imagine Jeremy taking us to task on the correct probabilistic equation inherent in that statement).

Four things especially struck us in Dr Müller's Editorial: (1) the high prevalence (20–40%) of mental health disorders among scientists and the general population, (2) that only a fraction of those afflicted receive professional help, (3) that many suffer in silence, concealing their condition even from their friends (as was the case for Jeremy), and (4) there remains a public stigmatism regarding mental health diseases *vs.* somatic diseases (despite some progress in recent decades). The latter three points are surely interdependent and reinforce a situation that makes it often difficult, even for friends and family, to help those they love and care about. As Dr Müller highlights, we may be more likely to discuss our prostate or breast cancer, than our psychological ailments.

We as biomedical research professionals should champion breaking the culture of silence surrounding mental health in our community. We encourage all to gain awareness and openness of mental health disorders where we work and live, through training how to best help those who are suffering, sometimes in silence, from these diseases. That awareness and sensitivity would honour Jeremy and, hopefully, help others or ourselves in the future.

Conference White Paper on mechano-electric coupling and mechano-chemo-transduction

In addition to the brief Editorial by Astrid Müller, this Special Issue includes one White Paper on the scientific foci of the 2018 meeting, one Topical Review, five original Research Papers, and a related Perspectives article. The UC Davis Cardiovascular Symposium series, *Systems Approach to Understanding Cardiac Excitation-Contraction Coupling and Arrhythmias*, is an on-going forum for cardiac researchers and physician-scientists to exchange ideas and build interdisciplinary collaborations. This international conference series commenced in 2010. The first symposium gathered about a hundred experimental investigators and mathematical modellers to carry out an overview and discussion of the contemperary issues in the cardiac excitation-contraction field. That set the stage for the subsequent biennial conferences focusing more deeply on certain critical areas. The topic of the 2012 conference was *Ca^{2+} channels and SR Ca^{2+} release*. In 2014 the topic was *Na^{+} channel and Na^{+} transport* (Bers & Chen-Izu, 2015) and the conference produced three White Papers (Chen-Izu *et al.* 2015; Clancy *et al.* 2015; Shattock *et al.* 2015). The 2016 topic was *K^{+} channels and regulation* (Bers & Chen-Izu, 2017) and produced two White Papers (Grandi *et al.* 2017; Chiamvimonvat *et al.* 2017). The 2018 topic was on *Mechanics and Energetics*. Together, this series of conferences is building in-depth quantitative understanding in each topic area and helping to combine these key areas to better integrate knowledge on complex heart disease mechanisms.

The 2018 symposium focused on cardiac mechanics and energetics in eight sessions: (1) Mechanics and energetics in heart diseases and arrhythmias; (2) Genetic mutations illuminate mechanics-energetics interplay; (3) Mechano-chemo-transduction; (4) Mechano-electro-transduction; (5) Mitochondria energetics in heart diseases and arrhythmias; (6) Mitochondrial Ca^{2+} and reactive oxygen species (ROS); (7) Feedbacks between energetics and excitation-contraction coupling; (8) Mechanics-energetics feedbacks and therapeutic targets.

This Special Issue of the *Journal of Physiology* is linked to the 2018 UC Davis Cardiovascular Symposium on *Mechanics and Energetics in Cardiac Arrhythmias and Heart Failure* (HF). The meeting was attended by 120 researchers from 12 countries in a workshop format aimed at assessing current state of knowledge in the field and identifying future directions for targeted research.

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The White Paper by Izu *et al.* (2020) summarizes conference presentations and discussions on the cardiac mechanics and mechanotransduction topics (mechano-electro-transduction or coupling (MEC) and mechano-chemo-transduction (MCT)). This symposium was timely because new research in these historically understudied areas has been recently boosted by the development of new techniques to control and measure mechanical load on single cardiac myocytes, enabling in-depth mechanistic studies at cellular and molecular levels.

In the paradigm of cardiac muscle excitation-contraction coupling, the MEC and MCT constitute feedback mechanisms from the cell contraction to the electrical activity and Ca^{2+} homeodynamics. Closing such feedback loops is essential to understanding how cardiac muscles sense mechanical load and transduce that information to biochemical reactions that regulate cell function in response to external loading. This White Paper comprises two parts, one covers key aspects of MEC and the other of MCT. The paper emphasizes current understanding, consensus, controversies, and pressing issues for future investigations (Izu *et al.* 2020). This is critically important for the long-term goal to integrate all relevant dynamic systems to gain a comprehensive understanding of cardiac E-C coupling, arrhythmias and heart failure (HF). Several additional papers are part of this Special Issue.

Computational modelling of mechanotransduction

Joca *et al.* (2020) developed a computational model to incorporate mechanotransduction features into the cardiac model of excitation-contraction coupling. Their model is based on experimental data linking mechanical stretch of resting cardiomyocyte to generation of NADPH oxidase 2 (NOX2)-dependent ROS, called X-ROS. This model expands from the existing models of Ca^{2+} signalling to include microtubule (MT)-dependent mechanotransduction through X-ROS. Informed and constrained by experimental data, their model aims to quantify the role of X-ROS on excitation-contraction coupling in healthy and pathological conditions. Moreover, such a computational model can be used to explore the effects of mechanical stretch, changes in MT network density and changes in xROS on cardiac Ca^{2+} handling and arrhythmogenic activities. This important step can be extended by additional quantitative data to further integrate the model into more comprehensive models to better understand the dynamic systems that govern cardiac function and diseases.

Pressure-overload induced changes in Na^+ and Ca^{2+} handling leading to heart failure

Ke *et al.* (2020) investigated pressure-overload induced HF using a trans-aortic constriction (TAC) mouse model during both compensated hypertrophy and then decompensated HF. The load-induced hypertrophy was associated with increased late Na^+ current and decreased Na^+/K^+-ATPase current, which due to Na^+/Ca^{2+} exchange elevated SR Ca^{2+} content and helped to maintain myocyte contraction in this stage. In contrast, the HF stage was associated with reduced SR Ca^{2+} content and spontaneous Ca^{2+} release. Thus, long-term remodelling led to deleterious consequences and decompensated HF. Their findings provide potential clues as to mechanical load induced remodelling in cardiomyocytes. Future studies will help decipher the mechano-transduction pathways involved.

Energetics and Ca^{2+} regulation of mitochondrial function

Wang *et al.* (2020) have written a Topical Review on mitochondrial Ca^{2+} regulation and energetics. Recent identification of the mitochondrial Ca^{2+} uniporter (MCU) and its associated proteins have been reported to play key roles in coupling Ca^{2+} homeodynamics to mitochondrial function and ATP production. While genetic knockouts of MCU abolish rapid mitochondrial Ca^{2+} uptake, they do not abolish all mitochondrial Ca^{2+}, and different functional knockout models differ in the penetrance of adverse phenotype or energetic deficiency. In their review, the authors reexamine the existing literature on mitochondrial Ca^{2+} regulation and propose other possible mechanisms, such as a non-MCU Ca^{2+} handling pathway and extra-mitochondrial Ca^{2+} regulation, that may contribute to the excitation-contraction-bioenergetics coupling in cardiac muscle.

Nickel *et al.* (2020) further tested the potential role of Ca^{2+}-calmodulin dependent protein kinase II (CaMKII) in regulating the MCU and Ca^{2+} uptake into mitochondria (which has been a controversial point). They performed rigorous experiments using the cardiac-specific CaMKII δ and γ double knockout (KO) mice (CaMKIIδ/γ DKO) and global CaMKIIδ KO mice, and discovered that CaMKII had no effect at all in controlling mitochondrial Ca^{2+} uptake in cardiomyocytes. Mitochondrial redox state and ROS production were also unchanged in CaMKIIδ/γ DKO. Their experimental data do not support the previous hypothesis that CaMKII modulates Ca^{2+} uptake via MCU and thereby mitochondria function and energetics in cardiomyocytes under physiological load conditions.

Metabolic remodelling in Duchenne muscular dystrophy heart

Hughes *et al.* (2020) investigated the remodelling of mitochondria energetics and cardiac dysfunction in Duchenne muscular dystrophy (DMD). Using the D2.B10-DMD^{mdx} /2J mice – an animal model that demonstrates skeletal muscle atrophy and weakness due to limited regenerative capacities and cardiomyopathy more akin to people with DMD – they discovered impairments in ADP-stimulated respiration and ADP attenuation of H_2O_2 emission. They found that the susceptibly to permeability transition pore opening and the subsequent cell death remained unchanged. Mitochondrial H_2O_2 emission was elevated despite no irreversible oxidative damage, suggesting an alternative redox signalling mechanism. Their findings add to an emerging view on how mutations or defects in structural proteins, possibly involved in mechanotransduction, could affect mitochondria ATP production and DMD-related cardiac cardiomyopathy.

Metabolic remodelling in type-2 diabetic heart

Cortassa *et al.* (2020) investigated type-2 diabetes (T2DM) induced metabolic remodelling of glucose, fatty acid and redox pathways that lead to HF. Previous data showed that palmitate or glutathione can preserve mitochondrial energy/redox balance and rescue β-adrenergic-stimulated cardiac excitation-contraction coupling. Their study further elucidates the mechanisms underlying the metabolic cardiac

remodelling in T2DM by combining metabolomics-fluxomics with bioinformatics and computational modelling. The results provide new insight as to how fatty acid such as palmitate can improve redox status via enhanced β-oxidation and decreased glucose uptake, suggesting a possible therapeutic strategy for treating T2DM hearts during peaks of hyperglycaemia and increased workload. The scientific significance and clinical relevance of their findings are further elaborated in the Perspectives article by Bertero *et al.* (2020).

Conclusion

The heart is a dynamic organ that beats rhythmically to perform its physiological function, which is dysregulated in heart diseases such as arrhythmias and HF. Cardiac function and diseases are governed by complex dynamic systems, including the electrical, Ca^{2+} handling, contractile, and metabolic systems. Each of these non-linear dynamic systems involves many molecules interacting with regulatory feedback loops. Hence, it is essential to combine experimental investigation with mathematical modelling to decipher complex mechanisms, test mechanistic insights, and understand physiological functions and pathological remodelling. Such in-depth quantitative understanding of the cardiac dynamics is critical for developing effective therapeutic strategies to combat heart diseases. This Special Issue focuses on two important research areas: mechanotransduction and energetics, which will help advancing the knowledge frontiers and therefore be of interests to readers.

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Additional information

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