EDITORIAL

Gordon Research Conference on Cardiac Arrhythmia Mechanisms 2023: early career investigators' views on emerging concepts and technologies

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Gordon Research Conferences (GRCs) offer an international forum for the presentation and discussion of cutting-edge research in the biological, chemical, physical and engineering sciences, bringing together outstanding scientists from the field. In a subset of GRCs, there is the Gordon Research Seminar (GRS), a meeting organised by and for early career investigators (graduate students and postdoctoral fellows) to provide a unique environment that encourages their discussions and interactions. The GRC on Cardiac Arrhythmia Mechanisms took place this year in Galveston, Texas, and marked the 20th year, celebrating the 10th edition. From 26 February to 3 March 2023, nearly 200 international researchers convened for the biennial meeting themed 'Advancing Arrhythmia Therapy by Bridging the Scales from Molecule to Organ'. This meeting was preceded by the 4th edition of the GRS on Cardiac Arrhythmia Mechanisms attended by more than 70 internationally diverse early career researchers. The GRC meeting was organised by chairs David Christini and Ursula Ravens, alongside vice-chairs Crystal Ripplinger and Edward Vigmond, with Enaam Chleilat and Jaclyn Brennan-McLean chairing the GRS.

Fruitful discussions held during the GRS/GRC inspired us, early career investigators, to briefly summarise what we believe are important emerging concepts and technologies in cardiac arrhythmia research. This editorial aims to highlight recent advances in sex-specific cardiac physiology, computational modelling, neural regulation of the heart, microscopy techniques and anti-arrhythmic technologies, reported in recently published work by several attendees.

Personalised medicine is an emerging concept that has gained increasing attention over the last decade. The aim of personalised medicine is to provide patient-specific diagnosis and treatment by considering intrasubject variability such as sex, age, comorbidities and genetic profiles. Sex is a clear differentiator in biology that has been overlooked for decades. Fortunately, studies considering sex-based differences at the computational, physiological and clinical level have gained in popularity over the past few years. In the past, research has predominantly been conducted on all-male populations, leading to a certain degree of bias in medicine. These assumptions often lead to inaccurate conclusions for female subjects by disregarding possible sex differences in physiology. With regard to arrhythmia research, the lack of female representation hinders our understanding of underlying mechanisms, and may lead to suboptimal diagnoses and treatments. This is evident as sex-specific differences in cardiac autonomic control (Caldwell et al., 2023) and ion channel function (Thibault et al., 2022) highlight female-specific targets for the treatments of arrhythmias. Furthermore, the advent of large-scale sex disease-based genomic datasets has opened new pathways for exploring the role of sex in cardiovascular disease and therapy (Deviatiiarov et al., 2023). It is also crucial to consider circumstances where sex hormones are altered, such as with age, and how these can impact cardio-protection against arrhythmias. Sex has been identified as a factor in the prevalence and recurrence of age-related atrial arrhythmias (Zink et al., 2020), further highlighting the need for continued research into personalised medicine.

Cardiac computational modelling and simulations have played an important role in advancing our understanding and treatment of cardiac arrhythmias. These relatively novel technologies offer an alternative to classical experimental methods, reducing ethical and economic barriers. A recent study on cardiotoxicity that combines computational modelling with human-induced pluripotent stem cell-derived cardiomyocytes (Clark et al., 2022) provides a prime example of how modelling and experimental approaches can be synergistically used in pre-clinical trials for regulatory decision-making, providing an animal-free alternative to existing protocols (Wadman, 2023). Furthermore, computational modelling offers a new strategy to guide drug development (Dasí et al., 2022) and personalised healthcare through the concept of the *digital twin* (Corral-Acero et al., 2020) – the creation of a digital version of the patient that provides tailored diagnosis and therapy (Azzolin et al., 2023). Patient-specific modelling is likely to be accelerated by the use of Gaussian process emulators (Rodero et al., 2023) that minimise computational costs compared to traditional biophysically based computer simulations (Solis-Lemus et al., 2023).

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Overall, computational models will only continue to become more advanced, providing more efficient alternatives to traditional experimental methods and playing a crucial role in future patient care.

Neural regulation of the heart is an exciting area of investigation, both for basic researchers and for clinicians alike. As more knowledge is gained about the inter-connectivity and co-localization of parasympathetic and sympathetic nerves and their regulation of cardiac rhythm, so too is the promise of perturbing these innervations against arrhythmogenesis. Newly discovered similarities between cardiac and neuronal isoforms of key ion channels suggest that neuronal phenotypes may be targeted instead of cardiac phenotypes to treat arrhythmias (Li et al., 2020). Advances in stem cell research are also revealing that neuronal phenotypes can contribute to increased neurotransmission and excitability in cardiac disease models (Winbo et al., 2021). Researchers are still uncovering the complex architecture of autonomic innervation in which pacemaking cells reside (Bychkov et al., 2022). Our increasing understanding of the influence of the neural system on cardiac function has already led to a new neuromodulation therapy for the treatment of atrial fibrillation (Hanna et al., 2021). Therefore, as cardiac researchers and neuroscientists continue to advance knowledge in their respective fields, opportunities to work at their intersection may have the potential to combat arrhythmias.

Emerging technologies can also serve as catalysts for research fields, as expanding the instruments available to investigators often leads to transformative new discoveries. A clear avenue for expansion is the microscopy toolkit, as imaging is often an essential step towards understanding the underlying mechanisms of arrhythmias. Recent advances in sample preparation techniques for electron microscopy may now be used to integrate temporal information at the near-atomic level. This allows for novel insights into 3D cardiac nanodynamics, improving the understanding of the behaviour of organelles and the role that they may play in a pathological setting (Kohl et al., 2022). Furthermore, innovative microscope design inspired by the Newtonian telescope has the potential to significantly enhance the researcher's toolkit. Specifically, such microscopes facilitate near-simultaneous high-resolution image acquisition of multiple Petri dishes without the need for moving components, which enables parallel long-duration recordings that are unachievable with conventional automated microscopes (Ashraf et al., 2021). Technology such as this has immense potential for shared remote operation in an incubator, which increases research accessibility beyond the lab. This is exciting as it represents a significant step towards democratising experimental resources and facilitating borderless collaboration among researchers. Furthermore, this technology has a strong synergy with the latest optogenetic tools (Heinson et al., 2023), which may enable a massively parallel, all-optical method to non-invasively investigate arrhythmia mechanisms in cardiomyocytes.

Collaborations between cardiac electrophysiologists, material scientists and surgeons are fuelling advances in novel anti-arrhythmic technologies and clinical therapies. Some of the most common developments in arrhythmia treatments include implantable devices and catheter ablations. Novel biointerfaces such as the wireless tissue-conformable graphene arrays may become a new generation of cardiac pacemakers as they have the ability to effectively detect and treat arrhythmias in mice (Lin et al., 2022). Alternatively, advancements in catheter ablation may go beyond the electronics, as outcomes are dependent on clinician delivery, rather than the tool. Near-infrared spectroscopy-empowered catheters can be used for guidance during ablation procedures, enabling clinicians with real-time monitoring of myocardial response for more effective lesion delivery (Park et al., 2021). Although this technique may improve the success rate of ablation therapies, it does not prevent arrhythmia recurrence. Integrating artificial intelligence with explainable machine learning algorithms may provide valuable diagnostics in the clinical setting, for locating atrial fibrillation drivers (Luongo et al., 2021) and determining patient outcome following ablation treatment (Bifulco et al., 2022).

In addition to highlighting the frontiers of our current technology and biological knowledge in this review, it is critical to promote sustainability in research by upholding ethical standards and transparency. However, the academic environment can hinder this by prioritising volume over quality due to fixed-term contracts and the need for attractive results, both of which are contributing to the ongoing reproducibility crisis (Begley & Ellis, 2012). Moreover, competition can create reluctance to share data and methodologies despite the FAIR (findable, accessible, interoperable and reusable) guiding principles for scientific data management and stewardship, which were developed by the scientific community that it is meant to serve. Reproducibility, transparency and *failing forward* as advocated in the GRS keynote given by Peter Kohl are necessary steps for excellence.

Alongside scientific excellence, the 2023 GRC/GRS provided positive momentum for the international scientific cardiac arrhythmia community that has been significantly impacted by the global pandemic. The widespread disruptions caused by COVID-19 led to the postponement of numerous conferences, hindering opportunities for collaboration, networking and dissemination of research. Nevertheless, the pandemic also spurred innovation, stimulated the desire for transformation, and has ultimately accelerated the adoption of new technologies and widespread digitalization.

During the meeting, attendees took a moment to pay tribute to two esteemed cardiac arrhythmia researchers and former GRC attendees who passed away in the last year: Mike Rosen (1938–2023), a renowned scientist in cardiac arrhythmias and electronic and stem cell pacemaker therapies, and Matthew Amoni (1991–2022), an emerging scientist in the field of ischaemic heart disease. Though their loss is deeply felt, their legacy of ground-breaking research will continue to inspire future generations of cardiac researchers.

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Additional information

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