Multimodal image integration to better explain human ventricular tachyarrhythmias

Impact

In this PhD thesis, I apply multimodal image integration to improve the understanding and management of potentially-lethal human ventricular tachyarrhythmias by the combined assessment of cardiac structure and function. The results of my work can aid the indication, timing and focus of ablation for ventricular tachycardia. Being trained in Technical Medicine (MSc), my scientific contributions should be contextualized within the broader framework of global developments in the field of medical technology, specifically cardiac electrophysiology, medical imaging, personalized computational heart modeling and artificial intelligence.

In **Chapter 2**, I provide a state-of-the-art review of the history, applications and future perspectives of electrocardiographic imaging (ECGI). Noninvasive ECGI has significantly advanced our insights of the electrical activity of the heart. However, further development, reproducibility, standardization and user-friendliness are necessary for ECGI's widespread clinical adoption. The contents of this Chapter inform clinicians and engineers about the benefits and pitfalls of ECGI, because only an in-depth understanding of both will allow for reasonable use of ECGI and careful interpretation of the data in clinical context. Moreover, we identify areas where further research is required. This can guide future studies into the technological advancement and standardization of ECGI, by academia and industry. Such advancements can in turn improve ECGI's clinical application, and therefore, personalized medicine and the understanding and treatment of cardiac arrhythmia syndromes. This Chapter is published in an open access book discussing the heritage and promise of electrocardiography and electrophysiology. The book is freely available (ISBN 978 90 67677 82 0).

In **Section 3.2**, I introduce a novel algorithm (UNISYS) that provides a standardized visualization and representation of any kind of single-layer ventricular data, e.g., electrical, mechanical, structural, or a combination of those. This can aid in the interpretation of results obtained by ECGI and other techniques involving ventricular anatomy. For example, regional electrical properties can be compared between subjects in a standardized manner by using UNISYS, such as in **Chapter 5**. Furthermore, UNISYS aids in the integration of multiple modalities, e.g., echocardiographic and ECGI-based measurements of the heart. Thus, UNISYS advances image integration in cardiology and therefore the understanding and management of heart disease. UNISYS can be of use to engineers, scientists and clinicians and is openly available at http://ecg-imaging.org/software/visualization-tools. The relevance of this tool is further demonstrated by the fact that world-wide at least five different research groups are currently (October 2023) using the algorithm routinely, helping to achieve standardization in the field. Furthermore, in **Section 3.3**, I identify the influence of using a static diastolic geometry on the inverse solution of ECGI. Although the heart is a contracting and moving organ, it is commonly approximated in a static diastolic state in ECGI. I show that the impact of this approximation is low in

general, but local deviations in electrical recovery time (RT) determination may occur, mainly because of flat or noisy epicardial T-waves. These deviations seem unrelated to the heart's contraction. Consequently, imaging of the heart anatomy for ECGI can be achieved with limited scanning time and radiation exposure, underpinning current practice. In **Section 3.4**, I investigate the variability in inverse reconstruction within one lead set, and between different lead set configurations. I show that in general, between-lead set variability is higher than within-lead set variability, except for RT determination. Variability of RT may be difficult in case of flat or noisy epicardial T-waves. The findings of **Sections 3.3** and **3.4** aid in the interpretation of ECGI by engineers and clinicians, by quantifying the complexities that come with two of its common approximations, and by better identifying the difficulties in RT determination. This further aids in the standardization of ECGI. The technical aspects of these findings may also be of use to other medical inverse problems, such as the reconstruction of electrical activity on the brain or stomach, and therefore also contribute to future research in neuroscience, and gastroenterology. The findings of Chapter 3 were published as 3 papers in Computing in Cardiology, thus reaching a broad audience of engineers and scientists in cardiovascular medicine.

In **Chapter 4**, I address the long-lasting controversy on the determination of RT from the intracardiac unipolar electrogram and ECGI. Accurate assessment of RT is crucial for understanding cardiac conditions related to (regional) abnormal electrical activity. Through novel and historical analyses, I identified the Wyatt method to be the most accurate for determining RT, which unifies RT measurement in experimental and clinical settings and thereby defines a standard for future studies in the field. This will aid basic and clinical scientists, and clinicians, to better examine and understand cardiac electrical recovery in patients. Even though it is known that local RT plays a crucial role in cardiac arrhythmia syndromes, it is often not considered in their clinical treatment, which could in part be caused by the controversy regarding the determination of RT. The unification of RT measurement can thus improve diagnostic assessment, treatment, risk prediction and management of cardiac arrhythmias and other repolarization-dependent conditions of the heart. As the measurement of repolarization in the heart requires clinical protocols and technological aspects that are different from conventional mapping procedures, the findings of this Chapter may also influence the development of mapping protocols and technology by industry. **Chapter 4** was published in *Frontiers in Physiology*, a multidisciplinary open-access journal—and therefore freely available (DOI: 10.3389/fphys.2023.1158003). *Frontiers in Physiology* has a diverse audience, primarily consisting of basic and translational scientists. Thus far (January 2024), it has been viewed and downloaded almost 1800 times. My thread on the social medium *X* was seen almost 4000 times.

In **Chapter 5**, I report on normal variation of the electrical characteristics of the ventricles of the heart, using ECGI. I evaluate the influence of sex, age, stability over time, and different diseases. I obtain new insights in (localized) differences

in activation and repolarization between individuals, sexes, and age groups. Although all subjects have a normal 12-lead ECG, I show that their underlying epicardial activation and recovery patterns can be profoundly different. My findings provide a reference, based on physiological variation in the human heart, to comprehend and contextualize cardiac electropathologies. Furthermore, these results reveal individual characteristics by ECGI, thus providing a type of cardiac *fingerprinting*. Thus, I contribute to the development of personalized approaches for patients with cardiac electropathologies and arrhythmias. Other functional readouts, such as cardiac mechanics, autonomic or drug responses can be easily added in the future, to provide the next level of understanding of these pathologies. We plan to make all outcome measures of this Chapter publicly available, to support open science. Preliminary results of this work were presented at the *European Society of Cardiology (ESC)* Congress (2020) and the *Computing in Cardiology* conference (2021), thus reaching broad communities of clinicians and engineers.

In the clinical studies for **Chapter 6**, we identify several *DPP6* missense variants associated with long-QT syndrome (LQTS) and J-wave syndrome (JWS) in patients with an increased arrhythmia risk and/or documented ventricular fibrillation (VF). Through a series of translational experiments, we show that DPP6 reciprocally regulates I_{Na} and I_{to} and demonstrate its consequences at the tissue and heart level. Our integrative findings contribute to the understanding of the genetic basis of VF in the structurally-normal heart. They can aid basic and clinical scientists in the development of targeted therapies for individuals with these genetic variants. Moreover, they lead to better management and the prevention of arrhythmic events, thereby alleviating anxiety and depression in persons at risk. Preliminary results of this work were presented at the *ESC* Congress (2022) and the annual meeting of the *ESC Working Group on Cardiac Cellular Electrophysiology* (2022), attended by many basic and clinical scientists, and cardiologists.

In **Chapter 7**, I present a personalized 3D model by multimodal image integration that incorporates high-resolution structural and electrical information for the management of ventricular tachycardia (VT). This proof-of-concept study enhances our personalized mechanistic understanding of scar-related VT, and could be further extended to non-structural heart disease. My pioneering study provides an advanced roadmap for catheter ablation in the clinical setting. This may lead to improved success rates of ablation procedures, reduced arrhythmia-recurrence rates, better cost-effectiveness of VT treatment, and enhanced patient safety and quality of life, benefiting patients suffering from VT and clinicians performing these invasive procedures. This Chapter was published in the open-access journal *Frontiers in Cardiovascular Medicine*, and freely available (DOI: 10.3389/fcvm.2023.1112980). Thus far (January 2024), it has been viewed and downloaded almost 1700 times. My post on the social medium *X* was seen over 1100 times.