Arrhythmogenic mechanisms in inherited and acquired cardiac diseases

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11

ENGLISH SUMMARY

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Dysregulation of cardiac electrical activity can lead to disturbances of normal cardiac rhythm. Such arrhythmias can occur in the setting of inherited, as well as acquired disease. Independent of the underlying disease, often, genetic and acquired risk factors both contribute to arrhythmogenesis and as such are both important for determining an individual's arrhythmic risk. Likewise, mechanisms underlying both types of factors must be addressed for development of antiarrhythmic therapies. The overarching objective of the current thesis was to discover mechanistic pathways involved in arrhythmia in inherited disease and define arrhythmic risk in COVID-19.

Part I – Arrhythmogenesis in inherited cardiac diseases

The first part of the thesis focused on arrhythmogenesis in the setting of inherited cardiac diseases.

In **chapter 2** we reviewed the epidemiology of primary electrical disorders, including an overview of reported founder populations causing these disorders. The prevalence of the different primary electrical disorders is difficult to establish due to the rarity of these conditions as well as the occurrence of genotype-positive, phenotype-negative individuals. Besides for long QT syndrome (LQTS), the prevalence of most of these conditions therefore remains to be established. In geographic regions harboring founder mutations such as those causing LQTS, the prevalence for these disorders is much higher. For most primary electrical disorders, genotype-phenotype correlations have been identified, but demographic characteristics are often lacking, due to scarcity of intensive research efforts in non-Western countries. In **chapter 3** we reviewed the contribution of genetic variants in the non-sarcomeric genes to the different cardiomyopathies. Although variants in these genes underlie only a minority of cardiomyopathy cases, they may be involved in both hypertrophic- and dilated cardiomyopathy, often through opposite biological effects, allowing them to provide us with insights into the pathophysiology of cardiomyopathies. These genes highlight common pathways for the different types of cardiomyopathy, although differences in types of variants result in a distinct genetic basis and a distinct phenotype.

In **chapter 4** we attempted to bridge the gap between the large number of loci that have been associated with electrical traits and the lag in the identification of the (likely) causal gene at these loci. By correlating the activity of putative enhancers with gene expression across 87 human tissue samples we predicted the cognate gene for 5,977 putative enhancers. Since a large part of GWAS loci are assumed to associate with disease by modulating the function of such enhancers, we then integrated this dataset with other omics data, to predict the most likely candidate gene at 256 ECG-associated GWAS loci. In total, we propose the most likely candidate gene for 68 heart rate/heart rate recovery/heart rate variability-, 47 PR-, 22 QRS- and 56 QT-interval associated loci. As a validation, we generated a knockout model for the gene *Tmem182*, which is a promising candidate gene for two independent PR-associated loci on chromosome 2. While exploratory electrophysiological studies in *Tmem182*$^{-/-}$ mice did not uncover an effect on PR duration, these mice seemed more vulnerable to supraventricular arrhythmias as compared to wild-type mice.

In **chapter 5** we investigated a Brugada syndrome (BrS)-associated locus for which the functional link to BrS was not yet proposed. Through *in silico* analysis of various omics datasets we provided

evidence that *WT1* is the causal gene at this locus. We demonstrated an association between the BrS GWAS lead SNP, rs72905083, and transcript abundance of *WT1* in human cardiac tissue, whereas PCHi-C data demonstrated chromatin contact between the promoter region of *WT1* and the associated region. We also showed that the activity of putative cardiac enhancers located within the BrS-associated region is associated with transcript abundance of *WT1*. Through functional studies in aged *Scn5a*$^{+/-}$ mice, we demonstrated that loss of *Wt1* partially mitigated conduction abnormalities. This effect was uncovered in the setting of an extremely challenged conduction reserve, through acute administration of ajmaline or pacing at the refractory period. Effects on conduction would concur with the central role of conduction slowing in the pathogenesis of BrS.

In **chapter 6** we dived deeper into electrophysiological mechanisms of the J-wave. In humans, J-waves can occur in a benign, as well as malignant setting. The latter includes rare inherited J-wave syndromes, consisting of BrS and early repolarization syndrome. In small rodents, such as mice, J-waves are present in the baseline ECG. We hypothesized that the J-wave is an evolutionary aspect, present in all small endothermic animals and is caused by early repolarization, which allows for short cardiac cycles and thus enables high heart rates, necessary in such animals. By comparing isolated hearts of two endothermic animals, namely mice and zebra finch, a bird species with high heart rates, we showed that both species exhibit a J-wave on the ECG, which results from early repolarization. We also showed that pharmacological blockade of I_{to} and I_{Kur}, the current underlying early repolarization in the mouse, slowed early repolarization and attenuated the J-wave in both species.

11

Part II – Arrhythmogenesis in COVID-19

The second part of this thesis was dedicated to arrhythmogenesis in COVID-19, an acquired viral infection, known to potentially cause acute respiratory distress syndrome. During the COVID-19 pandemic, early studies raised concerns about cardiac involvement of the disease, potentially resulting in high arrhythmic burden. One potential arrhythmic risk factor concerned the deployment of the drugs hydroxychloroquine and chloroquine ((H)CQ). These drugs can prolong action potential duration (APD) and QTc, increasing the risk for torsade de pointes, a life-threatening arrhythmia. **Chapter 7** provides an overview of the evidence for (H)CQ as a treatment in COVID-19 and as a potential arrhythmic risk factor. Although *in vitro* studies and early cohort studies provided evidence for a beneficial effect of (H)CQ, this was not confirmed by larger observational studies. In addition, based on studies investigating the use (H)CQ in other infectious disease, such as malaria, the reported prevalence of serious life-threatening arrhythmias related to the use of (H)CQ is low. However, we hypothesized that COVID-19 patients have increased vulnerability to (H)CQ induced QTc prolongation due to an already prolonged QTc at baseline. We further provided clinical recommendations regarding electrocardiographic monitoring when administrating (H)CQ to patients, since at the time, a total of 60 studies investigating the effect of (H)CQ were announced, potentially recruiting a total of 175,000 individuals.

Chapter 8 comprises an editorial comment on a study that investigated the prevalence of atrial fibrillation in COVID-19 patients and which provided evidence for increased in-hospital mortality

in COVID-19 patients with atrial fibrillation. By providing an overview of studies investigating the arrhythmic risk in COVID-19, we conclude that it is clear that the heart is involved in COVID-19 symptomatology. We further hypothesized that rhythm disorders are also to be expected in patients with long COVID. In **chapter 9** we investigated the prevalence of various types of arrhythmias in a large European COVID-19 cohort. In a total of 5,782 COVID-19 patients, we observed atrial fibrillation/atrial flutter in 12.0%, conduction disorder in 6.8% and ventricular arrhythmias in only 0.8%. We furthermore showed that *de novo* atrial fibrillation/atrial flutter was associated with increased risk of in-hospital mortality, specifically in male patients aged 60-72 years, whereas this association was not observed in female patients.