Electrophysiological patterning of the heart
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**Scope of the thesis**

Sudden cardiac death accounts for 300,000 deaths annually in the United States.\(^1\) Although the majority of sudden cardiac death is due to coronary heart disease, up to 5% is due to primary electrical or genetic ion channel abnormalities.\(^2\) To this category belong the Wolff-Parkinson-White (WPW), Brugada and Long QT syndrome as well as congenital atrioventricular (AV) block or acquired diseases of the sinus node.\(^3\) The mechanism of arrhythmia differs between these cardiac pathologies, but it may result, if untreated, in ventricular fibrillation or a-systole leading to sudden death.\(^2\) The majority of the patients with primary electrical disease or hereditary ion channel abnormalities are treated effectively by implantation of a electronic pacemaker (for sinus node dysfunction AV block or the Brugada syndrome\(^4,5\)), by radiofrequency ablation (in WPW patients\(^6\)), or pharmacologically (in most Long QT syndrome patients\(^7\)). In some of these patients an automatic internal cardioverter defibrillator is implanted to treat VF with electroshock. In a small percentage (<10%) of the patients sudden cardiac death is the first manifestation of the disease.\(^8,9\) Therefore, risk stratification of patients is important. Unfortunately, we lack information on specific markers of an increased risk of death from arrhythmias in the general population and among those with nonspecific and intermediate risk profiles. The general hypothesis underlying this thesis is that understanding of the normal embryonic development of the electrical properties of the heart would provide insight into the mechanisms of abnormal development and function, and therefore can be used to define factors that are important for electrical dysfunction. Thus, the thesis seeks to bridge the gap between embryonic cardiac development and lethal function which, could lead to the identification of new specific markers for an increased risk of arrhythmias occurring in adulthood. We use Brugada syndrome, WPW syndrome, Sick sinus syndrome and AV node dysfunction as models for this approach.

In **chapter 1** we introduce the term ‘electrophysiological patterning’ and explain which transcription factors are involved in generating the electrophysiological properties of structures in the ventricular myocardium and the AV node. In **chapter 2** we studied the role of T-box (Tbx) transcription factor 2 in patterning of the AV canal and its role in the formation of accessory pathways (related to WPW-syndrome). In **chapter 3** we investigated the role of transcription factor Nkx2-5 and Tbx3 in the formation, function and maintenance of the AV conduction system. In **chapter 4** we review the temporal and spatial expression of transcription factors in relation to electrophysiological heterogeneities that exist in the ventricular myocardium of the adult heart, with a main focus on the right ventricular outflow tract (RVOT, related to Brugada Syndrome). In **chapter 5** we studied the differences in function and gene expression between RVOT and the right ventricle, and explored the hypothesis that the slow conduction property and gene expression program of the embryonic outflow tract are maintained in the adult RVOT. In **chapter 6**, an editorial, we comment on a study that introduced a new family of cAMP binding proteins called Popeye-containing-domain proteins, which is involved in age and stress.
dependent sinus node dysfunction. In chapter 7 we related local activation and repolarization times to the surface electrocardiogram (ECG) of the mouse. In chapter 8 the thesis is summarized.

Reference List


