Pathophysiological mechanisms of arrhythmogenic right ventricular disorders
Hoogendijk, M.G.

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CHAPTER 1

Introduction

Mark G. Hoogendijk
Sudden cardiac death (SCD) is a leading cause of mortality in the industrialized world. Most cases are attributed to ventricular tachyarrhythmias and occur in the setting of coronary artery disease. The arrhythmogenic consequences of coronary artery disease have been studied extensively. Our understanding of the pathophysiological mechanisms of SCD in other patient groups, however, is often less complete. This thesis focuses on the pathophysiological mechanisms involved in two such groups: those with Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy (ARVC).

The Brugada syndrome

The Brugada syndrome is characterized by coved ST-segment elevation (≥0.2 mV) followed by a negative T wave in the right precordial leads. It was this hallmark ECG pattern that set the patients apart from other victims of idiopathic ventricular fibrillation (VF) at the introduction of the Brugada syndrome as a clinical entity in 1992. This electrocardiographic feature has become known as the ‘coved-type’ or ‘type 1’ Brugada ECG and will be referred at as the Brugada sign or Brugada ECG pattern throughout the remainder of this thesis.

A familial occurrence was suspected in 2 of 8 patients in the first case reports. Indeed, genetic mutations have been identified in Brugada syndrome patients. The first identified were loss-of-function mutations located in SCN5A, the gene encoding the pore-forming α-subunit of the cardiac sodium channel. These SCN5A mutations can be found in 15-25% of patients. Other loss-of-function mutations with clinically significant prevalence are located in the genes encoding the α1- and β2b-subunit of the L-type calcium channel. The reported combined prevalence of these mutations is 2-9%. According to the 2005 consensus report, the Brugada syndrome can be diagnosed if the Brugada ECG pattern is recorded in >1 right precordial leads and occurs in conjunction with indications of ventricular tachyarrhythmias, inducibility of these arrhythmias by programmed electrical stimulation or a suspected familial occurrence of the Brugada syndrome. A familial occurrence of the Brugada syndrome is suspected in the presence of a family history of sudden cardiac death at <45 years old or the presence of the Brugada ECG pattern in family members. Noteworthy, many other conditions can cause ST-segment elevation and may mimic the Brugada ECG pattern. Such conditions and alternative causes of syncope should be considered and excluded before diagnosing the Brugada syndrome.

Demography

The Brugada syndrome occurs predominately in men which outnumber women in a 2.6 : 1 ratio in the largest registry to date. The average age at diagnosis is in the fifth
decade of life. The prevalence of the Brugada syndrome is hard to estimate as the Brugada ECG pattern is dynamic and can even disappear temporarily. Screening of ECGs for the Brugada ECG pattern will therefore underestimate the prevalence of the Brugada syndrome. The Brugada ECG pattern could be identified in 0.8/1000 and 1.2/1000 ECGs recorded during medical checkup in a largely middle aged population in Japan. The prevalence of the Brugada ECG pattern in Western Europe and the United States of America using similar methods appears to be much lower.

The relation between the Brugada ECG pattern and ventricular tachyarrhythmias

Absence of mapping studies that univocally demonstrate the arrhythmogenic substrate in Brugada syndrome patients has left room for speculation and made the underlying pathophysiological mechanism subject of debate. What is generally agreed upon is that a single mechanism underlies both the Brugada ECG pattern and the ventricular tachyarrhythmias. Indirect support for this notion can be found in patients with a temporarily normalization of the ECG in whom the Brugada ECG pattern reappears prior to the initiation of a ventricular tachyarrhythmia. Secondly, premature ventricular complexes preceding and initiating ventricular tachyarrhythmia commonly have a vector opposite of the ST-segment of the Brugada ECG pattern indicating that both stem from the same myocardial area. Recently, a more direct demonstration of the origin of the Brugada ECG pattern and the associated arrhythmias has been provided in an epicardial mapping and ablation study in highly symptomatic Brugada syndrome patients. Unipolar electrograms recorded at the right ventricular outflow tract strongly resembled the Brugada ECG pattern and ablation at these sites resulted in a marked reduction in arrhythmic events and disappearance of the Brugada ECG pattern in most patients. Elucidation of the mechanism of the Brugada ECG pattern will therefore also elucidate the arrhythmogenic mechanism of the Brugada syndrome.

Genesis of electrocardiographic waveforms

QRS complex and T wave

Essential to this thesis’ aim of delineating the pathophysiological mechanism of the Brugada ECG pattern is the understanding of the genesis of the ECG. In healthy individuals, the ventricular electrocardiographic waveforms are usually limited to the QRS complex and the T wave which reflect the physiological heterogeneities during ventricular activation and repolarization. The ST-segment in healthy individuals is usually isoelectric with the exception of the precordial leads which may display a modest elevation of the QRS-ST junction termed early repolarization. The activation sequence underlying the QRS complex in man was clarified by Durrer et al. in 1970. Ventricular activation in the human heart is initiated and spreads from areas high on the left anterior paraseptal wall below the attachment of the mitral valve, the central left side of the intraventricular septum, the left posterior paraseptal area about
a third from the apex to the base and from the endocardium near the anterior papillary muscle of the tricuspid valve. Last activated are the posterobasal left and basal right ventricle. Repolarization is a much slower process from a cellular perspective than activation. Consequently, characterization of the T wave as a result of a specific repolarization sequence is inaccurate as the T wave reflects potential gradients present during all phases of cellular repolarization. The repolarization gradients underlying the T wave in man are subject of debate in the absence of whole heart mapping data of repolarization in the human heart. Nevertheless, the repolarization and activation sequence must generally have an opposite direction to account for the concordant direction of the QRS-complex and T wave.

**Figure 1.** Schematic drawing of three cardiomyocytes with the corresponding action potentials depicted in their center during three different phases of the cardiac cycle (QRS complex, ST-segment and T wave). The direction of activation (open) and repolarization fronts (closed) are indicated by arrows. The effect of activation and repolarization on the intra- and extracellular potentials is depicted by + and −. The ECG until the indicated phases is depicted in black to the right.

**ST-segment elevation**
ST-segment elevation is a common electrocardiographic feature that can occur in
many different cardiac conditions. Nonetheless, the action potential configurations underlying the ST-segment elevation in these conditions can be reduced to only six (Figure 2).

Figure 2. Schematic drawing of action potential configurations potentially underlying ST-segment elevation. AP = action potential.

The isoelectric ST-segment in man reflects the absence of a potential gradient during the action potential plateau phase of the ventricular myocardium. Disruption of the overlap in plateau phase of the ventricular myocardium is a binding factor of five action potential configurations underlying ST-segment elevation. The overlap can be disrupted by activation delay (e.g. bundle branch block), which will cause ST-segment deviation discordant with the QRS complex. Secondly, marked regional activation delay can obscure the distinction between the QRS-complex and the ST-segment. Consequently, the ensuing deflection may be misinterpreted as ST-segment deviation although it reflects activation and is therefore part of the QRS complex.

Thirdly, regional excitation failure in electrically coupled myocardium will lead to a large potential gradient with the excited neighboring myocardium. The action potential of the neighboring myocardium will be visible as a monophasic ST-segment elevation on the ECG. Regional changes in the action potential shape are a fourth reason of causing a potential gradient during the plateau phase of the action potential and of ST-segment elevation. Fifth, action potentials can be shortened to such an extent that the distinction between the ST-segment and the T-wave is obscured and the deflection may be misinterpreted to reflect ST-segment elevation. Alternatively, ST-segment elevation on the ECG can reflect depression during the diastolic interval (TQ-segment) which acts as a reference potential for the ST-segment. Regional changes in the resting membrane potential will cause such a TQ-segment depression.

These six action potential configurations are not exclusive. For example, TQ-segment depression, changes in the action potential shape and excitation failure all contribute to the ST-segment elevation in regional myocardial ischemia.

Hypothesized action potential configurations underlying the Brugada ECG pattern

The action potential configuration and thereby the mechanism of the Brugada syndrome has been debated for many years. Before initiation of the research incor-
porated in this thesis, two hypothesized mechanisms in particular were met with acclamation. The first hypothesis was based on intrinsic ventricular heterogeneities in the repolarization characteristics and suggested that a combination of subepicardial changes in the action potential shape and early completion of repolarization causes the Brugada ECG pattern.\textsuperscript{34} The second hypothesis considered marked activation delay in the right ventricle, via an unspecified mechanism, the action potential configuration underlying the Brugada ECG pattern.\textsuperscript{30} None of these hypotheses however, have been rigorously tested in patients.\textsuperscript{22} The challenges met in testing of these hypothesis is that the substrate of the Brugada syndrome is located subepicardially\textsuperscript{25} and difficult to assess directly in a clinical setting.

Factors to be incorporated in hypothesized mechanisms of the Brugada syndrome
In contrast with local mechanistic measurements, much information has appeared on modulators of the Brugada syndrome.\textsuperscript{11,22} The mechanisms by which some of these modulators, such as vagal activity of the autonomic nervous system\textsuperscript{23}, febrile illness\textsuperscript{38} and the eating of a copious meal\textsuperscript{39}, exert their effect is unclear. Other modulators have a more predictable effect on the myocardium and have been used in deductive reasoning on the mechanism of the Brugada syndrome.\textsuperscript{22} The cardiac sodium current ($I_{Na}$) appears to be the most potent of these modulators: sodium channel blockers can augment or provoke the Brugada ECG pattern\textsuperscript{40} and $SCN5A$ mutations are the most common identified mutations in patients.\textsuperscript{9} Conversely, the class Ia sodium channel blocker quinidine and isoproterenol can ameliorate the Brugada ECG pattern\textsuperscript{41,40} and have been used to prevent arrhythmic events.\textsuperscript{42,43} The effect of quinidine is generally considered to result from blockade of the transient outward current ($I_{to}$) and the effect of isoproterenol by augmentation of the L-type calcium current ($I_{CaL}$).\textsuperscript{11} Mutations leading to a loss-of-function of the L-type calcium channel have been identified in Brugada syndrome patients as well\textsuperscript{10,44}, albeit at a lower frequency than $SCN5A$ mutations.\textsuperscript{9} It therefore seems reasonable that any hypothesized mechanism of the Brugada syndrome should incorporate modulation by the $I_{Na}$, $I_{to}$ and $I_{CaL}$.

More controversial is the question whether structural abnormalities should be incorporated in hypothesized mechanisms of the Brugada syndrome as its diagnosis requires the exclusion of structural heart disease.\textsuperscript{11} Overt histological abnormalities have however, been observed in patients with the Brugada ECG pattern after sudden cardiac death\textsuperscript{45-47} and more subtle changes were found in endocardial biopsies of Brugada syndrome patients.\textsuperscript{48,49,50} Interestingly, the Brugada ECG pattern could also be provoked in patients with a preexisting cardiac condition leading to structural abnormalities such as ARVC\textsuperscript{51} and Chagas disease\textsuperscript{52}. This suggests that a factor in these patients, such as structural discontinuities, predispose them to development the Brugada ECG pattern.
CHAPTER 1

The Brugada syndrome in this thesis
In Chapter 2 of this thesis, the complete ventricular activation and repolarization characteristics are presented of the explanted heart of a loss-of-function mutation carrier in SCN5A (G752R) and dilated cardiomyopathy after provocation of right-sided ST-segment elevation by the sodium channel blocker Ajmaline. Local electrograms and histological examinations indicate that excitation failure in discontinuous myocardium underlies the ST-segment elevation via current-to-load mismatch. The feasibility of this hypothesis is tested in a computer model encompassing the heart and thorax.

In Chapter 3, an in vitro model is presented of ST-segment elevation via excitation failure by current-to-load mismatch. Subsequently, the modulation of current-to-load mismatch by \( I_{\text{to}} \) and \( I_{\text{CaL}} \) is tested in the same computer model used in Chapter 2.

In Chapter 4, the genetic background, function modulation and indications of structural abnormalities in the Brugada syndrome are reviewed with the aim to form a unifying hypothesis on the mechanism of the Brugada syndrome.

In Chapter 5, the overlap in features between idiopathic VF victims with inferolateral J-point elevation and the Brugada syndrome is explored in an editorial comment.

Arrhythmogenic right ventricular cardiomyopathy
ARVC is a myocardial disorder in which cardiomyocytes are replaced by fibrous tissue and adipocytes and an arrhythmogenic ventricular substrate is formed. For long, it was considered to be primarily a right ventricular condition of which the anterior aspect of the outflow tract, apex and inferior wall or so-called “triangle of dysplasia” were thought to be most severely affected.\(^53\) It has become clear however, that left ventricular involvement is common and that predominate left ventricle manifestations can even occur.\(^54\) In light of these observations, the term “arrhythmogenic cardiomyopathy” has recently been proposed as an improved nomenclature.\(^55\) ARVC can be progressive\(^56,57\) and is associated with a significant risk of cardiovascular mortality by sudden cardiac death and heart failure.\(^58,59,60\) To date, no therapy has been demonstrated to slow or prevent the development of ARVC.

The pathophysiological mechanism of arrhythmogenic right ventricular cardiomyopathy
Mechanical overload of the myocyte-myocyte junction is considered to be the pivotal mechanism in ARVC.\(^61\) This concept arose after the demonstration of mutations in ARVC patients which are located in the genes encoding the so-called desmosomal proteins, which are important components of the adhering junctions between cardiomyocytes.\(^62,63\) These mutations can be identified in ~40% of ARVC patients\(^54\) and are located in the genes encoding plakoglobin\(^64\), desmoplakin\(^65\), plakophilin-2\(^66\), desmoglein-2\(^67\) and desmocollin-2\(^68\). Mouse models based on the altered expression
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of desmosomal proteins\textsuperscript{69,70,71} recapitulate ARVC in man and have been used to study the pathophysiological mechanism. Besides reduced strength, increased load on the myocyte-myocyte junction has also been implicated to cause development or progression of ARVC. Endurance training increases the mechanical load on the heart and especially the right ventricle: a single episode of prolonged, strenuous exercise such as an Ironman Triathlon\textsuperscript{72} or ultramarathon at altitude\textsuperscript{73} results in a dilatation of specifically the right ventricle which resolves within 1-2 days after the race.\textsuperscript{72,73} In line with this concept, daily endurance training accelerates the development of the ARVC phenotype in the model of heterozygous plakoglobin deficient mice.\textsuperscript{70} Not surprisingly, a history of endurance training has been associated with a greater severity of ARVC.\textsuperscript{54}

Arrhythmogenic right ventricular cardiomyopathy in this thesis

In Chapter 6, the concept that mechanical overload of the myocyte-myocyte junction causes ARVC is challenged by testing of the hypothesis that pharmacological reduction of the mechanical load on myocyte-myocyte junction can prevent the development of ARVC in the model of trained heterozygous plakoglobin-deficient mice. If so, this would be the first demonstration of a pharmacological intervention that may prevent the development or progression ARVC.

In Chapter 7, the overlap of clinical features between the Brugada syndrome and ARVC is discussed to aid in the diagnostic process of these conditions.

Cardiac energy consumption during ventricular fibrillation

The last experimental chapter of this thesis focuses on the consequences rather than the cause of VF. VF causes the myocardium to contract uncoordinatedly at a high frequency and is followed rapidly by loss of the perfusion pressure\textsuperscript{74} and death if left untreated. Survival of out-of-hospital cardiac arrest by VF depends on the swift initiation of cardiopulmonary resuscitation to maintain some perfusion and early termination of VF by providing a countershock.\textsuperscript{74,75,76,77} Despite the high defibrillation success rate of countershocks, patients still spend time in VF after the first shock because of recurrences of VF.\textsuperscript{78,79,80} Such recurrences occur in 60-80\% of resuscitations for VF\textsuperscript{78,79,80} and cause such patients to spend a median of 4 minutes in recurrent VF.\textsuperscript{78} The duration spent in recurrent VF is inversely correlated with survival of cardiac arrest by VF.\textsuperscript{78} The effect of recurrent VF on the myocardium during resuscitation attempts is currently unknown.

In Chapter 8, the hypothesis is tested that ventricular fibrillation increases the cardiac oxygen consumption and hampers the recovery of the myocardial energy state and contractility. This hypothesis is tested during simulated resuscitations in the Langendorff-perfused porcine hearts.
References


CHAPTER 1


