Ventricular Arrhythmias and Sudden Cardiac Death
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When, 40 years ago, intracardiac stimulation and activation studies were started for the analysis of cardiac arrhythmias, nobody could have predicted the advances that were going to be made in the years thereafter in our understanding and management of ventricular arrhythmias and sudden death.

Since then an enormous amount of information has become available, leading to our current understanding of mechanisms, etiology, epidemiology, risk stratification, and management of these, unfortunately too often occurring, life-threatening situations.

The best way to present that knowledge, and also the relation between those different areas, is to put it in the form of a book.

We live in a time when information spreads rapidly by way of the internet. However, tunnel vision is one of the dangers of that medium: the subspecialist, looking only for what is new in his or her specialized area, may lose sight of the complete picture with its inherent dangers.

Therefore one has to welcome this book for its coverage and time of publication. By selecting the contributors carefully, the editors have succeeded in bringing together, in one book, an excellent and complete overview of what the cardiologist should know for optimal management of the patient with a ventricular arrhythmia. Among the many in-depth presentations one will find how to select the candidate for catheter ablation, when to implant an ICD, and what measures have to be taken to reduce sudden death out of hospital.

Hein J. Wellens
Maastricht, The Netherlands
August 2007
CHAPTER 1

The role of spatial dispersion of repolarization and intramural reentry in inherited and acquired sudden cardiac death syndromes

Charles Antzelevitch

Abstract

The cellular basis for intramural reentry that develops secondary to the development of transmural dispersion of repolarization (TDR) is examined in this review. The hypothesis that amplification of spatial dispersion of repolarization underlies the development of intramural reentry and life-threatening ventricular arrhythmias associated with inherited ion channelopathies is probed. The roles of TDR in the long-QT, short-QT, and Brugada syndromes as well as catecholaminergic polymorphic ventricular tachycardia are critically examined. In the long-QT syndrome, amplification of TDR is generally secondary to preferential prolongation of the action potential duration (APD) of M cells, whereas in the Brugada syndrome, it is due to selective abbreviation of the APD of right ventricular epicardium. Preferential abbreviation of APD of either endocardium or epicardium appears to be responsible for amplification of TDR in the short-QT syndrome. The available data suggest that the long-QT, short-QT, and Brugada syndromes are pathologies with very different phenotypes and etiologies, but which share a common final pathway in causing sudden cardiac death.

Keywords:

long QT syndrome; short QT syndrome; Brugada syndrome; polymorphic ventricular tachycardia; electrophysiology

Inherited sudden cardiac death secondary to the development of life-threatening ventricular arrhythmias have been associated with a variety of ion channelopathies such as the long-QT, short-QT, and Brugada syndromes. Table 1.1 lists the genetic defects thus far identified to be associated with these primary electrical diseases. These ion channel defects have been shown to amplify spatial dispersion of repolarization, in some cases with the assistance of pharmacologic agents that further exaggerate the gain or loss of function of ion channel activity. Before examining these interactions, we will review the basis for intrinsic electrical heterogeneity within the ventricular myocardium.

Intrinsic electrical heterogeneity within the ventricular myocardium

It is now well established that ventricular myocardium is comprised of at least three electrophysiologically as well as functionally distinct cell types: epicardial, M, and endocardial cells [1,2]. These three principal ventricular myocardial cell types differ with respect to phase 1 and phase 3 repolarization characteristics. Ventricular epicardial and M,
Table 1.1 Inherited disorders caused by ion channelopathies

<table>
<thead>
<tr>
<th>Rhythm</th>
<th>Inheritance</th>
<th>Locus</th>
<th>Ion channel</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-QT syndrome (RW)</td>
<td>TdP</td>
<td>AD</td>
<td>11p15</td>
<td>KCNQ1, KvLQT1</td>
</tr>
<tr>
<td>LQT1</td>
<td>AD</td>
<td>7q35</td>
<td>lKr</td>
<td>KCNH2, HERG</td>
</tr>
<tr>
<td>LQT2</td>
<td>AD</td>
<td>3p21</td>
<td>lNa</td>
<td>SCN5A, Na;1.5</td>
</tr>
<tr>
<td>LQT3</td>
<td>AD</td>
<td>4q25</td>
<td>lKr</td>
<td>ANK2, ANK2</td>
</tr>
<tr>
<td>LQT4</td>
<td>AD</td>
<td>21q22</td>
<td>lKr</td>
<td>KCNE1, minK</td>
</tr>
<tr>
<td>LQT5</td>
<td>AD</td>
<td>21q22</td>
<td>lKr</td>
<td>KCNE2, MIRP1</td>
</tr>
<tr>
<td>LQT6</td>
<td>AD</td>
<td>1q23</td>
<td>lKr</td>
<td>KCNJ2, Kir 2.1</td>
</tr>
<tr>
<td>LQT7</td>
<td>(Anderson-Tawil syndrome)</td>
<td>AD</td>
<td>6q8A</td>
<td>CACNA1C, Ca,1.2</td>
</tr>
<tr>
<td>LQT8</td>
<td>(Timothy syndrome)</td>
<td>AD</td>
<td>3p25</td>
<td>CAV3, Caveolin-3</td>
</tr>
<tr>
<td>LQT9</td>
<td>AD</td>
<td>11q23.3</td>
<td>lNa</td>
<td>SCN4A, Na, bA</td>
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<tr>
<td>LQT10</td>
<td>AD</td>
<td>11p15</td>
<td>lKr</td>
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</tr>
<tr>
<td>LQT11</td>
<td>AD</td>
<td>21q22</td>
<td>lKr</td>
<td>KCNE1, minK</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>PVT</td>
<td>AD</td>
<td>3p21</td>
<td>SCN5A, Nav1.5</td>
</tr>
<tr>
<td>BrS1</td>
<td>PVT</td>
<td>3p24</td>
<td>lNa</td>
<td>GPD1L</td>
</tr>
<tr>
<td>BrS2</td>
<td>PVT</td>
<td>12p13.3</td>
<td>lCa</td>
<td>CACNA1C, Ca,1.2</td>
</tr>
<tr>
<td>BrS3</td>
<td>PVT</td>
<td>10q12.33</td>
<td>lCa</td>
<td>CACNB2b, Ca, B2b</td>
</tr>
<tr>
<td>BrS4</td>
<td>PVT</td>
<td>11p15</td>
<td>lKr</td>
<td>KCNQ1, KvLQT1</td>
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<tr>
<td>Short-QT syndrome</td>
<td>VT/VF</td>
<td>AD</td>
<td>7q35</td>
<td>KCNH2, HERG</td>
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<tr>
<td>SQT1</td>
<td>VT/VF</td>
<td>11p15</td>
<td>lKr</td>
<td>KCNQ1, KvLQT1</td>
</tr>
<tr>
<td>SQT2</td>
<td>AD</td>
<td>17q23.1-24.2</td>
<td>lKr</td>
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<tr>
<td>SQT3</td>
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<td>12p13.3</td>
<td>lCa</td>
<td>CACNA1C, Ca,1.2</td>
</tr>
<tr>
<td>SQT4</td>
<td>AD</td>
<td>10p12.33</td>
<td>lCa</td>
<td>CACNB2b, Ca, B2b</td>
</tr>
<tr>
<td>SQT5</td>
<td>AD</td>
<td>1q42-43</td>
<td>lKr</td>
<td>RyR2</td>
</tr>
<tr>
<td>Catecholaminergic VT</td>
<td>VT</td>
<td>AR</td>
<td>1p13-21</td>
<td>CASQ2</td>
</tr>
<tr>
<td>CPVT1</td>
<td>VT</td>
<td>AR</td>
<td>1q42-43</td>
<td>CASQ2</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; JLN, Jervell and Lange-Nielsen; LQT, long QT; RW, Romano-Ward; TdP, Torsade de Pointes; VF, ventricular fibrillation; VT, ventricular tachycardia; PVT, polymorphic VT.

but not endocardial, cells generally display a prominent phase 1, due to a large 4-aminopyridine (4-AP)-sensitive transient outward current (\(I_{\text{to}}\)), giving the action potential either a spike-and-dome or a notched configuration. These regional differences in \(I_{\text{to}}\) were first suggested on the basis of action potential data [3] and subsequently demonstrated using patch clamp techniques in canine [4], feline [5], rabbit [6], rat [7], ferret [8], and human [9,10] ventricular myocytes.

The magnitude of the action potential notch and corresponding differences in \(I_{\text{to}}\) have also been shown to be different between right and left ventricular epicardium [11]. Similar interventricular differences in \(I_{\text{to}}\) have also been described for canine ventricular M cells [12]. This distinction is thought to form the basis for why the Brugada syndrome, a channelopathy-mediated form of sudden death, is a right ventricular disease.

Wang and co-workers [13] reported a larger L-type calcium channel current (\(I_{\text{Ca}^2+}\)) in canine endocardial versus epicardial ventricular myocytes, although other studies have failed to detect any difference in \(I_{\text{Ca}^2+}\) among cells isolated from epicardium, M, and endocardial regions of the canine left ventricular wall [14,15]. Myocytes isolated from the epicardial region of the left ventricular wall of the rabbit show a higher density of cAMP-activated chloride current when compared to endocardial myocytes [16]. \(I_{\text{to}2}\), initially ascribed to a K\(^+\) current, is now thought to be caused primarily by the calcium-activated chloride current (\(I_{\text{Cl(Ca)}}\)); it is thought to also contribute to the action potential notch but it is not known whether this current...
differs among the three ventricular myocardial cell types [17].

**Characteristics of the M cell**

Residing in the deep structures of the ventricular wall between the epicardial and endocardial layers, are M cells and transitional cells. The M cell, masonic midmyocardial Moe cell, discovered in the early 1990s, was named in memory of Gordon K Moe [2,18,19]. The hallmark of the M cell is that its action potential can prolong more than that of epicardium or endocardium in response to a slowing of rate or in response to agents that prolong APD (Figure 1.1) [1,18,20]. Histologically, M cells are similar to epicardial and endocardial cells. Electrophysiologically and pharmacologically, they appear to be a hybrid between Purkinje and ventricular cells [21]. Like Purkinje fibers, M cells show a prominent APD prolongation and develop early afterdepolarizations (EAD) in response to $I_{Kr}$ blockers, whereas epicardium and endocardium do not. Like Purkinje fibers, M cells develop delayed afterdepolarizations (DAD) more readily in response to agents that calcium load or overload the cardiac cell. $\alpha_1$ Adrenoceptor stimulation produces APD prolongation in Purkinje fibers, but abbreviation in M cells, and little or no change in endocardium and epicardium [22].

Although transitional cells are found throughout much of the wall in the canine left ventricle, M cells displaying the longest action potentials (at basic cycle lengths (BCLs) $\geq 2000$ ms) are often localized in the deep subendocardium to midmyocardium in the anterior wall [23], deep subepicardium to midmyocardium in the lateral wall [18], and throughout the wall in the region of the right ventricular (RV) outflow tracts [2]. M cells are also present in the deep cell layers of endocardial structures, including papillary muscles, trabeculae, and the interventricular septum [24]. Unlike Purkinje fibers, M cells are not found in discrete bundles or islets [24,25] although there is evidence that they may be localized in discrete muscle layers. Cells with the characteristics of M cells have been described in the canine, guinea pig, rabbit, pig, and human ventricles [4,18,20,23–44].

Isolated myocytes dissociated from discrete layers of the left ventricular wall display APD values that differ by more than 200 milliseconds at relatively slow rates of stimulation. When the cells are in a functional syncytium that comprises the ventricular myocardium, electrotonic interactions among the different cells types lead to reduction of the APD dispersion to 25–55 milliseconds. The transmural increase in APD from epicardium to endocardium is relatively gradual, except between the epicardium and subepicardium where there is often a sharp increase in APD (Figure 1.2). This has been shown to be due to an increase in tissue