Idiopathic Ventricular Fibrillation and Early Repolarization

11

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Abstract

In this chapter, an overview is provided on idiopathic ventricular fibrillation (IVF) and early repolarization. Idiopathic ventricular fibrillation is a tragic and notoriously difficult disease entity to manage. The IVF patients in whom a cardiac arrest occurs are generally considered healthy and do not show any currently identifiable abnormalities that denote their increased risk for malignant and life-threatening arrhythmias. Importantly, IVF can be inheritable and tear through families. The number of patients who survive their first manifestation of the disease is low, and the recurrence rate of IVF is appreciable. Treatment in patients who survived their event is performed by implantation of a cardioverter defibrillator (ICD) and a decrease of the risk of IVF recurrence may be achieved by prescription of quinidine. During a VF storm, administration of isoproterenol can be essential, and possibly also sedation might be effective. Research into the origin and genetic underpinning of IVF is limited by its malignant character, yet has revealed genetic variants in the *DPP6* gene and *CALM1* gene that impact on cellular cardiac electrophysiology. In contrast, early repolarization is a description of electrocardiographic variants with elevation, slurring, or notching in the terminal QRS complex or early ST segment. Although considered a benign electrocardiographic characteristic for many decades, in the past decade associations have been made with a propensity to sudden cardiac arrest by VF. Importantly, early repolarization is of very common occurrence in many young and healthy individuals. The description of a rare malignant association has spurred scientific interest in this phenomenon. Fortunately, its benign prognosis is still valid for the vast majority of individuals who display an early repolarization pattern. The challenge for the future will be to delineate benign

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from malignant variants of early repolarization, the development of aids in risk stratification and a better understanding underlying pathophysiology on cellular and genetic level, to further guide clinicians and patients.

11.1 Idiopathic Ventricular Fibrillation

11.1.1 Introduction

Ventricular fibrillation (VF) is a chaotic electrical and mechanical activity of the cardiac ventricles and always results in severe hypotension leading to haemodynamic collapse. When not treated within minutes, the shortage of sufficient perfusion of the brain and other organs will result in permanent damage and ultimately death. Likewise, VF is still the most common cardiac rhythm documented at the time of sudden cardiac arrest and sudden cardiac death (Viskin and Belhassen 1990; Huikuri et al. 2001; Hulleman et al. 2015).

The cause of VF is not always known or uncovered afterwards, but in the majority of cases, atherosclerotic coronary artery disease is the underlying aetiology either due to acute myocardial ischemia or due to scar tissue that has developed after myocardial ischemia. This scenario is also considered to occur in the general population without previous symptoms as a sequence of previously silent coronary artery disease resulting at one time in an atherosclerotic plaque rupture, leading to obstruction in the coronary artery, myocardial ischemia, subsequent VF and cardiac arrest, and ultimately death when resuscitation is not directly started and/or not effective (Chugh et al. 2008). However, there are many more disease aetiologies that may proceed to VF, both cardiac and noncardiac in origin, such as intracranial haemorrhage, pulmonary embolism, myocarditis, cardiomyopathies, valvular heart disease, congenital cardiac anomalies and accessory pathways (Viskin and Belhassen 1990; Corrado et al. 2003; Puranik et al. 2005; Elliott et al. 2008; Maron et al. 2009; Postema et al. 2011a).

A specific group of causes of VF is inheritable cardiac disease, which may result in an excessively high VF occurrence in multiple family members. This is likely due to genetic mutations that share a propensity for the development of a substrate and/or trigger for VF. Such mutations may either disrupt the cardiac architecture, e.g. due to excessive hypertrophy, fibrosis or dilatation, or change the normal cardiac action potential morphology resulting in anomalous depolarization or repolarization characteristics (Postema et al. 2011a). Importantly, VF may not only occur at advanced age but also young adults, teenagers, children and even newborns may be at risk due to these underlying disease entities.

The scope of the problem of VF is large but not very easy to count because it takes only minutes before VF deteriorates in asystole and subsequent death, necessitating fast recognition and treatment. As a reference, in the United States, the estimations of cardiac arrest and subsequent sudden death range between 180,000 and 400,000

victims per year (Chugh et al. 2008; Zipes and Wellens 1998). In prospective studies, an incidence rate of 55 adult cardiac arrest cases per 100,000 person-years was documented (Berdowski et al. 2010). Because of the rising risk factors for cardiovascular disease such as obesity and diabetes, it is thought that these numbers will increase in the next decades (Chugh et al. 2008). There are several large efforts worldwide to investigate the occurrence, causes and modifiable factors of VF and cardiac arrest in the community. One such effort is the Amsterdam-based ARREST study. These investigators actually documented 15% *decline* in VF as the initial cardiac rhythm in cardiac arrest victims between 1995–1997 and 2006–2012 (Hulleman et al. 2015). This decline was explained by less initial VF (and thus more bradycardia, asystole or pulseless electrical activity) and an increase in unwitnessed cardiac arrest. The survival rates of out-of-hospital cardiac arrest victims are very low globally, around 7% (Berdowski et al. 2010). However, when the initial rhythm is VF, survival rates are better, around 17% (Berdowski et al. 2010). Likewise, the increased use of implantable cardioverter defibrillators (ICDs) to directly recognize and treat commencing VF was found to result in an estimated 33% decrease of cardiac arrest due to VF (Hulleman et al. 2012).

For the prevention of a first or recurrent episode of VF, it is very important to recognize the factors that precede the substrate and triggers that cause VF, as a means to treat these factors and prevent its occurrence. As mentioned, many disease entities may result in a higher propensity to VF. However, in some cases the cause of VF remains unknown, even after extensive evaluations. These cases can be labelled as idiopathic VF (IVF). It is thought that IVF accounts for approximately 5% of all VF cases (Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States 1997), although with the increasing knowledge of today, this percentage might currently be even lower.

Although IVF thus involves only a minority in the total burden of VF, it is a notoriously difficult disease entity to manage. This is because there are no signs to adequately identify the propensity to VF of these patients when they are still asymptomatic, and the first event is often lethal. Subsequently, modifiable factors are not recognizable nor treatable. In addition, IVF generally occurs in young patients, children and young adults, previously thought to be healthy. In addition, IVF may also tear through families because it might be inheritable, adding to its tragic character.

11.1.2 IVF Diagnosis

The diagnosis of IVF may well not be straight forward. There are two main obstacles that form the basis of the difficulties we have with an IVF diagnosis; (Viskin and Belhassen 1990) it is a very rare entity where only a minority survives the first manifestation of the disease and can proceed to a diagnostic evaluation, and (Huikuri et al. 2001) it is a *per exclusionem* diagnosis.

In those who are successfully resuscitated from a first VF episode, several evaluation schemes are available. These should include a detailed documentation of the event, medical history, family history, physical examination, electrocardiography (ECG), blood chemistry (including blood counts, electrolytes and cardiac enzymes) and other investigations aimed at diagnosing coronary artery disease (e.g. coronary angiography, also considering evaluation of coronary spasm) and/or structural heart disease (e.g. echocardiography, cardiac magnetic resonance imaging). The registration of the arrhythmia(s) can be very useful in this effort to delineate the course and origin of the event. When the diagnosis is not (fully) established after the previous investigation rounds, the further evaluations should be considered: exercise testing (in search of signs of ST-segment changes, abnormal conduction or repolarization characteristics or provocation of arrhythmias), Holter monitoring (also for abnormal conduction or repolarization or arrhythmias), toxicology screening, cardiac biopsies and/or drug provocation testing with sodium channel blocking drugs (e.g. ajmaline, flecainide or procainamide, in search of Brugada syndrome) or adrenaline (in search of long-QT syndrome or catecholaminergic polymorphic ventricular tachycardia) (Postema et al. 2009a, 2011a; Wolpert et al. 2005; Krahn et al. 2005). Clearly, depending on the particular case, there will be a differentiation in the necessity and order of these investigations. Coronary angiography in particular will be one of the first steps in the evaluation also because of the potential of therapeutic options during the procedure.

When no clues to the origin of the VF episode are found, an IVF diagnosis can be made. For the patient, this diagnosis may not have direct consequences as a secondary prevention ICD will generally be indicated (Priori et al. 2015; Zipes et al. 2006). However, choices for drug treatment to prevent IVF recurrences may well affected by an IVF diagnosis. For example, quinidine might be a life-saving treatment option in IVF (Dock 1929; Ten Sande et al. 2016) but can have devastating results in long-QT syndrome due to its QT prolonging effects (Jervell and Lange-Nielsen 1957; Selzer and Wray 1964). In addition, for the family members an IVF diagnosis in the index patient may have consequences. In about 5–20% of IVF victims, a family history of sudden unexpected deaths at young age is indeed present (Belhassen et al. 1999; Haissaguerre et al. 2002; Noda et al. 2005). When there is a possible or clear family history of inheritable IVF, the screening of the family members is particularly difficult because even the index patient does not have a phenotype that is indicative of the disease, apart from IVF. Primary prevention ICDs in the family members, based on the available data that underscores the age at which the risk is exceptionally high, might be the ultimate preventive treatment option in these families (Ten Sande et al. 2016; Alders et al. 2009; Postema et al. 2011b). However, implanting ICDs in these (often) young patients will surely result in ICD-related complications, which needs to be carefully weighed against the possible benefits (Olde Nordkamp et al. 2013, 2016).

Genetic analysis of the index patient might in some cases with a clear familial occurrence reveal the underlying genetic substrate (Alders et al. 2009; Marsman et al. 2014). This, however, often requires many years of dedicated research and particularly large families with multiple patients who survived the IVF event and

who are able to undergo the necessary evaluations and comparisons in search of common genetic denominators.

When there is no VF documentation in a resuscitated or suddenly deceased patient, the sudden cardiac arrest or sudden death may well be due to another disease entity as opposed to IVF. Still, as previously mentioned, VF will only continue for minutes and will ultimately deteriorate into asystole. When asystole commences, the changes of survival decrease rapidly, and thus the possibilities to make an IVF diagnosis decrease simultaneously. When the patient does not survive the event, a detailed family history is still of paramount importance, as this may provide clues to an inheritable disease entity. When there is indeed a suspicion of inheritable disease, detailed evaluations of the family members will still be appropriate (Postema et al. 2011a; van der Werf et al. 2010).

11.1.3 IVF and Channelopathies

In the past centuries, sudden cardiac deaths in young and otherwise healthy individuals have challenged many families and doctors. Our ever-increasing knowledge on cardiac disorders and possibilities to delineate different phenotypes with an increased risk for malignant arrhythmias has impressively changed our understanding of sudden cardiac arrest. Importantly, what was considered idiopathic or without known cause in the past can at present be a clear and distinct disease entity which is recognizable and often also treatable. As such, many distinct disease entities have been described in the past 70 years (Table 11.1).

For nearly all of these disease entities, except for malignant early repolarization syndrome, a strong genetic background underlying these entities has been uncovered as well. The genetic mutations that are involved in these syndromes all impact on cardiac architecture (e.g. hypertrophic cardiomyopathy or arrhythmogenic (right) ventricular cardiomyopathy) or on cellular electrophysiology affecting either depolarization or repolarization characteristics (e.g. Brugada syndrome and long-QT syndrome). Interestingly, there are also overlap syndromes due to specific mutations which combine separate disease entities in individual patients (Bezzina et al. 1999; Postema et al. 2009b).

Although it is regarded that IVF is heritable in 5–20% of cases, there have until present only been two genetic substrates uncovered to explain the heritability of IVF (Alders et al. 2009; Marsman et al. 2014). In 2009, a haplotype involving the *DPP6* gene was found to be coinciding with IVF in several large and distantly related families involving over 600 family members (Alders et al. 2009). This gene is implicated in the transient outward current (I_{to}) in cardiac Purkinje tissue in particular and is believed to upregulate I_{to} (Alders et al. 2009; Xiao et al. 2013). This process may explain the propensity to short-coupled extrasystoles and VF in these patients although the exact pathophysiological mechanisms remain to be clarified (Fig. 11.1). In 2013/2014, a mutation in CALM1 was found to be associated with familial IVF (Marsman et al. 2014). This gene is implicated in calcium handling through calmodulin. Interestingly, mutations in this gene had earlier been implicated

Table 11.1 Milestone publications describing distinct disease entities with a propensity to inheritable malignant cardiac arrhythmias that were previously considered idiopathic

Year	Syndrome	Authors	Diagnosis by
1951	Long-QT syndrome	Jervell and Lange-Nielsen (1957)	ECG, exercise testing, Holter monitoring
1958	Hypertrophic cardiomyopathy	Teare (1958)	Post-mortem, echocardiography, ECG, biopsy
1978	Catecholaminergic polymorphic ventricular tachycardia	Coumel et al. (1978)	Exercise testing, Holter monitoring, adrenaline provocation
1982	Arrhythmogenic right ventricular cardiomyopathy/ dysplasia	Marcus et al. (1982)	Post-mortem, ECG, echocardiography, MRI, biopsy, Holter monitoring
1992	Brugada syndrome	Brugada and Brugada (1992)	ECG, sodium channel blocker provocation
2000	Short-QT syndrome	Gussak et al. (2000)	ECG
2008	VF associated with early repolarization	Haissaguerre et al. (2008)	ECG
2009	IVF associated with *DPP6*	Alders et al. (2009)	Genetic analysis
2013	IVF associated with *CALM1*	Marsman et al. (2014)	Genetic analysis

Table adapted from Postema et al. (2011a). IVF denotes idiopathic ventricular fibrillation. ECG denotes electrocardiogram

in cases of catecholaminergic polymorphic ventricular tachycardia (CPVT) and long-QT syndrome (LQTS) (Nyegaard et al. 2012; Crotti et al. 2013). Both *DPP6* and *CALM1* have not been replicated in other IVF families until date. Although this might partly be due to the rarity of the disease and the many years of intensive research that coined these discoveries, it also illustrates the probably diverse genetic background in the remainder of IVF families.

In this particular case, the patient went into VF storm without preceding symptoms, and after multiple ICD shocks on recurrent VF out of the hospital, atrial fibrillation developed and lasted until presentation in our clinic. On arrival at our cardiac care unit, VF initiated again from a short-coupled extrasystole from the RV free wall (putatively from Purkinje network) and was now captured on 12 L ECG. Further episodes of VF were prevented by administration of isoprenaline.

11.1.4 IVF Prognosis and Treatment

In contrast to the good long-term prognosis without VF recurrences in patients who survive their first episode of VF during acute myocardial ischemia (de Jong et al. 2009), the prognosis of patients with IVF is rather poor. It is reported that around 25–46% of the IVF patients have recurrent VF events, including recurrent VF storms

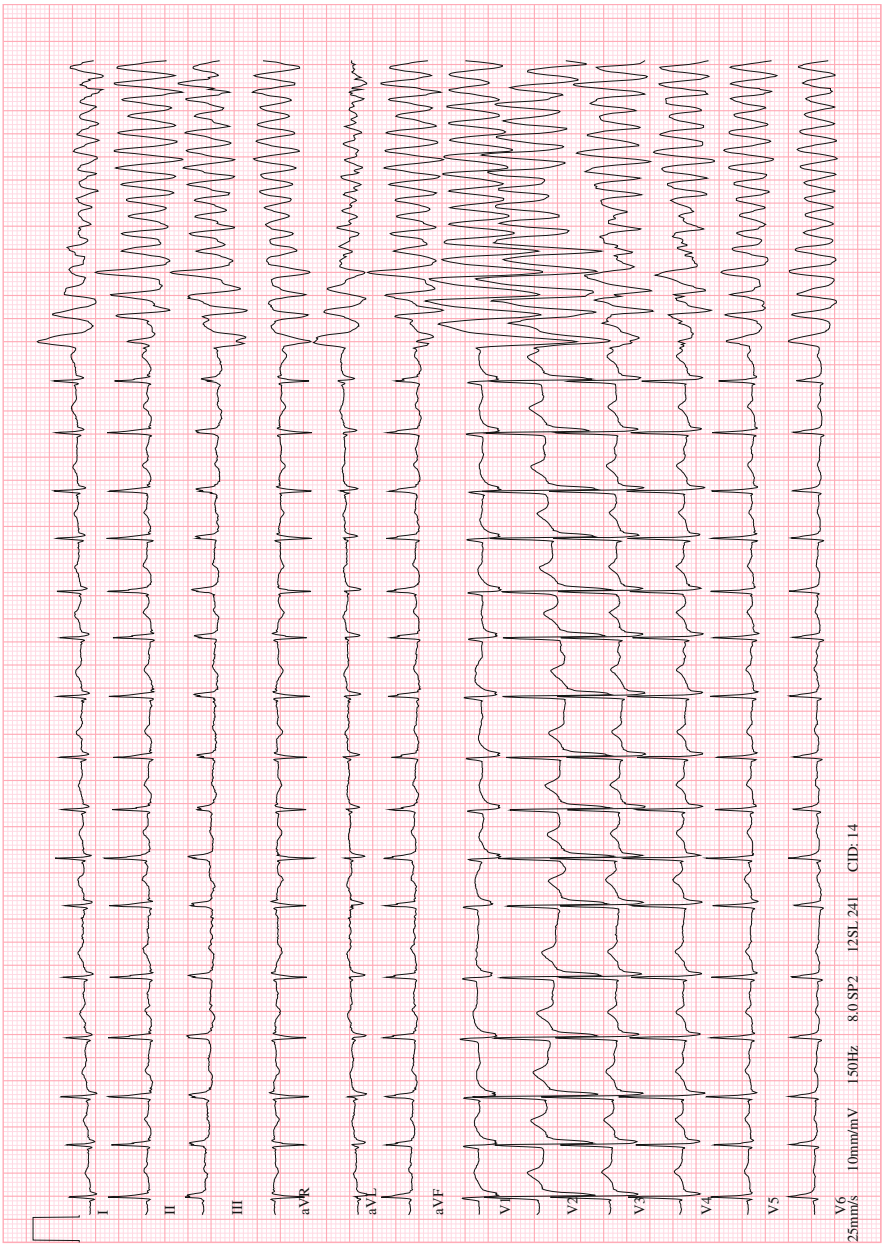


Fig. 11.1 Onset of ventricular fibrillation (VF) in a DPP6 patient

(Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States 1997; Ten Sande et al. 2016; Wever et al. 1993; Remme et al. 2001; Wever and Robles de Medina 2004). Although ICDs are designed to lower the risk of dying from VF, a risk of dying from cardiac arrhythmia even with an ICD remains (Brugada et al. 2009; Sacher et al. 2013a). Regrettably, this risk includes morbidity and mortality from ICD-related complications (Olde Nordkamp et al. 2013, 2016). In addition, patients with IVF are generally much younger and in much better general condition than patients who receive an ICD for primary or secondary prevention in ischemic cardiomyopathy. The exposure time of the IVF patients to possible ICD-related complications is thus much longer (Postema et al. 2011a).

As to antiarrhythmic drug therapy in IVF to decrease the recurrence rate of VF, there are therapeutic options. Importantly, the efficacy of the use of these drugs differs between patients, probably because of different, but currently unrecognized, underlying pathophysiology. In *DPP6*-related IVF, for example, beta blockers and amiodarone are considered to be ineffective. Instead, the drugs of choice in these patients are quinidine and isoproterenol (Ten Sande et al. 2016). This knowledge base is particularly important when there is need of treatment during VF storm. In VF storm isoproterenol is a quick-acting drug that can (only) be provided intravenously. In addition, sedation (either conscious sedation or deep sedation including intubation and respiratory support) might have antiarrhythmic effects. Whether high-frequency pacing also has beneficial effects is currently unknown in this specific patient population. However, addition of quinidine surely is effective in many of these patients either during or after VF storm to prevent or lower VF recurrence rates on the short and long term. Importantly and similarly to Brugada syndrome, low-dose quinidine might already be effective (Marquez et al. 2012). A potential problem of quinidine during VF storm is its oral administration route and hours of time to peak effect, necessitating treatment by other means during the acute phase (e.g. with isoproterenol). In general, in most IVF patients, quinidine will be the drug of choice for long-term therapy (Postema et al. 2011a; Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States 1997; Ten Sande et al. 2016; Wever et al. 1993). The difficulties on the availability of quinidine that have recently been encountered due to the threat of the manufacturers to terminate its production are therefore extremely alarming (Viskin et al. 2007, 2013; Wilde and Langendijk 2007).

11.1.5 IVF Conclusions

Idiopathic ventricular fibrillation (IVF) is a tragic and notoriously difficult to treat disease entity. Its hallmark is a presentation with sudden cardiac arrest due to VF, in individuals who were previously considered healthy and who do not show any other remarkable features upon rigorous evaluations. Its idiopathic nature and the low numbers of patients who survive its first manifestation trouble past and future

research and development of effective treatment. In a considerable number of cases, IVF appears to be inheritable and threatens the lives of family members in a wide age range. In recent years, there has been progress in our understanding of IVF by the recognition of genetic variations that segregate with the phenotype. As such, presymptomatic family members can be identified and preventive treatment can be offered. Prevention of sudden cardiac death is now predominantly succeeded by implantation of implantable cardioverter defibrillators (ICDs). However, ICDs in this young and otherwise healthy population will coincide with ICD-related complications in the majority of patients during their lifetime. A better selection of patients who may benefit from preventive ICD therapy is therefore warranted. Drug therapy with quinidine in chronic and acute settings, and with isoproterenol in acute settings, can be life-saving options as well. Importantly, exclusion of non-IVF-related cardiac arrest is important as these drugs may aggravate the clinical condition of patients with other disease etiologies.

11.2 Early Repolarization

11.2.1 Introduction

Early repolarization is a morphological description of electrocardiographic variants in the terminal QRS complex or early ST segment. Although its definition is changing and debated throughout the past years and decades, it encompasses either ST or J-point elevation, and/or notching or slurring of the terminal QRS complex, and is particularly present in (relatively) healthy individuals without acute or chronic cardiac disease (e.g. acute myocardial infarction, chronic heart failure or bundle branch block, where ST-segment changes and abnormal terminal QRS morphology can be expected).

Since the early years of electrocardiography, such variants in the terminal QRS complex and ST segment have been noted. In 1936, in Cleveland, Ohio, Shipley and Hallaran described a prevalence of ST elevation and terminal QRS slurring or notching in 16–44% of cases in a series of young and apparently healthy adults (Shipley and Hallaran 1936). Such variations would today most probably be recognized as ‘early repolarization’. In 1936, Shipley and Hallaran still used a string galvanometer (although already portable at that time), allowing analysis of three to four leads (lead I, II and III with or without one extra chest lead). However, in the years thereafter between 1947 and 1966, also with more modern electrocardiographs allowing analysis of 12 leads and also vectorcardiography, these phenomena were similarly noted. In particular, early repolarization patterns appeared to be present in young and athletic individuals and even more so in those from African descent (Myers and Klein 1947; Goldman 1953, 1960; Hiss et al. 1960; Seriki and Smith 1966).

In 1951, Grant, Estes and Doyle coined the term ‘early repolarization’ (Grant et al. 1951). In their paper on spatial vector electrocardiography combined with more traditional electrocardiography including (at least) 6 chest leads, they describe their

experience in 3000 cases recorded in their hospital. Interestingly, they noted in the young and supposedly healthy individuals in their cohort that 'the repolarization forces are often unusually large in magnitude, producing large T waves and measurable ST-segment deviation in the limb as well as the precordial leads'. They continue their paper with some hypotheses on the cause of these repolarization forces and particularly on how a distinction can be made with pathology (e.g. in the presence of abnormal T-wave vectors). However, at the same time, they note that 'Occasionally, the S-T vector due to normal early repolarization forces is difficult to distinguish from the S-T vector due to acute pericarditis' (Grant et al. 1951). Importantly, longitudinal studies in these cases of normal ST elevation showed that these early repolarization changes can be present for years (Grant et al. 1951). Their notion that ST-segment deviations can be a normal variant with a benign prognosis lasted for over half a century thereafter, until a possible association was suggested with malignant ventricular arrhythmias (Haissaguerre et al. 2008; Rosso et al. 2008; Tikkanen et al. 2009).

11.2.2 Early Repolarization Definitions

From the 1950s, there have been different definitions of early repolarization, which partly complicates comparisons over the years. In 1961, Wasserburg, Alt and Lloyd considered early repolarization to consist of the following: (1) an elevated take-off of the ST segment and J-junction of the QRS complex, varying from 1 to 4 mm (0.1–0.4 mV), relative to succeeding T-P interval (isoelectric line), (2) a downward concavity of the ST segment and (3) symmetrically limbed T waves which are often of large amplitude (Wasserburger and Alt 1961). Interestingly, the authors also described the associated phenomenon of notching and slurring: 'the elevated S-T junction arose from a distinct notch on the downstroke of the R wave in most instances, occasionally it would be represented only as a well-defined slur. Thus, it superficially resembled a reversed Wolff-Parkinson-White pattern with notching at the distal segment of the QRS complex rather than at its inception' (Wasserburger and Alt 1961). The comparison with reversed Wolff-Parkinson-White patterns is especially memorable because current automatic algorithms to detect early repolarization are importantly coined on this feature (personal communication with Macfarlane 2016).

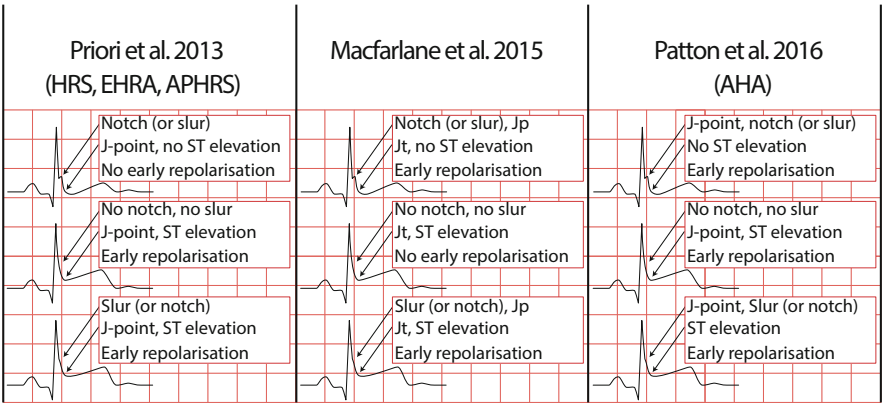
Between 2013 and 2016, there have been three international consensus reports on the definitions of early repolarization patterns, and unfortunately all three define different criteria. In 2013, the Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA) and the Asian Pacific Heart Rhythm Society (APHRS) consensus statement (Priori et al. 2013) first defines a distinction between an early repolarization pattern and early repolarization syndrome. This mirrors the previous distinction between a Brugada ECG pattern and Brugada syndrome. In early repolarization, this distinction makes even more sense as the pattern is extremely prevalent in young and healthy persons. The distinction between pattern and syndrome is made by the absence or presence of otherwise unexplained cardiac

arrest or documented malignant ventricular arrhythmias. Moreover, the authors state the following electrocardiographic definition: the presence of J-point elevation ≥1 mm (0.1 mV) in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG. The authors do not touch upon the presence or absence, nor the value, of concomitant terminal QRS notching or slurring.

In contrast, in 2015 an international group of authors (Macfarlane et al. 2015) defined an early repolarization pattern to be *only* attributable to patients who display terminal QRS notching or slurring, where the notch should be entirely situated above the baseline, and the onset of a slur also be situated above the baseline. In addition, the peak of the notch or the onset of the slur should be ≥0.1 mV in ≥2 contiguous inferior and/or lateral leads and the QRS duration ≤120 ms. These authors specifically do not require J-point elevation (J-termination or 'Jt') as a criterion for early repolarization.

And lastly, in 2016 a consensus statement by the American Heart Association (AHA) includes for the definition of early repolarization, in contrast to the two earlier reports, either ECGs with or without terminal QRS notching or slurring and with or without ST elevation (Patton et al. 2016). In addition, the J-point elevation ≥0.1 mV in ≥2 contiguous inferior and/or lateral leads should in the presence of a notch or slur be measured at the peak of the notch or at the start of a slur, instead of the traditional definition of the J-point at the end of the notch or slur.

The differences between these criteria are depicted below in the figure.



The differences between these three reports in the definition of electrocardiographic patterns of early repolarization and in clinical distinctions between those who only display the ECG features without any evidence of previous, or suspicion of future malignant arrhythmias, and those who did have malignant arrhythmias, clearly show a significant part of the difficulties we face with the past and future data on this subject. This not only impacts on the recognition of the phenomenon of early repolarization but will also impact on the therapeutic consequences that may be inflicted on these patients.

Only several years ahead of these reports, in 2009, early repolarization was labelled as 'A statement that is used frequently to characterize a normal QRS-T variant with J-point elevation' by the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Association (HRS) (Rautaharju et al. 2009). However, in 2008, just before the AHA/ACC/HRS publication a possible association with malignant ventricular arrhythmias and sudden death was published in two reports (Haissaguerre et al. 2008; Rosso et al. 2008). Apparently, these reports could not be incorporated in the paper by the AHA/ACC/HRS committees.

11.2.3 Early Repolarization Associations with Malignant Arrhythmias

In 2008 the groups in Bordeaux, France, and Tel Aviv, Israel, published almost simultaneously on a possible association between early repolarization patterns and a history of sudden cardiac arrest (Haissaguerre et al. 2008; Rosso et al. 2008). In these papers, in cohorts of patients with a history of unexplained ventricular fibrillation, a subset of these patients appeared to have a far larger than expected prevalence of early repolarization patterns ($n = 64/142$ and $n = 19/45$, respectively). This association with sudden cardiac arrest was one year later verified in a larger general population cohort from Finland (Tikkanen et al. 2009). In addition, there has been further focus on the morphology of the subsequent ST segment on the association with ventricular arrhythmias (Viskin et al. 2013; Tikkanen et al. 2011). In these analyses, it appears that the association with a history of cardiac arrest of an early repolarization pattern with an accompanying horizontal or downsloping ST segment is particularly strong, while an upsloping ST segment appears to have a more benign evolution. However, about 30% of the patients with a history of cardiac arrest in the previous reports displays an upsloping 'benign' early repolarization pattern (Adler et al. 2013; Sacher et al. 2013b).

These data were truly pivotal for igniting medical and scientific interest in early repolarization patterns in patients and individuals from the general population. Particularly difficult in the association with malignant ventricular arrhythmias is the knowledge base that this electrocardiographic characteristic is very prevalent (as mentioned before, with a prevalence up to 44%) in healthy and young individuals.

11.2.4 Early Repolarization and Genetic Mutations

Although the prevalence of early repolarization patterns is large in the general population, its association with genetic mutations is only anecdotal and frustrated by a lack of segregation data for those with documentation of malignant arrhythmias. One year after their 2008 paper on the association between an early repolarization pattern and a history of cardiac arrest, the Bordeaux group published a paper on a genetic analysis of one of the cases (Haissaguerre et al. 2009a). In this study a

severely affected young female patient who had suffered from over a hundred VF events was genetically evaluated with a panel of 21 candidate genes (*KCNQ1*, *KCNE1*, *KCNH2*, *KCNE2*, *KCNJ2*, *KCNJ8*, *KCNJ11*, *ABCC9*, *KCNJ5*, *KCNJ3*, *KCND3*, *IRX3*, *IRX5*, *SCN5A*, *SCN1B*, *NCX1*, *CACNA1C*, *CACNB2*, *CALR*, *CASQ2* and *ANK2).* This study revealed a missense variant in *KCNJ8*, p.S422 L. The *KCNJ8* gene encodes for the Kir6.1 subunit of the ATP-sensitive potassium (K-ATP) channel in heart and could thus be involved in aberrant action potential morphology and possibly also to an increased tendency towards the development of an early repolarization pattern and arrhythmias. This same mutation was not found in a, rather limited, control set of alleles ($n = 764$) and was also not uncovered in 156 other patients with a history of unexplained VF and early repolarization pattern. In addition, segregation data was not available as the mother of this patient did not have the mutation and the father denied testing.

In the following year, 2010, the *KCNJ8*-S422 L variant was replicated in a cohort of patients with Brugada syndrome or early repolarization syndrome (Medeiros-Domingo et al. 2010). In this cohort, the variant was uncovered in 1 out of 101 unrelated patients with Brugada syndrome and in 1 out of 14 patients with early repolarization syndrome. Moreover, the same variant was not documented in 1200 control alleles. Additionally, a gain-of-function effect was suggested by additional analyses using patch-clamping in heterologous co-expression with SUR2A in COS-1 cells.

Interestingly, the possible association of this variant with early repolarization and cardiac arrest was downplayed 4 years later. In 2014, it appeared that 4% of individuals in a cohort of Ashkenazi Jews carried the exact same *KCNJ8*-S422 L variant (Veeramah et al. 2014). Carriers of the variant did not display early repolarization patterns, and a possible association with possible malignant arrhythmias could also not be made.

Again in 2010, a possible association with cardiac calcium channel mutations and early repolarization syndrome was made (Burashnikov et al. 2010). In this study involving patients with Brugada syndrome, early repolarization syndrome and idiopathic ventricular fibrillation, variants were uncovered in the *CACNA1C*, *CACNB2* and *CACNA2D1* genes involved in cardiac calcium channels, in 4 out of 24 patients with early repolarization syndrome. These variants were not present in 400 tested reference alleles. However, segregation data was (again) not available.

In 2014, yet another gene, *ABCC9*, was implicated in early repolarization syndrome (Hu et al. 2014). In 5 out of 150 patients with either Brugada syndrome or early repolarization syndrome (number of patients with either syndrome was not reported), an *ABCC9* variant was uncovered. Three of these patients also carried a putatively pathogenic variant in other susceptibility genes (*SCN5A*, *CACNA1C* and *SCN10A*). The *ABCC9* gene encodes the sulfonylurea receptor 2 (SUR2) which interacts with Kir6.1 to form functional K-ATP channels. Functional analyses implicated that these *ABCC9* variants also affected the cardiac K-ATP channel with a gain-of-function effect.

The sparsity of genetic associations in patients with early repolarization syndrome led the European Society of Cardiology committee on ventricular arrhythmias

to the conclusion that no clear familial evidence of familial transmission of early repolarization syndrome exists (Priori et al. 2015). However, there are two reports on a remarkable high prevalence of early repolarization patterns in families (Nunn et al. 2011; Gourraud et al. 2013). In these reports, families of early repolarization syndrome patients displayed a remarkable higher prevalence (23–61%) of early repolarization patterns as compared to their remaining relatives or unrelated controls. Despite these observations, more detailed underpinning of early repolarization patterns nor early repolarization syndrome has not yet surfaced.

11.2.5 Early Repolarization Syndrome Prognosis and Treatment

Like most patients who survived a cardiac arrest, patients with an early repolarization syndrome diagnosis after cardiac arrest have a high recurrence rate of malignant arrhythmias. A secondary prevention implantable cardioverter-defibrillator (ICD) is thus recommended in those with a reasonable life expectancy with a class I indication (Priori et al. 2013). In addition, in those patients with a suggested 'malignant' variant of an early repolarization pattern (downsloping) and symptoms (highly) suggestive of malignant ventricular arrhythmias, an ICD as primary prevention can be considered (Priori et al. 2013).

In contrast, in asymptomatic patients with suggested malignant variants of early repolarization pattern, and certainly not in patients with 'benign' early repolarization patterns (upsloping), preventive invasive or non-invasive therapies are not indicated (class III recommendation) (Priori et al. 2013). Importantly, other risk stratification modalities, such as electrophysiological studies with programmed stimulation to investigate VT/VF inducibility, do not seem to be of value (Mahida et al. 2015).

As for medical treatment, during VT/VF storm isoproterenol has been used effectively to suppress arrhythmias (Haissaguerre et al. 2009b), while chronic VT/VF suppression has been reached with quinidine therapy (Haissaguerre et al. 2009b). Importantly, many other tested drugs in the setting of this specific population with early repolarization syndrome and arrhythmias, did not seem to be of specific value (mexiletine, verapamil, flecainide, propafenone, pilsicainide and also amiodarone). However, amiodarone did seem to be effective in 1 out of 6 patients during VF storm.

11.2.6 Early Repolarization Conclusions

Early repolarization patterns, whether described as ST elevation and/or terminal QRS notching or slurring, have been described since the early years of electrocardiography. This phenomenon is very prevalent in young and otherwise healthy individuals, and even more so in athletes and individuals from African descent, and has until recently been evaluated as a benign condition. However, in the last decade an association with an increased propensity for malignant ventricular arrhythmias, sudden cardiac arrest and sudden death has been documented. With

this sharp contrast between a prevalent and benign electrocardiographic phenomenon and an association with malignant ventricular arrhythmias and sudden death, a highly interesting but likewise difficult situation has emerged in the interpretation of early repolarization patterns. To complicate the matter further, international consensus has not even been reached on the definitions of early repolarization with three different definitions in three different international expert panels/guidelines. Still, consensus is rather clear on the treatment of individuals with early repolarization patterns; only those with proven or highly suspected malignant ventricular arrhythmias are currently candidates for invasive treatment (implantable cardioverter defibrillators) and drug treatment (isoproterenol during VT/VF storm and quinidine long-term therapy). Genetic associations have been anecdotal despite numerous efforts and are not supported by proof of genetic segregation with the phenotype. Future efforts to further delineate benign from malignant variants of early repolarization, aids in risk stratification and a better understanding underlying pathophysiology on cellular and genetic level, are imperative to further guide clinicians and patients in this matter.

Compliance with Ethical Standards

Sources of Funding None.

Conflict of Interest None.

Ethical Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

Adler A, Rosso R, Viskin D, Halkin A, Viskin S. What do we know about the "malignant form" of early repolarization? J Am Coll Cardiol. 2013;62:863–8.

Alders M, Koopmann TT, Christiaans I, et al. Haplotype-sharing analysis implicates chromosome 7q36 harboring DPP6 in familial idiopathic ventricular fibrillation. Am J Hum Genet. 2009;84:468–76.

Belhassen B, Viskin S, Fish R, Glick A, Setbon I, Eldar M. Effects of electrophysiologic-guided therapy with class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc. 1999;10:1301–12.

Berdowski J, Berg RA, Tijssen JGP, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. Resuscitation. 2010;81:1479–87.

Bezzina C, Veldkamp MW, van den Berg MP, et al. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. Circ Res. 1999;85:1206–13.

Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992;20:1391–6.

Brugada P, Brugada J, Brugada R. When our best is not enough: the death of a teenager with Brugada syndrome. J Cardiovasc. 2009;20:108–9.

Burashnikov E, Pfeiffer R, Barajas-Martinez H, et al. Mutations in the cardiac L-type calcium channel associated with inherited J wave syndromes and sudden cardiac death. Heart Rhythm. 2010;7:1872–82.

Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of sudden cardiac death: clinical and research implications. Prog Cardiovasc Dis. 2008;51:213–28.

Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? J Am Coll Cardiol. 2003;42:1959–63.

Coumel P, Fidelle J, Lucet V, Attuel P, Bouvrain Y. Catecholamine-induced severe ventricular arrhythmias with Adams-stokes syndrome in children: report of four cases. Br Heart J. 1978;40:28–37.

Crotti L, Johnson CN, Graf E, et al. Calmodulin mutations associated with recurrent cardiac arrest in infants. Circulation. 2013;127:1009–17.

de Jong JS, Marsman RF, Henriques JP, et al. Prognosis among survivors of primary ventricular fibrillation in the percutaneous coronary intervention era. Am Heart J. 2009;158:467–72.

Dock W. Transitory ventricular fibrillation as a cause of syncope and its prevention by quinidine sulphate with case report and discussion of diagnostic criteria for ventricular fibrillation. Am Heart J. 1929;4:709–14.

Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on myocardial and pericardial diseases. Eur Heart J. 2008;29:270–6.

Goldman MJ. RS-T segment elevation in mid- and left precordial leads as a normal variant. Am Heart J. 1953;46:817–20.

Goldman MJ. Normal variants in the electrocardiogram leading to cardiac invalidism. Am Heart J. 1960;59:71–7.

Gourraud J-B, Le Scouarnec S, Sacher F, et al. Identification of large families in early repolarization syndrome. J Am Coll Cardiol. 2013;61:164–72.

Grant RP, Estes EH, Doyle JT. Spatial vector electrocardiography; the clinical characteristics of S-T and T vectors. Circulation. 1951;3:182–97.

Gussak I, Brugada P, Brugada J, et al. Idiopathic short QT interval: a new clinical syndrome? Cardiology. 2000;94:99–102.

Haissaguerre M, Shoda M, Jais P, et al. Mapping and ablation of idiopathic ventricular fibrillation. Circulation. 2002;106:962–7.

Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med. 2008;358:2016–23.

Haissaguerre M, Chatel S, Sacher F, et al. Ventricular fibrillation with prominent early repolarization associated with a rare variant of KCNJ8/K channel. J Cardiovasc. 2009a;20:93–8.

Haissaguerre M, Sacher F, Nogami A, et al. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. J Am Coll Cardiol. 2009b;53:612–9.

Hiss RG, Lamb LE, Allen MF. Electrocardiographic findings in 67,375 asymptomatic subjects. X. Normal values. Am J Cardiol. 1960;6:200–31.

Hu D, Barajas-Martínez H, Terzic A, et al. ABCC9 is a novel Brugada and early repolarization syndrome susceptibility gene. Int J Cardiol. 2014;171:431–42.

Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001;345:1473–82.

Hulleman M, Berdowski J, de Groot JR, et al. Implantable cardioverter-defibrillators have reduced the incidence of resuscitation for out-of-hospital cardiac arrest caused by lethal arrhythmias. Circulation. 2012;126:815–21.

Hulleman M, Zijlstra JA, Beesems SG, et al. Causes for the declining proportion of ventricular fibrillation in out-of-hospital cardiac arrest. Resuscitation. 2015;96:23–9.

Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J. 1957;54:59–68.

Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States. Survivors of out-of-hospital cardiac arrest with apparently normal heart. Need for definition and standardized clinical evaluation. Consensus statement of the joint steering committees of the unexplained cardiac arrest registry of Europe and of the idiopathic ventricular fibrillation registry of the United States. Circulation. 1997;95:265–72.

Krahn AD, Gollob M, Yee R, et al. Diagnosis of unexplained cardiac arrest: role of adrenaline and procainamide infusion. Circulation. 2005;112:2228–34.

Macfarlane PW, Antzelevitch C, Haissaguerre M, et al. The early repolarization pattern: a consensus paper. J Am Coll Cardiol. 2015;66:470–7.

Mahida S, Derval N, Sacher F, et al. Role of electrophysiological studies in predicting risk of ventricular arrhythmia in early repolarization syndrome. J Am Coll Cardiol. 2015;65:151–9.

Marcus FI, Fontaine GH, Guiraudon G, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation. 1982;65:384–98.

Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. Circulation. 2009;119:1085–92.

Marquez MF, Bonny A, Hernandez-Castillo E, et al. Long-term efficacy of low doses of quinidine on malignant arrhythmias in Brugada syndrome with an implantable cardioverter-defibrillator: a case series and literature review. Heart Rhythm. 2012;9:1995–2000.

Marsman RF, Barc J, Beekman L, et al. A mutation in CALM1 encoding calmodulin in familial idiopathic ventricular fibrillation in childhood and adolescence. J Am Coll Cardiol. 2014;63:259–66.

Medeiros-Domingo A, Tan B-H, Crotti L, et al. Gain-of-function mutation S422L in the KCNJ8-encoded cardiac K(ATP) channel Kir6.1 as a pathogenic substrate for J-wave syndromes. J Heart Rhythm Soc. 2010;7:1466–71.

Myers GB, Klein HA. Normal variations in multiple precordial leads. Am Heart J. 1947;34:785–808.

Noda T, Shimizu W, Taguchi A, et al. Malignant entity of idiopathic ventricular fibrillation and polymorphic ventricular tachycardia initiated by premature extrasystoles originating from the right ventricular outflow tract. J Am Coll Cardiol. 2005;46:1288–94.

Nunn LM, Bhar-Amato J, Lowe MD, et al. Prevalence of J-point elevation in sudden arrhythmic death syndrome families. J Am Coll Cardiol. 2011;58:286–90.

Nyegaard M, Overgaard MT, Søndergaard MT, et al. Mutations in calmodulin cause ventricular tachycardia and sudden cardiac death. Am J Hum Genet. 2012;91:703–12.

Olde Nordkamp LRA, Wilde AAM, Tijssen JGP, Knops RE, van Dessel PFHM, de Groot JR. The ICD for primary prevention in patients with inherited cardiac diseases: indications, utilization and outcome. A comparison with secondary prevention. Circ Arrhythm Electrophysiol. 2013;6:91–100.

Olde Nordkamp LRA, Postema PG, Knops RE, et al. Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: a systematic review and meta-analysis of inappropriate shocks and complications. Heart Rhythm. 2016;13:443–54.

Patton KK, Ellinor PT, Ezekowitz M, et al. Electrocardiographic early repolarization: a scientific statement from the American Heart Association. Circulation. 2016;133:1520–9.

Postema PG, Wolpert C, Amin AS, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). Heart Rhythm. 2009a;6:1335–41.

Postema PG, van den Berg MP, van Tintelen JP, et al. Founder mutations in the Netherlands. SCN5a 1795insD, the first described arrhythmia overlap syndrome and one of the largest and best described characterised families worldwide. Neth Heart J. 2009b;17:422–8.

Postema PG, van der Werf C, Wilde AA. Idiopathic ventricular fibrillation. In: Baars H, Doevendans P, van der Smagt J, editors. Clinical cardiogenetics. London: Springer; 2011a. p. 229–38.

Postema PG, Christiaans I, Hofman N, et al. Founder mutations in the Netherlands. Familial idiopathic ventricular fibrillation and DPP6. Neth Heart J. 2011b;19:290–6.
Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes expert consensus statement on inherited primary arrhythmia syndromes. Heart Rhythm. 2013;10:1932–63.
Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace. 2015;17:1601–87.
Puranik R, Chow CK, Duflou JA, Kilborn MJ, McGuire MA. Sudden death in the young. Heart Rhythm. 2005;2:1277–82.
Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association electrocardiography and arrhythmias committee, council on clinical cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53:982–91.
Remme CA, Wever EF, Wilde AA, Derksen R, Hauer RN. Diagnosis and long-term follow-up of the Brugada syndrome in patients with idiopathic ventricular fibrillation. Eur Heart J. 2001;22:400–9.
Rosso R, Kogan E, Belhassen B, et al. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. J Am Coll Cardiol. 2008;52:1231–8.
Sacher F, Probst V, Maury P, et al. Outcome after implantation of cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study—part 2. Circulation. 2013a;128:1739–47.
Sacher F, Lim HS, Haissaguerre M. Sudden cardiac death associated with J wave elevation in the inferolateral leads: insights from a multicenter registry. J Electrocardiol. 2013b;46:456–60.
Selzer A, Wray HW. Quinidine syncope. Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. Circulation. 1964;30:17–26.
Seriki O, Smith AJ. The electrocardiogram of young Nigerians. Am Heart J. 1966;72:153–7.
Shipley RA, Hallaran WR. The four-lead electrocardiogram in two hundred normal men and women. Am Heart J. 1936;11:325–245.
Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J. 1958;20:1–8.
Ten Sande JN, Postema PG, Boekholdt SM, et al. Detailed characterization of familial idiopathic ventricular fibrillation linked to the DPP6 locus. Heart Rhythm. 2016;13:905–12.
Tikkanen JT, Anttonen O, Junttila MJ, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med. 2009;361:2529–37.
Tikkanen JT, Junttila MJ, Anttonen O, et al. Early repolarization: electrocardiographic phenotypes associated with favorable long-term outcome. Circulation. 2011;123:2666–73.
van der Werf C, van Langen IM, Wilde AA. Sudden death in the young: what do we know about it and how to prevent? Circ Arrhythm Electrophysiol. 2010;3:96–104.
Veeramah KR, Karafet TM, Wolf D, Samson RA, Hammer MF. The KCNJ8-S422L variant previously associated with J-wave syndromes is found at an increased frequency in Ashkenazi Jews. Eur J Hum Genet. 2014;22:94–8.
Viskin S, Belhassen B. Idiopathic ventricular fibrillation. Am Heart J. 1990;120:661–71.
Viskin S, Antzelevitch C, Marquez MF, Belhassen B. Quinidine: a valuable medication joins the list of “endangered species”. Europace. 2007;9:1105–6.
Viskin S, M Wilde AA, Guevara-Valdivia ME, et al. Quinidine, a life-saving medication for Brugada syndrome, is inaccessible in many countries. J Am Coll Cardiol. 2013;61(23):2383–7.
Wasserburger RH, Alt WJ. The normal RS-T segment elevation variant. Am J Cardiol. 1961;8:184–92.

Wever EF, Robles de Medina EO. Sudden death in patients without structural heart disease. J Am Coll Cardiol. 2004;43:1137–44.

Wever EF, Hauer RN, Oomen A, Peters RH, Bakker PF, Robles de Medina EO. Unfavorable outcome in patients with primary electrical disease who survived an episode of ventricular fibrillation. Circulation. 1993;88:1021–9.

Wilde AA, Langendijk PN. Antiarrhythmic drugs, patients, and the pharmaceutical industry: value for patients, physicians, pharmacists or shareholders? Neth Heart J. 2007;15:127–8.

Wolpert C, Echternach C, Veltmann C, et al. Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. Heart Rhythm. 2005;2:254–60.

Xiao L, Koopmann TT, Ordög B, et al. Unique cardiac purkinje fiber transient outward current β-subunit composition: a potential molecular link to idiopathic ventricular fibrillation. Circ Res. 2013;112:1310–22.

Zipes DP, Wellens HJ. Sudden cardiac death. Circulation. 1998;98:2334–51.

Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association task force and the European Society of Cardiology Committee for practice guidelines (writing committee to develop guidelines for Management of Patients with Ventricular Arrhythmias and the prevention of sudden cardiac death): developed in collaboration with the European heart rhythm association and the Heart Rhythm Society. Circulation. 2006;114:e385–484.