Prediction of Life-Threatening Arrhythmias – Still an Unresolved Problem

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Key Words

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Abstract

A major challenge in current cardiology is to predict who will die suddenly from ventricular arrhythmias. Ventricular arrhythmias are the most common cause of sudden cardiac death, occurring in about 1–2:1,000 inhabitants yearly, and is most frequently due to coronary artery disease. Patients with increased risk of ventricular arrhythmias can be offered medical treatment and ultimately an implantable cardioverter defibrillator (ICD). Left ventricular ejection fraction (EF) is currently the main risk stratification tool used to select patients for ICD therapy. However, EF is insufficient in predicting arrhythmic risk. A number of techniques have been presented to improve arrhythmic risk stratification without having reached clinical utility. Conduction abnormalities and dispersion of action potential duration forms the substrate for malignant ventricular arrhythmias in infarcted tissue as in several cardiomyopathies. The ability to assess electrical dispersion in patients noninvasively has been limited. Myocardial strain by echocardiography has been presented

as an accurate tool for assessing myocardial function and timing. Inhomogeneous and dispersed myocardial contraction has been related to the occurrence of ventricular arrhythmias and seems to be a promising tool in risk stratification. This review focuses on arrhythmia mechanisms and novel echocardiographic tools for assessing risk of ventricular arrhythmias.

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Introduction

Ventricular arrhythmia remains the most common cause of sudden cardiac death in Western societies occurring in 1–2:1,000 inhabitants per year [1]. A major challenge in current cardiology that is still an unresolved problem is to predict who will die suddenly from ventricular arrhythmias. The most frequent cause of ventricular arrhythmias and sudden cardiac death in individuals over the age of 30 is coronary artery disease, while inherited cardiac disease is the most frequent cause in individuals below 30 years of age [1]. Unfortunately, in the majority of patients dying suddenly, death is the first symptom of the heart disease [2]. Risk stratification and

Fig. 1. ECG with markedly prolonged QT interval of 660 ms.

prevention of sudden death may therefore be of value in certain selected groups of individuals, but there is currently lack of powerful tools for screening of the general population where the majority of sudden cardiac deaths occur.

When a patient has been identified to have increased risk of ventricular arrhythmias, treatment can be offered both in terms of medication and ultimately with an implantable cardioverter defibrillator (ICD). Several studies have demonstrated that ICD therapy reduces mortality from ventricular arrhythmias in patients with ischemic heart disease [3–6]. The occurrence of ventricular tachycardia (VT) is a strong predictor of further arrhythmic events [7].

In patients who have survived a malignant ventricular arrhythmia, ICD implantation for secondary prevention is well established. The major challenge is to select patients for ICD primary prevention therapy, that is, to predict who is at risk of dying suddenly among patients in whom arrhythmic events have not yet occurred.

This review will include risk stratification in patients with increased risk of ventricular arrhythmias and sudden cardiac death with inherited cardiac diseases and patients with coronary artery disease.

Long QT Syndrome

The long QT syndrome (LQTS) is an inherited cardiac arrhythmic disease predisposing to life-threatening ventricular arrhythmias and sudden cardiac death. LQTS is characterized by prolongation of the QT interval on ECG (fig. 1).

LQTS has served as a model of understanding the genesis of ventricular arrhythmias during the past decades.

LQTS is caused by mutations in genes encoding for cardiac ion channels which are leading to prolonged action potential duration and dispersion of action potential repolarization. Both prolonged action potential duration with development of early afterdepolarization and dispersion of electrical repolarization are considered to be important mechanisms causing ventricular arrhythmias in these patients [8] (fig. 2).

Risk stratification of ventricular arrhythmias in LQTS patients is currently based on history of syncope-, genotype-, gender- and heart rate-corrected QT interval (QTc) on ECG [9]. QTc is the most important current tool to screen patients with unexplained syncopes and to predict who is at risk of dying suddenly in known LQTS mutation carriers. However, substantial overlap in QTc values between LQTS patients with and without arrhythmic events make risk stratification challenging.

Genetic testing has become more available in the last years, resulting in a large amount of known individuals carrying an LQTS-related mutation. The penetrance of the disease is variable and a substantial proportion of mutation carriers will remain asymptomatic during lifetime. The overall risk that adult mutation carriers with no symptoms of LQTS will experience arrhythmias during their later lifetime is low and QTc has failed to be a significant predictor of outcome in these individuals [10]. Prophylactic treatment involves lifelong β -blocker therapy and requires adequate compliance. Decisions regarding preventive treatment are often difficult.

Genotyping has achieved clinical usefulness in risk stratification. LQT1 patients (*KCNQ1* mutations) have excellent protection of β -blocker medication, while protection is not 100% in LQT2 (*HERG* mutations) and insufficient in LQT3 patients (*SCN5A* mutations) [9]. LQT2 patients are particularly exposed to arrhythmic risk by QT-prolonging drugs. Double mutation carriers, patients with Jervell and Lange-Nielsen syndrome, have the most severe phenotype and concomitant deafness [11]. ICD therapy is indicated in LQTS patients with aborted cardiac arrest or arrhythmic events despite β -blocker medication. Although ICD is a life-saving therapy in these patients, there are also several negative aspects associated with this therapy especially in young patients. Inappropriate shocks due to prominent T waves is one example of specific complications that can occur in these patients in addition to the complications associated with young age at ICD implantation with a number of lead and battery replacements during life-long therapy [12].

Left ventricular (LV) function has been considered to be normal in LQTS patients and echocardiography in

Fig. 2. Mechanisms of arrhythmias in LQTS. Potassium channels (IKr and IKs, circled) are the most frequently affected ion channels in LQTS. Defect ion channels lead to a prolongation of action potential duration (mid left figure). Action potential prolongation is inhomogeneously distributed throughout the ventricles leading to dispersion of electrical repolarization (mid right figure).

these patients has traditionally been performed only to exclude additional or to differentiate from other heart diseases. There is, however, support for the assumption that prolonged action potential duration and electrical dispersion may cause wall motion abnormalities in these patients which can be assessed by echocardiography [13, 14] (fig. 3).

New Echocardiographic Modalities

Modern echocardiographic techniques have been developed during the last decades including tissue Doppler imaging and strain echocardiography (STE) [15]. The advantages of these techniques are better regional assessment of myocardial function and timing. Minor degrees of myocardial contraction heterogeneity and subtle contraction dyssynchrony can be demonstrated by these techniques [16]. STE is based on conventional grey scale echocardiographic images and provides segmental analyses of 16 LV segments. Measurements can be done simultaneously from multiple regions of interest. STE has been showed to be a very accurate method for assessment of LV function and is a validated technique [17]. Visual assessment of regional myocardial function from two-dimensional image is the standard echocardiographic method to assess ventricular function and has had that position since the introduction of two-dimensional echocardiography. The method has also been established as a clinically important tool in detecting regional ventricular function, but has limited ability to detect more subtle

Fig. 3. M-mode recording from an LQTS patient. Red lines indicate the end of the T wave from the ECG below. Contraction duration in the interventricular septum is prolonged and exceeds the time of the end of the T wave.

changes in function and changes in timing of myocardial motion throughout systole and diastole. Visual assessment of myocardial function has therefore been unsuccessful to detect regional wall motion abnormalities in LQTS patients.

Fig. 4. Strain curves from a healthy individual (left panel) and from an LQTS patient (right panel). Contraction duration is prolonged in the LQTS patient compared to the healthy individual. Modified from Haugaa et al. [18].

Fig. 5. Myocardial strain curves from 6 different locations in a healthy individual (left panel) and a LQTS patient (right panel). White arrows indicate timing of maximum myocardial shortening. The LQTS patient shows pronounced dispersion in timing of contraction defined as mechanical dispersion compared to the healthy individual.

Studies in LQTS Patients

Accurate assessment of myocardial function by myocardial velocities and strain has revealed that LQTS patients have prolonged myocardial contraction [18, 19] (fig. 4). This may be due to the prolonged action potential duration in these patients and is in accordance with experimental studies showing that a prolongation of the action potential duration is associated with a prolonged contraction [20].

Furthermore, strain studies showed that prolonged contraction duration was inhomogeneously distributed throughout the ventricles in LQTS patients leading to a dispersion of contraction duration defined as mechanical dispersion (fig. 5). Importantly, in these studies, prolonged and dispersed myocardial contraction was associated with a higher risk of cardiac arrhythmias in LQTS patients. Mechanical dispersion by myocardial strain showed better sensitivity and specificity in predicting arrhythmic events compared to QTc [19]. Optimal cutoff value for mechanical dispersion was ≥ 33 ms and identified LQTS mutation carriers with a history of events with a sensitivity of 76% and a specificity of 91%. QTc ≥ 460

ms showed a sensitivity of 42% and a specificity of 81% to identify mutation carriers with a history of events.

The echocardiographic technique may be proposed as an additional risk stratification tool in LQTS patients. Specifically, the method may be of help in decisions about preventive β -blocker therapy in adult asymptomatic mutation carriers.

The specific patterns of myocardial contraction abnormalities reported may depend on the concomitant electrical disorder in these patients and may represent the mechanical consequence of electric arrhythmogenic factors. LQTS may no longer be regarded as a purely electrical disease [21].

Brugada Syndrome

The Brugada syndrome (BrS) has an estimated prevalence of 1:10,000 and is associated with high mortality [22]. Mutations in genes encoding for the cardiac sodium channel are found in 20–30% of patients with BrS. Typical ECG changes with ST elevation in right precordial

leads (≥ 2 mm concave ST segment elevation in ECG lead V1 and V2) are hallmarks of the disease and can be present spontaneously or appear after pharmacological challenge with sodium channel blockers such as flecainid. Risk prediction of ventricular arrhythmias in patients and relatives of patients with BrS is difficult. Spontaneous ECG changes are markers of increased risk. Holter monitoring may be used to detect transient ECG changes. The role of electrophysiological study in risk stratification was initially reported to be significant, but has been debated and regarded as not predictive of ventricular arrhythmias in a recent study of >1,000 patients with BrS [23].

Patients after Myocardial Infarction

Patients after myocardial infarction (MI) are at high risk for cardiac arrhythmic events and sudden cardiac death [1]. The immediate and 30-day mortality after MI has decreased markedly over the last 10–15 years. The decreased mortality is mainly due to proper treatment with percutaneous coronary intervention and thrombolysis, but is also due to improved medical therapy as β -blockade and ACE/inhibitors. Currently, LV ejection fraction (EF) is the primary parameter used to select patients for ICD therapy after MI. Impaired EF is shown to be a marker of increased cardiovascular mortality and sudden cardiac death. Earlier echocardiographic studies have observed that an EF of 40% serves as the threshold for identifying high-risk individuals [24]. However, EF has reduced sensitivity in predicting sudden death; less than 50% of patients with prior MI who die suddenly have EF below 30% [25]. A number of other diagnostic tests have been proposed to improve the accuracy for selection of patients for ICD therapy. Currently available data, however, are not sufficient to routinely recommend additional risk-stratification methods for selection of patients for ICD therapy [6].

Pathophysiological Mechanisms of Arrhythmias and Possible Methods to Detect and Predict Them

An unresolved question is what factors cause a patient after MI, who may remain stable for months after the infarction, to suddenly become electrically unstable and develop malignant arrhythmias. To predict which patients are most likely to develop life-threatening ventricular arrhythmias, one first needs to understand the patho-

physiological mechanisms behind them. There is general agreement that ventricular arrhythmias need a substrate and a trigger to occur.

Substrates of Arrhythmias after MI

The presence of myocardial scar forms the substrate for malignant arrhythmias [26]. Heterogeneity in scar tissue creates areas of slow conduction that generate dispersion of cardiac action potentials and provide the substrate for ventricular arrhythmias [27]. The normal beating human heart has a certain dispersion of repolarization. Action potentials in the endocardium last longer than in the epicardium due to different ionic movements. Gradients of long to short action potential durations from the apex to the base have also been demonstrated. The overall electrical activity is reflected in a normal QRS complex and a normal T wave. In infarcted tissue, however, pronounced electrical dispersion, including both activation time and refractoriness, is a known arrhythmogenic substrate [28–30].

Inhomogeneous start of action potentials in infarcted tissue due to areas of slowed conduction is the background behind the predictive value of signal averaging electrocardiogram (SAECG) in post-MI patients. The SAECG compares and averages around 300 consecutive QRS complexes to produce a filtered QRS complex that provides information on the presence of ventricular late potentials. Presence of late potential is an indicator of slowed conduction and has been documented in 25–50% of patients after MI [31]. Late potentials showed to be a good predictor for malignant arrhythmias in patients with low EF in the MUSTT study [7]. With the increasing use of primary percutaneous coronary intervention in the treatment of AMI, the prognostic value of the SAECG has become less clear. The usefulness of SAECG in risk assessment of ventricular arrhythmias is limited by a low positive predictive value but may be used to identify low-risk patients due to a relatively high negative predictive value of about 90%.

Inhomogeneous start of action potentials in infarcted tissue will lead to an inhomogeneous end of repolarization. The measurement of QT dispersion on ECG as an indicator of dispersion of ventricular repolarization was presented as a promising tool in risk stratification of arrhythmias two decades ago [32]. However, the method has not achieved the clinical value as initially expected due to challenges in T-wave definition and poor reproducibility [33]. Electrical alternans of the T-wave (that is, alternating amplitude from beat to beat) on the ECG is thought to be due to dispersion of repolarization and has

Fig. 6. Homogenous timing of myocardial contraction by STE in a healthy individual as well as mechanical dispersion in an ICD patient with and without arrhythmias during follow-up. The ICD patient with recurrent arrhythmias showed most pronounced mechanical dispersion indicated by white arrows. Modified from Haugaa et al. [41].

been demonstrated to be associated with life-threatening ventricular arrhythmias after MI [34]. Due to a low positive predictive value, and similar to SAECG, the value of T-wave alternans in risk stratification may actually be in deciding which patients are least likely to benefit from ICD therapy.

Electrophysiological testing in patients with previous AMI is an invasive method to investigate if the scarred myocardium is able to sustain re-entrant ventricular arrhythmias. Electrophysiological testing is recommended in some of the current guidelines for selection of post-MI patients for prophylactic ICD therapy who have symptoms suggestive of VT [1]. Drawbacks are the invasive nature and the wide range of reported sensitivity of the method. The future role of this test may lie in its combined use with other and noninvasive tests to refine the selection of potential ICD recipients.

It has been shown that a sub-threshold stimulus on the body surface can modulate the QRS complex so that slow conduction in some areas can be detected. The so-called Wedensky index may be a predictor for malignant ventricular arrhythmias after MI. The Wedensky index indicates a high negative predictive value regarding the occurrence of VT [35]. Prospective studies will show the value of this technique.

Triggers of Arrhythmias after MI

Ectopic activity from the border zone of the myocardial scar is an important trigger. This trigger can be en-

hanced by sympathetic stimulation and detected by 24-hour Holter recording. It has been shown that the presence of nonsustained VT predicted sudden cardiac death in a modern post-MI population and may be useful in those with EF >35% [36]. Increased sympathetic activity favors the development of cardiac arrhythmias, whereas increased vagal tone appears to be protective [37]. Sympathetic and parasympathetic activity can be detected indirectly by heart rate variability analysis and heart rate turbulence, but none of these methods have come into general clinical practice due to low sensitivity and specificity.

Triggers like ectopic activity can be enhanced by low potassium concentration, eventually together with low calcium concentration, and prolongation of the sodium current.

Imaging Techniques for Risk Stratification of Arrhythmias beyond EF

The extent of scar tissue has been correlated with the risk of arrhythmias in patients after MI. MRI studies have demonstrated that quantification of the peri-infarct zone by contrast-enhanced cardiovascular MRI was an independent predictor of mortality following AMI [38] and that tissue heterogeneity in the peri-infarct zone was likely to provide the proarrhythmic substrate [39]. This approach is interesting and needs to be further investigated.

STE in Patients after MI

Strain measurements by echocardiography has recently been demonstrated to be a more accurate tool for quantification of myocardial function after MI compared to EF using MRI studies as a gold standard [40]. Furthermore, reduced LV function by global strain has been shown to predict appropriate ICD therapy in a population of 85 post-MI patients with ICD, while EF did not [41]. Assessment of cardiac function as a risk predictor of cardiac arrhythmias may be refined by STE, representing a more regional measure compared to EF.

The principles of mechanical dispersion as an arrhythmogenic factor were tested in post-MI patients. Post-MI patients with recurrent arrhythmic events showed a more dispersed myocardial contraction assessed by STE compared to post-MI patients without arrhythmic events (fig. 6) [41]. Mechanical dispersion was a strong predictor of malignant ventricular arrhythmias, independently of EF and predicted arrhythmias with a hazard ratio of 1.24 (95% CI 1.07–1.43, $p < 0.01$). EF was no significant predictor of arrhythmias in multivariate analyses [41]. These findings supported the idea that tissue heterogeneity in and around scarred myocardium leads to a dispersed myocardial contraction and is associated with risk of arrhythmic events.

In post-MI patients, measurements of mechanical dispersion may add important information about risk of arrhythmia independently of EF. These findings support the idea that mechanical dispersion might be useful to identify risk of arrhythmias in post-MI patients with relatively preserved EF who do not fulfill current ICD indications. Future trials should investigate if dispersed contraction can be used to select additional patients for ICD therapy among the majority of post-MI patients with relatively preserved EF in whom current ICD indications fail.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy which accounts for a substantial proportion of sudden unexpected cardiac death in previously healthy young individuals [42]. Prevalence has been estimated to be at least 1 in 1,000 [42]. Recent molecular genetic reports have revealed ARVC as mainly a desmosomal disease. Penetrance is age and gender dependent and the phenotype is highly variable.

Mechanisms for arrhythmias in early stages of ARVC are probably due to dysfunction of desmosomal proteins

and disturbed cell to cell coupling [43]. In later stages of ARVC when structural abnormalities in the myocardium have developed, re-entrant ventricular arrhythmias can occur due to the scar-related substrate. Therefore, electrical conduction disturbances with consequent electrical dispersion have been suggested as an important mechanism of ventricular arrhythmias [44, 45].

In ARVC, late potentials are frequently found indicating areas with slow conduction, mainly in the right ventricle. This can sometimes be seen in standard 12-lead ECG as an epsilon wave in V1. In addition, repolarization abnormalities can be visible on ECG as T wave inversion. In the most common right ventricular type of ARVC, a negative T wave is found from V1 to V3. However, risk stratification of affected patients is still incomplete. Neither family history nor genotype have been predictors of outcome. The available data suggest that young age, prior cardiac arrest, fast VT with different morphologies, syncope, severe RV dysfunction and LV involvement are potential predictors of sudden death and worse outcome [46].

STE in Patients with ARVC

In all stages of ARVC, electrical conduction delay with consequent electrical dispersion has been suggested as a mechanism of ventricular arrhythmias [44, 45]. The novel method of mechanical dispersion may therefore have a potential role as risk stratification tool in ARVC [47].

Dispersion of Myocardial Contraction in Different Cardiac Conditions

In this report, mechanical dispersion has been reviewed as a possible risk stratification tool in LQTS patients, in post-MI patients and in ARVC patients. The mechanisms for arrhythmias in LQTS, ARVC and in infarcted myocardial tissue are different, but have similarities regarding electrical dispersion. In LQTS patients, inherited ion channel defects result in prolonged APD. Inhomogeneous prolongation of APD in LQTS results in dispersed electrical repolarization, which is regarded as an important arrhythmia mechanism. In ARVC patients, mechanisms of arrhythmias are probably stage dependent, but electrical dispersion has been considered to be of importance in early and later stages of the disease [44, 45]. In post-MI patients delayed start of ventricular activation in scarred myocardium leads to a dispersed recovery of excitability [29], finally resulting in dispersed electrical repolarization. One might therefore speculate that

electrical dispersion may be regarded as the final common pathway of arrhythmia mechanism in all three conditions.

The extent of mechanical dispersion is influenced by the concomitant contractile impairment in infarcted tissue and presence of fibrosis in ARVC which is not present in LQTS patients. Contractile impairment will pronounce mechanical dispersion. The ranges and values of mechanical dispersion which are related to increased arrhythmic risk will therefore not necessarily be interchangeable between different myocardial diseases.

Echocardiography is readily available and is therefore suitable as a widespread risk stratification tool. However, as other imaging techniques, observer dependency is significant for echocardiographic measurements. This is well known from variations in EF measurements. We believe that strain measurements are equally observer dependent. To overcome this problem, each laboratory has

to gain experience in strain measurements. Strain measurements by speckle tracking technique have been successfully automated by commercially available software (Echopac; GE Vingmed). The time intervals needed for calculations of mechanical dispersion are automated and relatively easily available in this software.

In summary, prediction of malignant ventricular arrhythmias remains a major challenge. No single test has the accuracy needed to predict sudden death and the use of several parameters in combination seems to be the most promising way of future risk prediction. More sophisticated methods are needed to get better clinical tools for predicting malignant ventricular arrhythmias. Modern echocardiographic techniques contribute to an accurate assessment of myocardial function and timing and may be useful as additional risk stratification tools in patients at risk of ventricular arrhythmias.

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