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Selection of High-risk Patients for Device Intervention with the New Advances in Technology

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Clinical medicine involves the accurate diagnosis of the patient's clinical disorder and appropriate therapy to treat the disease condition. All therapies have the potential for some adverse side effects, and in each clinical therapeutic decision one is involved in risk-benefit considerations. Patients with more severe disorders are considered high-risk patients, and, as a general rule, the therapy is associated with greater potential risk. This is particularly true in patients with life-threatening cardiac conditions where the available therapy may have serious adverse side effects.

Death from cardiac disease may be due to complex cardiac arrhythmias such as ventricular fibrillation that results in sudden cardiac death or from mechanical dysfunction of the heart with heart failure. The two conditions, the electrical and mechanical abnormalities, frequently co-exist, especially in patients with acquired cardiac disorders like coronary heart disease and non-ischemic cardiomyopathy. In many of the genetic cardiac conditions like long QT syndrome, the patients are at risk only for cardiac arrhythmias and sudden death.

In the identification of high-risk cardiac patients for the prevention of sudden death and heart failure, traditional clinical factors are utilized for risk stratification. More recently various genetic, biochemical, and electrical markers have become available to identify patients at increased risk for fatal events. This is true for treatment of cardiac patients with medicines and surgery, and is especially important for patients requiring device therapy with the implantable cardiac defibrillator (ICD) or with cardiac resynchronization therapy (CRT) without (CRT-P) or with an associated defibrillator (CRT-D) capability. The focus of this report will be on the risk stratification for two cardiac conditions in which device therapy is now available to treat patients with high-risk heart disorders including: 1) the genetic Long QT syndrome; and 2) coronary heart disease with reduced ejection fraction (EF 30%).

Genetic Long QT Syndrome (LQTS)

Background

The LQTS is an inherited disorder in which there is prolongation of cardiac repolarization due to genetic mutations involving one or more ion channels. These mutations alter the flux of potassium, sodium, or calcium ions across the cellular cardiac membrane resulting in

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prolongation of the myocardial ventricular action potential and of the QT interval on the electrocardiogram.¹ This alteration in the electrical activity of the heart increases the likelihood of cardiac arrhythmias that can result in syncope or sudden death. Presently, mutations have been identified in 12 different ion-channel genes with the major forms of LQTS involving the slowly activating and rapidly activating potassium channels (I_{Ks} [LQTS1] and I_{Kr} [LQTS2], respectively) and in the sodium channel (I_{Na} [LQTS3]). The high-risk clinical factors relate to the length of the QTc interval: normal (<470ms); prolonged (470–499ms); and very prolonged (QTc ≥ 500ms). Patients with very prolonged QTc intervals, i.e., ≥ 500ms, are at high risk for life-threatening ventricular tachyarrhythmias.² Patients who experience a syncopal episode are at increased risk for a subsequent fatal arrhythmic event.² It also appears that males are at greater risk for a fatal event before adolescence, with females at greater risk after adolescence. Standard therapy for patients with LQTS involves treatment with beta-blocker medication, but ICD therapy is indicated in patients who are at very high risk.³

New Advances in LQTS Risk Stratification

The two new advances in the identification of high-risk LQTS patients involve the characteristics of the mutation: 1) the location in the ion-channel structure and/or the degree of the functional abnormality of the mutated ion-channel; and 2) the alteration in the dynamic relationship of the QT interval to the RR interval.

We have recently shown that mutations in the LQT1 gene (KCNQ1) that are located in the intracytoplasmic connecting loops between the 2nd – 3rd and the 4th – 5th transmembrane segments of the ion channel are associated with a 3.7-fold increased risk of cardiac events ($p < 0.001$) when compared to mutations in other locations. These mutations in the connecting loops alter the normal physiologic function of the sympathetic nervous system on the ion-channel kinetics.⁴ In the LQT2 form of LQTS, mutations located in the pore region of the KCNH2 channel protein, are associated with a 1.5-fold increased risk for cardiac events ($p = 0.006$).⁵ In the LQT3 form of LQTS involving the SCN5a sodium channel, mutations may be associated with increased late sodium current, increased window current, or both functional defects. In our preliminary studies, patients with mutations having both functional defects are at a 2.48-fold increased risk of cardiac events ($p = 0.001$) when compared to patients with a single functional defect.

Recently, Couderc and associates investigated the dynamic QT-RR relationship in a select group of LQT1 patients with mutations in the intracytoplasmic connecting loops.⁶ These LQT1 Patients with C-loop mutations have an abnormal regulation of ventricular repolarization consistent with an impaired beta-adrenergic I_{Ks} regulation that is reflected by a less steep diurnal QT-RR slope measured on Holter ECG recordings. This alteration in the QT-RR profile may provide insights into LQT-1 patients who are more susceptible to known adrenergic triggers. This type of information may help select high-risk patients for more aggressive therapeutic interventions.

Acquired Heart Disease

Background

In patients with ischemic heart disease or non-ischemic cardiomyopathy and reduced ejection fraction, several randomized clinical trials have shown that ICD therapy is associated with a 25–30% reduction in mortality as a result of reduction in sudden cardiac death from ventricular fibrillation.⁷ In addition, CRT-D therapy has been associated with reduction in heart failure events and death in high-risk cardiac patients having wide QRS complexes (> 150ms), especially those with left bundle branch block conduction disturbance.^{8–10}

Risk Stratification

In patients in the MADIT-II ICD trial, post-hoc analysis has shown that patients with one or more of the following clinical risk factors obtained the best benefit from ICD therapy (age>70; NYHA class III or early IV; atrial fibrillation; QRS>120ms; and BUN in the 27–50mg/dl range vs. <27mg/dl).¹¹ Those with none of these risk factors or those with BUN>50mg/dl obtained no benefit from ICD therapy. Holter-recorded frequent ventricular ectopic beats and/or non-sustained ventricular tachycardia as well as inducible, non-suppressible ventricular tachycardia have been identified as risk factors in earlier studies¹², but such factors are not currently being utilized in risk stratification of high risk cardiac patients. To date, there have been no sophisticated studies of electrical risk factors that have been identified to improve risk stratification of cardiac patients with acquired heart disease. It would appear that studies of the repolarization T-loop and characteristics of the time interval from the peak of the T wave to the end of the T wave (Tp-Te) may have value, and this requires further investigation.

In patients enrolled in the MADIT-CRT trial with NYHA Class I–II functional class, EF 30%, and QRS 130ms, CRT-D therapy was associated with greater than a 30% reduction in heart failure or death, whichever came first, when compared to ICD therapy.⁹ Patients with QRS duration 150ms and women obtained a significantly better benefit than patients with QRS in the 130–149ms range and men, respectively. Post-hoc analyses revealed that patients with left bundle branch block conduction disturbance obtained a uniquely beneficial result when compared to patients with right bundle branch block and those with intraventricular conduction disturbances.¹⁰ It is clear that the left bundle branch block creates a unique myocardial dyssynchrony that is very responsive to pacing of the left ventricle through pacing leads positioned in the coronary veins. Further electrical characterization of the subdivisions of the left bundle branch block conduction disturbance may be helpful in improving risk stratification for cardiac resynchronization therapy.

Conclusion

The recent clinical therapeutic studies involving high-risk cardiac patients with genetic or acquired heart disease provide valuable insights into the potential for new advances in the technology for improving risk stratification to identify patients who can benefit from device therapy.

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