Abstract. While post-myocardial infarct patients with frequent ventricular premature contractions or nonsustained ventricular tachycardia (NSVT) are at an increased risk of sudden arrhythmic death, the empirical use of antiarrhythmic agents for such patients is no longer justified after the results of the Cardiac Arrhythmia Suppression Trial. A series of major breakthroughs in the design and clinical application of the implantable cardioverter defibrillator (ICD) have taken place over the past two decades since its invention by M Mirowski. Although there is a general consensus for the effectiveness of the ICD therapy in aborting sudden arrhythmic death, it is unknown whether the use of the ICD therapy results in prolonged survival. Three randomized clinical trials directed to the survivors of cardiac arrest due to ventricular tachycardia (VT) or ventricular fibrillation (VF) are currently in progress, comparing the ICD therapy with drug therapy (amiodarone, beta blockers, and sotalol). Already over seventeen hundred patients have been randomized and followed in these three clinical trials. All three trials continue currently indicating no emergence of statistically significant differences in total mortality between the two therapy groups. Prophylactic application of the ICD has been studied in the MADIT (Multicenter Automatic Defibrillator Implantation Trial) – the first randomized clinical trial dealing with implantable defibrillators. This study enrolled post-transmural infarct patients having documented NSVT, left ventricular dysfunction (ejection fraction 35% or lower) and inducible and nonsuppressible NSVT. The study was recently terminated because of an emergence of a highly statically significant lower mortality with the ICD therapy than with conventional drug therapy. The future for patients at an increased risk of sudden cardiac death is much brighter with further refinement of the ICD system and antiarrhythmic drug therapy, and with further improvement in the therapy directed at the underlying structural heart disease. (Keio J Med 45 (4): 313-317, December 1996)

Key words: ventricular arrhythmia, sudden cardiac death, implantable cardioverter defibrillator, amiodarone, antiarrhythmics

Introduction

In the United States (population about 250 million) heart disease remains a health problem of epidemic proportion, in 1994 causing 734,000 cardiac deaths despite the remarkable decline in an age-adjusted cardiac death rate achieved since the middle of 1960’s.1-3 In the same year in the United States, human immunodeficiency (HIV) infection caused 42,000 deaths.2 About 300,000 of the cardiac deaths occur suddenly, most the result of ventricular fibrillation (VF) or ventricular tachycardia (VT).4 Furthermore, 100,000–150,000 people annually are successfully resuscitated. Most of the patients dying from or surviving life-threatening ventricular tachyarrhythmias suffer from significant structural heart disease – coronary artery disease comprising about 80% of the structural heart diseases in the United States. Significant advances have taken place during the past decade in elucidating electrophysiological mechanisms for the initiation and maintenance of ventricular fibrillation.5,6

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In this article we will review the recent progress achieved in the prevention and therapy of sudden cardiac arrhythmic deaths, with an emphasis on two dominant therapeutic modalities – implantable cardioverter defibrillator (ICD) and amiodarone.

**Previous Studies for Prevention of Sudden Cardiac Death**

**CAPS and CAST**

In patients surviving acute myocardial infarction, cardiac pump failure and ventricular arrhythmias including ventricular premature contractions (VPC’s) and ventricular tachycardia (VT) are independent predictors of one year cardiac mortality, mostly in the form of sudden cardiac death. One year cardiac mortality was a function of the VPC’s detected in predischarge ambulatory ECG recordings independent from the effect of left ventricular failure. This relationship along with the availability of several antiarrhythmics gave birth to the VPC hypothesis: Does suppression of the post-MI VPC’s with antiarrhythmics lead to a reduction in sudden cardiac death?

The Cardiac Arrhythmia Pilot Study (CAPS) and the Cardiac Arrhythmia Suppression Trial (CAST), both supported by the National Institute of Health (NIH), unexpectedly revealed that the use of flecainide, encainide or moricizine in the post-MI patients with frequent VPC’s and non-sustained VT resulted in increased rates of both overall and sudden cardiac death rates in spite of the continued suppression of the VPC’s. Therefore, “routine” prophylactic suppression of post-MI VPC’s or relatively asymptomatic nonsustained VT with antiarrhythmics is no longer recommended. In addition, the therapy with these antiarrhythmic drugs in the post-infarct patients resulted in increased death rates in both sudden arrhythmic and nonsudden nonarrhythmic deaths. Thus, these drugs exerted not only serious proarrhythmic side effects but also serious negative inotropic side effects.

**Beta blockers**

Multiple long-term randomized clinical trials with various beta blockers for post-infarct patients were conducted prior to the era of the CAPS and CAST studies. Long-term use of beta-blockers was associated with reduced non-sudden and sudden cardiac death rates. Clinicians need to be reminded that these beneficial effects of beta blockers were realized more in post-MI patients with cardiac failure than those without and that beta blockers are safely administered in most of the post-MI patients with left ventricular failure.

**Amiodarone and d,l-sotalol**

A recent meta-analysis of multiple amiodarone clinical trials suggested a 29% reduction in cardiac death rate in the amiodarone group as compared to the placebo group. Moreover, in the survivors of VF implanted with cardioverter defibrillators amiodarone therapy was associated with a reduced frequency of ICD shocks. Since then two more studies with conflicting results have been published. Furthermore, in the annual scientific meetings of the American College of Cardiology in March 1996, the results of two prospective randomized amiodarone trials on post-MI patients were disclosed – CAMIAT (Canadian Myocardial Infarction Amiodarone Trial) and EMIAT (European Myocardial Infarction Amiodarone Trial). In the former, which is similar in design to the CAST trials, amiodarone therapy resulted in a 40–50% reduction in arrhythmic death but in no reduction in nonarrhythmic death rate. Severe amiodarone toxicity was rare. Another Class III agent having a weak beta-blocking effect, d,l-sotalol, was recently shown to be superior to other antiarrhythmics (excluding amiodarone) in the prevention of death and recurrent ventricular arrhythmias. Clinical applicability of the result of this study, however, remains uncertain.

**Coronary artery bypass graft surgery**

In the survivors of cardiac arrest having operable coronary stenoses, successful coronary revascularization abolished inducible ventricular arrhythmias in those patients whose cardiac arrests were due to VF but not in those due to VT, hinting myocardial ischemia played a crucial role in the VF patients. Thus, those survivors of cardiac arrest due to VF having operable coronary stenoses should undergo coronary artery bypass surgery – which may have to be followed by either implantation of an ICD or drug therapy including amiodarone or a beta blocker.

**Implantable Cardioverter Defibrillators (ICD’s)**

**Development of ICD’s**

Since the first clinical implantation of an ICD in 1980 by Mirowski and his associates, we have witnessed a series of major breakthroughs in the design and clinical application of the ICD (see Fig 1). By the beginning of 1995, as many as 50,000 ICD units had been implanted worldwide. Advances made in the ICD field since 1980 faithfully traced each of the footsteps left by the cardiac pacemakers of various designs since the late 1950’s. The original implantable pacemakers were bulky, non-programmable and asynchronous; the generators were implanted subcutaneously in the upper abdominal area...
and myocardial electrodes were inserted via thoracotomy. For the ICD’s during the first decade, two defibrillating electrodes (either two epicardial patch electrodes or one epicardial patch and one SVC electrode) and two sensing myocardial electrodes were implanted via thoracotomy. ICD devices were bulky and heavy (almost 0.5Kg), and the generators were implanted subcutaneously in the upper abdomen. Furthermore, the initial ICD devices were non-programmable, capable of discharging only defibrillating monophasic shocks and the cutoff rate for ICD firings being pre-set at the factory. Perioperative mortality rates were high at around 4%.

ICD devices are now much smaller, lighter and multi-programmable, electrodes are inserted transvenously without thoracotomy and generators are implanted prepectorally (with operative mortalities 1% or lower). In addition, the ICD’s of the current generation have the following refined features (see Fig 2); biphasic shock waves for lower defibrillation threshold (DFT); both high and low energy defibrillating shocks and low energy cardioverting shocks; antitachycardia pacing (ATP); computerized storage of therapy history and of intracardiac ECG’s recorded immediately before and after the ICD therapy; non invasive programmed electrical stimulation and T-wave shock for noninvasive EP testings; VVI pacing for bradycardia; automatic periodic capacitor formation.34,25

Clinicians, however, frequently need to deal with various problems inherent to the complexity of the ICD system and to the severity of underlying structural heart diseases (see Fig 3): Inappropriate shocks and/or ATP triggered by atrial tachyarrhythmias, notably atrial fibrillation/flutter (see Fig 3) and sinus tachycardia; infection of ICD pocket; hematoma in the ICD pocket in patients requiring anticoagulation; discomfort around and erosion of the skin over an ICD device, especially in those patients implanted with earlier bulky ICD generators; fear of ICD shocks; rise in DFT with time or with the use of some antiarrhythmics, particularly amiodarone; adverse interactions between the co-existing ICD system and pacemaker, resulting in non-sensing of VT/VF by an ICD, multiple counting of paced beats leading to inappropriate shocks, pacemaker reprogramming, and noncapture/nonsensing after ICD shocks; inappropriate triggering of ICD shocks by intrinsic or environmental electrical noises; occasional discrepancy between clinical and induced VT/VF in terms of the efficacy of defibrillation and ATP.36,39

**ICD’s vs sudden cardiac death and overall cardiac mortality**

As witnessed in the recent past with many of the newly emerged therapies, randomized clinical trials on the ICD’s were not conducted initially mainly because of the prevailing but unfounded concept that the benefit of ICD’s in saving patients from sudden arrhythmic death was so striking that withholding their use in such patients would be unethical.40,41 While there is a general consensus for the utility of ICD therapy in aborting sudden cardiac death (see Fig 1 and 2), unexpected trends were revealed in recent retrospective case-controlled studies.40–43 For instance, in a retrospective study on sixty consecutive patients implanted with ICD’s and 120 medically treated patients, sudden deaths were fewer in the ICD recipients.
than in control.\textsuperscript{42} Although actuarial survival was higher in the ICD recipients for the first three years than in the medical group, two survival curves converged beyond the first three years.\textsuperscript{42} This convergence of the overall mortality rates most likely resulted from progressive deterioration in the underlying structural heart disease.

**Randomized prospective clinical trials comparing ICD and drugs**

Three randomized clinical trials directed to the survivors of VT or VF are currently in progress in three countries, the CASH (Cardiac Arrest Study Hamburg), CIDS (Canadian Implantable Defibrillator Study) and AVID (Antiarrhythmics vs Implantable Defibrillator).\textsuperscript{44–47} The Canadian and American AVID studies are similarly designed to determine whether survival of patients with life-threatening ventricular arrhythmias is better with an ICD or drug therapy (amiodarone in the CIDS and amiodarone and d,l-sotalol in the AVID).\textsuperscript{45–47} At this writing, well over seventeen hundred patients have been randomized and followed in these three clinical trials. All of the three trials continue currently, indicating no emergence of statistically significant differences in total mortality between the ICD and drug therapy groups.

Prophylactic use of implantable defibrillators has been also studied in one randomized clinical trial, MADIT (Multicenter Automatic Defibrillator Implantation Trial) – the first randomized clinical study dealing with implantable defibrillators.\textsuperscript{48} This study was started in 1990, had enrolled post-transmural infarct patients having documented nonsustained VT, LV dysfunction (LVEF 35% or lower), and inducible and nonsuppressible VT in electrophysiological testings.\textsuperscript{48} The patients satisfying these criteria had been randomized to implantable cardioverter defibrillator therapy (95 patients) or to conventional medical therapy (101 patients). At one month after randomization, amiodarone was prescribed in 74% of the conventional group and 2% of the ICD group. The trial was terminated in March 1996 because of an emergence of a highly statistically significant benefit of the ICD therapy over the conventional therapy (15 deaths in the ICD group and 39 deaths in the conventional group, \(p = 0.009\)). This beneficial effect existed in both thoracotomy ICD and transvenous ICD patients. In addition, 60% of the ICD group patients received ICD discharges within two years after enrollment. Many of these patients are considered to have died without their implanted ICD’s.

**Conclusion**

On one hand three drugs including amiodarone, beta blockers and d,l-sotalol are promising in high risk patients with diverse types of ventricular tachyarrhythmias. On the other hand, efficacy of the ICD therapy in reducing sudden cardiac death rate is impressive. Currently three randomized clinical trials comparing ICD and drug therapies for the survivors of sudden cardiac death are underway in three countries. These trials are expected to generate invaluable clinical information, i.e. better delineation of the indications for ICD and drug therapy, which can be used to triage high risk patients to ICD or drug therapy. As for the prophylactic application of ICD’s for patients at an increased risk of sudden cardiac death, the recently terminated MADIT trial demonstrated a highly significant benefit in reducing cardiac death rates in the post-transmural infarct patients having LV dysfunction, nonsustained VT, and inducible nonsuppressible VT.

The future for patients at an increased risk of sudden cardiac death is much brighter with further refinement of the ICD system and antiarrhythmic drug therapy, and with further improvement in the therapy directed at the underlying structural heart disease.

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