Management of malignant ventricular arrhythmias and cardiac arrest

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Sudden cardiac death continues to be a major health problem in the United States, accounting for ~400,000 deaths per year. The last 10 yrs have seen major advances in the primary and secondary prevention of this problem. In patients who have survived an episode of cardiac arrest, the AVID study conclusively established the superiority of the implantable cardioverter defibrillator over empiric amiodarone. For patients with recurrent hemodynamically destabilizing ventricular tachycardia and ventricular fibrillation, intravenous amiodarone has emerged as a potent therapeutic agent, especially when other agents such as lidocaine and procainamide have not been effective. Finally, recent work has focused on the risk stratification of patients for sudden cardiac death. Both the MADIT and MUSTT studies suggest that patients with coronary artery disease, reduced ejection fraction, and nonsustained ventricular tachycardia who are inducible to a sustained ventricular arrhythmia at electrophysiology testing have improved survival with an implantable cardioverter defibrillator. (Crit Care Med 2000; 28[Suppl.]:N165–N169)

KEY WORDS: sudden cardiac death; implantable cardioverter defibrillator; amiodarone; risk stratification

Sudden cardiac death (SCD) is a major health problem in the United States. Estimates suggest that SCD accounts for 300,000 to 400,000 deaths yearly in the United States (1, 2), and SCD comprises ≥50% of all cardiovascular deaths. The causes of SCD are typically a rapid sustained ventricular tachyarrhythmia and, less commonly, a bradyarrhythmia (3). The major public health dilemma has been to identify patients before their cardiac arrest because considerably <20% of cardiac arrest victims will survive to hospital discharge (4, 5). Over the past two decades there have been significant advances in the evaluation and treatment of patients with malignant ventricular tachyarrhythmias. In this article, we review the management of cardiac arrest survivors, patients with recurrent hemodynamically destabilizing tachyarrhythmias and patients with nonsustained ventricular arrhythmias who may be at risk of sudden death.

Management of Cardiac Arrest Survivors. Patients who have survived an episode of cardiac arrest are estimated to have a 1-yr recurrence rate of up to 22% (2–7). An earlier approach to these patients relied on the use of electrophysiologic (EP) testing (8). By using programmed electrical stimulation of the heart, sustained ventricular tachyarrhythmias can be induced (9). Several early studies demonstrated that serial electrophysiologic-pharmacologic testing could be used to predict drug efficacy in patients with ventricular tachycardia (10, 11). Patients were typically studied in the baseline state to determine their inducibility of ventricular tachycardia. After adequate oral loading with an antiarrhythmic agent, repeat EP testing was then performed. Patients in whom inducible ventricular tachycardia (VT) was suppressed with antiarrhythmic agents were thought to have a good prognosis (12, 13). However, it was known that inducible sustained VT during amiodarone therapy did not necessarily portend a poor long-term prognosis (14). An alternative method to judge drug efficacy proposed by the Lown group (15) was to quantitate suppression of spontaneous ventricular arrhythmias.

The Cardiac Arrest in Seattle: Conventional vs. Amiodarone Drug Evaluation trial (CASCADE) was designed to evaluate EP testing or Holter-guided antiarrhythmic therapy with "conventional" drugs (eg, quinidine) vs. empirical therapy with amiodarone (16). Although this trial was testing two drug methods to treat cardiac arrest survivors, nearly 50% of the patients also received an implantable cardioverter defibrillator (ICD). Overall, 228 patients in this trial with out-of-hospital cardiac arrest not associated with a Q-wave myocardial infarction were randomized to amiodarone or conventional antiarrhythmic therapy. The mean left ventricular ejection fraction (LVEF) was 35%, and 82% had underlying coronary artery disease. The 2-yr survival rate free from cardiac death, resuscitated ventricular fibrillation or defibrillator shock was 82% for amiodarone-treated patients and 69% for conventionally treated patients. After 4 yrs of follow-up, these survival values were 66% vs. 52%, respectively ($p = .007$). This study suggested that amiodarone given empirically was more effective than other antiarrhythmic agents guided by the results of ambulatory monitoring or EP testing. However, CASCADE did not test the value of EP testing with amiodarone, and the high ICD use precluded accurate mortality analysis because ICD shocks should not be taken as a surrogate for mortality.

The concept that early defibrillation was an important element in resuscitation from cardiac arrest has been recognized for years. In 1985 the ICD developed by Mirowski et al. (8, 17) was approved for use by the US Food and Drug Administration. The original hope that ICDs would significantly reduce the mortality of high-risk patients for sudden death has been demonstrated repeatedly by several investigators (8, 17–22). Winkle et al. (18) described 270 patients who received an ICD and reported a 99% sudden death free survival rate at 1 yr and a

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96% sudden death free survival rate at 5 yrs; overall survival was 92% at 1 yr and 75% at 5 yrs. Powell and colleagues (19) retrospectively reviewed the records of 331 patients receiving electrophysiologic-guided antiarrhythmic drug therapy or an ICD. The total mortality was 29% in 150 patients who had an ICD vs. 62% in the 181 patients treated with electrophysiologically guided therapy. Further, retrospective studies also suggested that the ICD was superior to amiodarone in the prevention of sudden death in high-risk patients. However, many of these early studies were nonrandomized, and the issue of optimal therapy for patients who had survived a cardiac arrest was unclear. As ICD technology evolved, the morbidity associated with ICD implantation decreased dramatically, largely because of the nonthoracotomy approach. Although the original ICDs were implanted by a thoracotomy and abdominal pocket, subsequent systems were developed that were smaller and could be placed in a subcutaneous pocket, much like a pacemaker, using a transvenous lead system. As a result, it became important to evaluate prospectively the survival benefit of an ICD vs. antiarrhythmic drug therapy in cardiac arrest survivors and patients with sustained VT.

The Antiarrhythmics vs. Implantable Defibrillator trial (AVID) was designed to address this issue (20). Patients who had been resuscitated from near-fatal ventricular fibrillation, ventricular tachycardia with syncope, or who had sustained ventricular tachycardia with a LVEF $<40\%$ and symptoms suggesting hemodynamic compromise were randomized to therapy with an antiarrhythmic drug or therapy with an implantable defibrillator. Antiarrhythmic therapy consisted of electrophysiologically directed sotalol treatment or empirical amiodarone, but only 13 patients received sotalol, making this an ICD vs. amiodarone trial. The trial screened 6,035 patients and enrolled 455 patients with ventricular fibrillation and 561 with ventricular tachycardia. More than half of the enrolled population had congestive heart failure, and the mean LVEF was 31%. Overall survival was significantly greater with the ICD, with an 81% 2-yr survival vs. 75% in the amiodarone-treated group ($p < .02$). At 1 yr and 2 yrs the reduction in mortality with the ICD was 39% and 27%, respectively. Patients treated with an ICD had a better survival throughout the course of the study. This effect was noted in each of the various subgroups analyzed with the exception of patients with a LVEF $>35\%$. The AVID trial conclusively established the superiority of implantable cardioverter defibrillator therapy over empirical amiodarone for the treatment of patients with malignant ventricular tachycardia and ventricular fibrillation. Thus, patients who survive a cardiac arrest unrelated to an unequivocal reversible event (e.g., myocardial infarction) should receive an ICD unless there are contraindications to use of an ICD.

Acute Management of Patients with Recurrent Hemodynamic Destabilizing Ventricular Tachycardia and Ventricular Fibrillation. Although the preceding discussion has concerned the long-term management of patients with episodic sustained VT or who have been resuscitated from a cardiac arrest, there have been significant recent advances in the acute treatment of patients with recurrent or incessant ventricular tachycardia and ventricular fibrillation. The initial approaches as outlined in the American Heart Association's Advanced Cardiac Life Support (23) have contributed to an increase in survival in patients with cardiac arrest. After the initial survey of airway, breathing, and circulation, rapid defibrillation is the most important predictor of subsequent survival from malignant ventricular arrhythmias (24). It has been estimated that the probability of successful resuscitation declines 2% to 10% per minute from the onset of symptoms (25).

After a sequence of three rapid defibrillation shocks, pharmacologic therapy is usually considered. Current pharmacologic therapy consists of intravenous epinephrine 1 mg every 3–5 mins as an adrenergic stimulant. Although clear-cut data are lacking, other primary antiarrhythmic agents such as lidocaine, procainamide, and bretylium have also been used in advance cardiac life support algorithms. Procainamide, however, has been limited by the significant time (up to 20 mins) to load the agent in the acute situation.

In the past several years, intravenous amiodarone has emerged as a potent therapeutic alternative. Amiodarone is primarily a Class III antiarrhythmic agent that prolongs repolarization, but it also has class I, II, and IV properties. The onset of antiarrhythmic effects of oral amiodarone requires several days of loading. Early nonrandomized reports suggested that the intravenous formulation might have an acute efficacy at terminating malignant ventricular arrhythmias, even those refractory to standard therapeutic agents (26–28). Kowey and colleagues (29) compared intravenous amiodarone and bretylium in 302 patients with recurrent ventricular tachycardia and ventricular fibrillation refractory to the usual standard therapy including intravenous lidocaine. Patients were randomly assigned to bretylium (4.7 grams total over 48 hrs) vs. low-dose amiodarone (230 mg over 48 hrs) vs. high-dose intravenous amiodarone (1.8 grams over 48 hrs). These investigators reported that the event rate over the first 48 hrs was comparable between the bretylium group and the high-dose amiodarone group. Similar results were also reported in the secondary analysis of time to first event and the portion of patients requiring additional infusions of amiodarone or bretylium. The overall mortality in the 48-hr double-blind period was 13.6% and did not differ significantly among the three treatment groups. The authors concluded that bretylium and amiodarone have comparable efficiencies for the treatment of malignant ventricular arrhythmias. However, bretylium was associated with a significantly higher incidence of hypotension, which has been a limiting factor in its use.

The efficacy of intravenous amiodarone in terminating even the most malignant ventricular arrhythmias was subsequently demonstrated in other studies and has initiated plans to incorporate intravenous amiodarone into advanced cardiac life support protocols. A recent study by Kudenchuk and colleagues (30) reported on the use of amiodarone for resuscitation after out-of-hospital cardiac arrest resulting from ventricular fibrillation. In this study, patients who had an out-of-hospital cardiac arrest unresuscitated by three shocks were randomized to a double-blind infusion of 300 mg iv of amiodarone vs. placebo. Overall, 246 patients received amiodarone and 258 patients received placebo. The presenting rhythm was ventricular fibrillation in 84% of patients. A significantly greater percentage of patients who received amiodarone survived to hospital admission (44% vs. 31%). Additionally, if there was return of spontaneous circulation before administration of the study drug, 64% of amiodarone-treated patients survived to hospital admission compared with 41% of placebo-treated patients. The authors concluded that in patients with out-of-hospital cardiac arrest resulting from re-

fractory ventricular arrhythmias, treatment with intravenous amiodarone resulted in a significantly higher survival rate to hospital admission. However, this study was underpowered to detect any differences in the survival of patients to hospital discharge. Of all study patients, 33 of 246 treated with intravenous amiodarone and 34 of 258 patients treated with placebo survived to hospital discharge. In contrast, of those patients with the spontaneous return of circulation, 24% of the intravenous amiodarone-treated patients and 15% of the patients who received placebo survived to hospital discharge.

In summary, intravenous amiodarone has emerged as an important therapeutic agent in the acute management of sustained ventricular arrhythmias. In our practice, we reserve the agent for patients in whom intravenous lidocaine or procainamide have not been effective or for those patients in whom we wish to use oral amiodarone and desire a rapid clinical response. The loading bolus is 150 mg given over 10 mins, usually through a central venous catheter, followed by an infusion of 1 mg/min for 6 hrs and 0.5 mg/min thereafter. Repeat boluses of 150 mg may be given as needed for recurrent arrhythmias, and some patients require longer periods of the higher dose of l mg/min. Further, it is not uncommon for patients with recalcitrant, recurrent VT/VF to require intravenous amiodarone plus lidocaine or procainamide during the first few days of therapy. Several issues have yet to be determined, including the long-term management of patients who receive intravenous amiodarone (31) and the optimal duration of intravenous amiodarone therapy before switching to oral therapy.

Predictability and Management of Patients at Risk for Sudden Cardiac Death. *Pari passu* with the advances in the secondary prevention of SCD and in the acute treatment of malignant ventricular arrhythmias, there has also been substantial progress in the primary prevention of SCD (8). Thus, the goal is to identify a patient's risk of sudden death before their first episode of sustained ventricular tachycardia or cardiac arrest. Marked decreased LVEF (32), nonsustained ventricular tachycardia (32, 33), and previous myocardial infarction have all independently been associated with a substantial 1-yr risk of a malignant ventricular arrhythmia. Approaches for the primary prevention of sudden death have included antiarrhythmic drug therapy guided by ambulatory monitoring or EP testing, empirical drug treatment with amiodarone, or an ICD.

The Cardiac Arrhythmia Suppression Trial (CAST) was a randomized placebo controlled trial designed to test the hypothesis that the suppression of premature ventricular contractions and nonsustained ventricular tachycardia after myocardial infarction would improve survival (34). This concept has been termed the "PVC Suppression Hypothesis." Three agents, encainide, flecainide, and moricizine, were selected. Patients were randomized to one of these three agents or to placebo. The CAST data and safety monitoring board terminated the encainide and flecainide limbs of the trial prematurely when preliminary data showed an increased mortality compared with placebo (34). Even although these drugs successfully suppressed spontaneous ventricular arrhythmias, arrhythmic death was more common in patients treated with encainide and flecainide (4.5%) than with placebo (1.2%) with a relative risk of death of 3.6. The total mortality with flecainide or encainide was greater than placebo as well (7.7% compared with 3%). CAST II included only moricizine, but was terminated prematurely when statistical evidence suggested that there would be no survival benefit with moricizine (35). These two studies demonstrated that in the early post-myocardial infarction period, suppression of premature ventricular contractions does not necessarily increase survival, and, more importantly, certain antiarrhythmic drugs can actually increase mortality, likely by their proarrhythmic effects. The effect on mortality is clearly related to the antiarrhythmic agent used. For example, d,1 sotalol (36) and amiodarone (37, 38) have neutral survival benefits, but d-sotalol (without the beta-blocker properties of the d,1 sotalol) worsened survival (39).

In summary, none of the primary prevention antiarrhythmic drug trials in patients with coronary artery disease have shown a survival benefit for any agent, and some drugs increase mortality in those patients. However, the data suggest that sotalol and amiodarone can be used safely in patients after myocardial infarction if they are needed to suppress symptomatic supraventricular or ventricular tachyarrhythmias.

A very different picture has emerged concerning the use of an ICD for the primary prevention of SCD. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) studied the hypothesis that prophylactic ICD therapy as compared with conventional medical therapy, as defined by the individual investigator and not the study design, would improve survival in a high-risk group of patients (21). Patients with a previous myocardial infarction, a LVEF $<35\%$, and nonsustained ventricular tachycardia underwent electrophysiologic testing. Patients with inducible sustained ventricular tachycardia not suppressed with intravenous procainamide were selected for randomization. Of 344 patients, 253 remained inducible after intravenous procainamide, and 196 patients were randomized to receive conventional therapy or ICD therapy. The average follow-up was 27 months. In the ICD group, there were 15 deaths compared with 39 deaths in conventionally treated patients (hazard ratio, 0.6; $p = .0009$). The observed improvement in mortality was present immediately and continued for the duration of the study. This landmark study was the first report of a successful prophylactic strategy to prevent sudden cardiac death in a high risk population and, as a result, the US Food and Drug Administration approved the use of ICDs as a class I indication for patients with coronary disease who had inducible, nonsuppressible ventricular arrhythmias.

The Multicenter Unsustained Tachycardia Trial (MUSTT) is a primary prevention study that included patients with coronary artery disease, LVEF $<40\%$, and

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nonsustained ventricular tachycardia (22). The hypothesis was to determine whether electrophysiologically guided therapy could decrease risk of SCD and cardiac arrest. This trial screened 2,202 patients; 767 were inducible at electrophysiology study and 704 elected to participate in the trial. In contrast to the MADIT trial, a true "placebo" group was included. Patients were randomized in this group to no antiarrhythmic therapy vs. electrophysiologic-guided therapy. Of those patients randomized to electrophysiologic-guided therapy, the initial treatment consisted of an antiarrhythmic agent; amiodarone could be administered after two prior unsuccessful antiarrhythmic drug trials. An ICD could be implanted after the failure of one agent. Of the 704 patients who elected participation, 353 were randomized to no antiarrhythmic therapy and 351 to electrophysiologic-guided therapy. Of those 351 patients, 158 were discharged receiving an antiarrhythmic drug and 161 received an ICD. The mean follow-up was 39 months. After 2 yrs the primary end point of cardiac arrest or arrhythmic death occurred in 18% of the nontreated patients and in 12% of patients treated with electrophysiologic-guided therapy. In 5 yrs these values were 32% and 25%, respectively (risk ratio, 0.73). In patients with an ICD, the 5-yr risk of cardiac arrest or arrhythmic death was 9%, whereas in electrophysiologic-guided therapy patients who did not receive a defibrillator the corresponding risk was 37%. The overall 5-yr mortality was 24% in patients treated with an ICD and 55% in those not treated with an implantable defibrillator. In fact, the entire survival benefit was a result of the ICD, and drug selection guided by electrophysiologic study offered no reduction in mortality in these patients. The authors concluded that MUSTT-type patients with inducible sustained ventricular tachycardia at electrophysiologic study should be treated with an ICD. Taken together, the MUSTT and MADIT data make a strong case for clinicians to search for these high-risk patients and treat them with an ICD if sustained ventricular tachycardia is induced at electrophysiologic study.

Future Directions. The MADIT and MUSTT studies required inducibility of VT at electrophysiologic study for inclusion. However, although patients with inducible VT are at increased risk for an arrhythmic death (40), the test is not that sensitive and other clinical factors may be as important (41). Two ongoing trials address whether ICDs have a role in the primary prevention of sudden death in patients with low LVEFs regardless of their inducibility of ventricular tachycardia.

In the Sudden Cardiac Death Heart Failure Trial, the hypothesis is that amiodarone or an ICD, or both, will improve survival in patients with congestive heart failure (42). Inclusion criteria are an LVEF $<30\%$ and Class II to III heart failure. Patients are randomized to conventional medical therapy plus placebo, conventional therapy plus amiodarone, or conventional therapy plus an ICD. The end point is overall mortality and the planned follow-up is at 2.5 yrs. This trial began enrollment in 1997 and includes patients with both ischemic and nonischemic cardiomyopathy.

The MADIT II trial is a follow-up to the original MADIT study (43). The hypothesis of this study is that an ICD will prevent sudden death in patients with coronary artery disease and reduced LVEF. Criteria for this trial include evidence of a previous myocardial infarction and coronary artery disease as well as an ejection fraction $<30\%$. This is a true primary prevention trial for implantable defibrillators. Patients are randomized to an ICD vs. no ICD with the end point being total mortality. Enrollment for this trial began in January 1998.

CONCLUSIONS

In summary, the past two decades have witnessed remarkable advances in the management of patients with malignant ventricular arrhythmias. The ICD has shown value both in primary and secondary prevention of SCD. Importantly, current trials are underway to define more precisely the populations of patients who will benefit from the ICD in the primary prevention of SCD.

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Erratum

In the April 2000 supplement to *Critical Care Medicine*, formerly *New Horizons,* the affiliation of Lucas Liaudet, MD, first author of the article, "Biology of Nitric Oxide Signaling," on pages N37–N52, was misstated. Dr. Liaudet is with the Department of Pulmonary Medicine of Children's Hospital Medical Center, Cincinnati, Ohio, rather than the Department of Pulmonary Biology.