Evaluation and Treatment Strategies in Patients at High Risk of Sudden Death Post Myocardial Infarction

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Summary: Over 50 percent of deaths in patients who survive an acute myocardial infarction are due to fatal ventricular tachyarrhythmias. Patients who survive an episode of sustained ventricular arrhythmia are at highest risk of recurrent cardiac arrest. Electrophysiologic studies have been found to be useful in guiding therapy and reducing mortality in these patients and in patients with syncope due to arrhythmic etiology. Evaluation and treatment of nonsustained ventricular tachycardia post infarction remains somewhat controversial. A recently published trial (MADIT), however, showed improved survival with an implanted defibrillator in patients with coronary disease and asymptomatic nonsustained ventricular tachycardia. Asymptomatic patients post infarction at high risk include those who have significant left ventricular dysfunction, late potentials, high-grade ventricular ectopy, and abnormal heart rate variability. These tests individually, however, have a low positive predictive accuracy. This, combined with the fact that antiarrhythmic drugs are frequently not effective and can be proarrhythmic, leaves the best treatment for these patients uncertain. It is known, however, that beta-adrenoreceptor blocking agents do reduce mortality after an acute myocardial infarction. Early studies have shown mixed results relating to sudden death and total mortality with amiodarone. To date, no other antiarrhythmic drug has shown benefit, while several have been shown to be harmful. Recent studies have also shown some beneficial effects of angiotensin-converting enzyme inhibitors, carvedilol, a third-generation beta-blocking agent with vasodilator properties, and the angiotensin II receptor antagonist losartan. However, their precise role in reducing sudden death needs to be defined further.

Key words: ventricular arrhythmias, myocardial infarction, electrophysiologic study, antiarrhythmics

Introduction

The cause of death in patients who survive an acute myocardial infarction (MI) is multifactorial and is in the range of 3 to 5% per year in the era of thrombolytic therapy.^{1, 2} More than 50% of these cardiac deaths, however, are sudden in nature and studies have shown that patients who succumb to sudden cardiac death (SCD) usually have sustained ventricular tachycardia (VT) degenerating into ventricular fibrillation (VF).² A great deal of new information has emerged concerning the mechanisms, electrophysiologic behavior, and management of a variety of ventricular tachyarrhythmias in patients who are post infarction.^{3–6} These arrhythmias range from asymptomatic premature ventricular contractions (PVCs) to the potentially lethal sustained VT or VF.

This communication is not intended to present the extensive body of knowledge available regarding various types of sustained ventricular arrhythmias post infarction, but is meant to be a comprehensive description covering salient features of the risks and therapy in high-risk patients who have sustained an acute MI. For the purpose of this review, patients will be categorized into those who develop nonsustained VT or sustained VT or VF after an acute MI, and asymptomatic high-risk patients who are post infarction.

Sustained Ventricular Tachycardia and Fibrillation Post Myocardial Infarction

The most severe arrhythmia in the early period, that is, within 48 to 72 h after acute MI is VF. This has been associated with a much higher in-hospital mortality in the GISSI trial (10.8 vs. 5.9% for those without VF) due primarily to worsened left ventricular function and subsequent cardiogenic shock.⁷ After hospital discharge, however, long-term prognosis in these patients is similar to those who did not have VF. Thus, no specific electrophysiology evaluation or guided therapy appears necessary in patients with VF early in the course of their acute MI.

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After the acute infarction phase, the majority of hemodynamically significant arrhythmias occur in the first 6 months post MI.⁸ In patients resuscitated from cardiac arrest without a new infarction, the 1- and 2-year rate of recurrence of cardiac arrest is approximately 30 and 45%, respectively.^{9, 10} Fortunately, the recurrence rate appears to be declining because of aggressive therapy for arrhythmias and the underlying ischemic heart disease.¹¹

It is generally agreed that in survivors of SCD an electrophysiologic study is indicated.¹² In an antiarrhythmic drug-free state, ventricular arrhythmias can be initiated during electrophysiologic studies in 70 to 80% of these patients. Sustained monomorphic VT constitutes one third to one half of the inducible arrhythmias with polymorphic VT/VF, and nonsustained VT accounting for the remaining arrhythmias.¹³⁻¹⁵

For those SCD survivors with inducible monomorphic VT, electrophysiology-guided therapy may be tried, especially if the VT is hemodynamically tolerated. When successful, electrophysiology-guided treatment has been shown to be useful in reducing the estimated risk of recurrence of cardiac arrest to 6% at 1 year and to 15% at 3 years in 23 and 30% of patients who continue to have inducible arrhythmias.¹⁵ In the study of Mitchell *et al.*,¹⁶ invasive testing predicted drug efficacy better than noninvasive testing. A recently published trial, Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) suggested no overall significant difference in recurrence of arrhythmias between therapy guided by invasive and noninvasive methods.¹⁷ Several major problems with this study remain, however. First, the design of this trial did not permit conclusions about the absolute value of electrophysiologic study or Holter monitoring in guiding therapy, as a large number of patients did not receive a drug that was predicted to be effective, thus rendering the statistical results clinically unimportant. Second, the group of patients included in the study was a carefully selected minority, as only 20% of the study population had survived cardiac arrest. Third, patients were entered into the ESVEM trial only if they had sufficient PVCs and inducible sustained VT. In this regard, it is relatively common for cardiac arrest survivors to have insufficient spontaneous ventricular arrhythmias to guide drug therapy. Despite these inherent limitations, survival among patients with coronary artery disease was better in patients randomly assigned to electrophysiologic study than in those assigned to Holter monitoring ($p = 0.02$). Electrophysiology-guided treatment thus continues to be the preferred method in patients who have survived cardiac arrest and in whom antiarrhythmic drugs are given as primary therapy.

Patients who remain inducible despite drug therapy, those with hemodynamically unstable VT, and patients with no inducible arrhythmias in whom no obvious reversible cause resulting in cardiac arrest can be identified, are candidates for implantable cardioverter defibrillators (ICDs), a therapy which has been shown to reduce SCD significantly.¹⁸⁻²⁰ Persistent inducibility of VT/VF on antiarrhythmic drugs, absence of coronary artery revascularization, reduced left ventricular ejection fraction (LVEF) (≤ 0.30) and the absence of

ICD have been shown to be independent predictors of recurrent cardiac arrest in this patient population.^{15, 18-20}

Unexplained Syncope Post Infarction

In patients with underlying structural heart disease such as prior MI, syncope is likely to be due to an underlying arrhythmic etiology.²¹⁻²³ In patients with syncope and underlying structural heart disease, the incidence of SCD in 1 year follow-up has been reported to be $24 \pm 7\%$.²⁴ In a recent study of consecutive patients evaluated at our institution,²³ 71% of patients with structural heart disease had abnormal electrophysiologic results, with sustained monomorphic VT being the most common finding. Electrophysiology-guided therapy prevented the recurrence of syncope in 96% of patients, and there was no SCD during a follow-up period of 18 months in patients who were treated with guided therapy including pharmacologic therapy, ablation, and ICDs. Thus, these patients should be evaluated by electrophysiologic study and, if positive, treated aggressively.

Nonsustained Ventricular Tachycardia Post Infarction

The significance of nonsustained VT post infarction depends upon the time at which monitoring is performed. The highest prevalence of nonsustained VT is found during the acute phase of MI and has little prognostic significance. Nonsustained VT documented 2-4 weeks post infarction is associated with higher risk of SCD.²⁵ The finding of nonsustained VT in itself, however, is not specifically predictive of SCD and is only moderately sensitive. In a total of 1,736 patients in four studies followed up for 12-48 months, there were 200 cardiac deaths of which 126 (63%) were sudden.²⁵ The risk of SCD in patients with nonsustained VT (14%) was approximately twice that of patients without VT (6%). However, only 39 of the 126 (31% sensitivity) sudden deaths occurred in patients with nonsustained VT. Sudden death accounted for 60% of the cardiac deaths in patients with nonsustained VT, and for 64% of the deaths in patients without VT, suggesting a low positive predictive accuracy.

Several studies have looked at the role of programmed electrical stimulation in predicting SCD in patients with nonsustained VT.^{26, 27} The incidence of arrhythmic events (almost all being cardiac arrest) during a follow-up of 14-28 months in patients with no inducible arrhythmias, inducible arrhythmias that were suppressed with antiarrhythmic medications, and persistently inducible arrhythmias on antiarrhythmic medications was 9, 7, and 45% respectively.²⁷ Although electrophysiologic evaluation can identify low- and high-risk patients, the true role of antiarrhythmic agents in inducible sustained arrhythmias cannot be assessed because of the lack of a placebo-controlled randomized limb. A recently published Multicenter Automatic Defibrillator Implantation Trial (MADIT)²⁸ compared the efficacy of an ICD with conventional therapy in post MI patients. In this study, patients with prior MI: LVEF ≤ 0.35 ; a documented episode of asymptomatic unsustained VT; and

inducible nonsuppressable VTs on electrophysiologic studies had improved survival on prophylactic therapy with an ICD compared with conventional therapy. Several other ongoing trials such as the Multicenter Unsustained Tachycardia Trial (MUSTT) should help gain more insight into the treatment of nonsustained VT post infarction.²⁹

Post Infarction Asymptomatic High-Risk Patients

Risk Stratification

Several noninvasive and invasive methods such as LVEF, signal averaged ECG (SAECG), frequent PVCs, defined as > 10/h, and heart rate variability have been used to evaluate and stratify the risk in postinfarction patients who are asymptomatic.³⁰ These tests, however, although sensitive, have a low positive predictive accuracy (Table I).

Left ventricular function is one of the most important independent risk factors in postinfarction patients who are asymptomatic. In four large multicenter trials with 3,000 patients post infarction, patients with LVEF <0.40 were 1.6 times more likely to have ventricular arrhythmias than those with LVEF $\leq$ 0.40.³¹ The presence of ventricular ectopy and LV dysfunction is associated with increased risk for SCD.¹² The causal role of ventricular ectopy and SCD remains controversial, however, and there are inherent limitations of low sensitivity and specificity and timing of Holter monitoring.

In the recently published American College of Cardiology/American Heart Association guidelines there are no indications for doing electrophysiologic studies for PVCs alone.¹²

The SAECG has been used for further definition of the high-risk population post infarction. The technique is used to detect late potentials which represent fragmented electrograms from areas of remote infarction in patients who are likely to develop reentrant arrhythmias. In over 1,000 patients post infarction, who had SAECG and were followed up for approximately 11 months, 20% of those with late potentials had arrhythmic events, whereas only 3% of those without late potentials had events.³⁰ The use of SAECG, however, has important limitations as, although the negative predictive value is high (96–99%), the positive predictive accuracy is low, ranging from 12 to 27%.³⁰

Heart rate variability and baroreceptor sensitivity are also being investigated to risk stratify postinfarction asymptomatic patients.^{32,33} Impaired heart rate variability, defined as < 20 ms, has been used as a noninvasive index of autonomic balance. Poor survival has been reported in patients with decreased heart rate variability. However, further detailed randomized studies such as ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) will help assess the role of these parameters in these patients. Attempts to combine multiple noninvasive variables can improve the positive predictive value, but whether treatment will alter long-term outcome remains to be proven. The role of invasive electrophysiologic studies for risk stratification also remains highly controversial,³⁰ and the positive predictive accuracy of electrophysiologic testing in asymptomatic patients post MI is not higher than that of noninvasive tests.

Management of Postinfarction High-Risk Patients

The use of antiarrhythmic drug therapy for asymptomatic postinfarction ectopy is not uniformly effective and frequently can cause potentially lethal side effects. Even though PVCs by themselves do not produce serious symptoms, they have often been treated under the assumption that such abnormalities represent warning arrhythmias. Important new data in antiarrhythmic therapy were obtained by the Cardiac Arrhythmia Suppression Trial (CAST).³⁴ In the CAST trial, postinfarction patients who had asymptomatic PVCs suppressed by encainide or flecainide were randomly assigned to long-term drug therapy or placebo. There was a 3.6 fold greater incidence of sudden death and/or cardiac arrest in patients treated with encainide or flecainide compared with the group randomized to placebo (43 vs. 16 patients; $p = 0.0004$). The harm of these drugs was seen in every subset of patients and throughout the study period, suggesting that adverse interaction between these drugs and randomly occurring ischemic events may have led to increased mortality.

A third drug, moricizine, was recently tested in CAST II.³⁵ This also showed a significant proarrhythmic effect, though it seemed to occur primarily during the first days of therapy. During the initiation of therapy, there was a significantly higher mortality among patients treated with moricizine (2.3 vs. 0.3% in the placebo group, $p < 0.02$). In two less rigorously controlled trials, comparing mexilitine with placebo in 630

TABLE I Comparison of noninvasive variables in the prediction of arrhythmic events

	Sensitivity (%)	Specificity (%)	Positive predictive accuracy (%)	Negative predictive accuracy (%)
Ventricular ectopic beats	54	82	16	82
Ejection fraction < 40%	46	75	10	75
Late potentials	63	81	17	81
Heart rate variability < 20 ms	92	77	17	77

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TABLE II Summary of the randomized placebo-controlled intervention trials postmyocardial infarction with beta-adrenergic blocking drugs

Trial (Ref.)	No. of patients	Entry time	Beta blocker	Dose	Follow-up	Mortality		
						Beta blockers (%)	Placebo (%)	p Value
Göteborg (38)	1,395	<48 h	Metoprolol	15 mg IV + 200 mg/day	24 months	92/698 (13.2)	120/697 (17.2)	0.04
ISIS-I (39)	16,027	<12 h	Atenolol	5–10 mgm IV + 100 mg/day	12 months	691/8,037 (10.7)	703/7,990 (12)	0.01
Multicenter International Study (40,41)	3,038	7–28 days	Practolol	400 mg/day	14 months	47/1,524 (3.1)	75/1,514 (4.8)	0.02
Norwegian International Study (42)	1,884	7–28 days	Timolol	20 mg/day	17 months	98/945 (10.6)	152/939 (17.5)	0.0003
BHAT (43)	3,837	5–21 days	Propranolol	180–240 mg/day	25 months	138/1,916 (7.2)	188/1,921 (9.8)	0.005
MIAMI (44)	5,778	<24 h	Metoprolol	15 mg IV + 200 mg/day	15 days	123/2,877 (4.3)	142/2,901 (4.9)	NS

Abbreviations: IV = intravenous, NS = not significant.

patients and comparing disopyramide with placebo in almost 2,000 patients post infarction, the mortality was slightly higher in the treatment groups, that is, 8 versus 5% in mexilitine versus placebo group, and 7 versus 6% in disopyramide versus placebo group.^{36,37} Finally, a meta analysis of 10 studies of empiric long-term treatment with Type I antiarrhythmic agents after MI found no benefit and suggested they may shorten survival after MI.³⁸ Thus, there is no indication for empiric treatment of asymptomatic ectopy in post MI patients with Type I antiarrhythmics.

Beta-adrenoreceptor blocking agent therapy, however, has been unequivocally associated with a reduction in the rate of SCD, both during early and delayed interventions post MI (Table II).^{39–45} The beneficial effect of these agents is most marked in patients with LV dysfunction. The exact mechanism by which beta-adrenergic receptor blocking agents work is unclear but is thought to be due to reduced myocardial oxygen demand and prominent antifibrillatory effects in ischemic myocardium. Despite this, only 27% of patients in the CAST trial were receiving beta blockers.³³ A more aggressive use of beta blockers in post MI patients is clearly indicated.

The Basel Antiarrhythmic Study of Infarct Survival (BASIS) was the first study to demonstrate the benefit of amiodarone in a small number of patients with frequent PVCs post infarction,⁴⁶ and several additional small trials appear to confirm this.^{47–49} However, in BASIS, these benefits were seen only in patients with LVEF ≥ 0.40 and did not last beyond 12 months.⁵⁰ Recently published studies, however, the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), the European Myocardial Infarction Arrhythmia Trial (EMIAT), and the trial on Amiodarone in Congestive Heart Failure and Asymptomatic Ventricular Arrhythmias have shown no significant improvement in total mortality.^{51–53}

Sotalol, like amiodarone, is usually classified as a class III antiarrhythmic agent. Preliminary data from the Survival With Oral D-Sotalol (SWORD) trial, a trial similar in design to CAST, has found a proarrhythmic effect from d-sotalol,⁵⁴ a pure class III antiarrhythmic. In a prior clinical trial in post MI patients using sotalol (the racemic mixture, having class III effects and beta-blocking effects), a significant difference from placebo in total and SCD mortality was not seen.⁵⁵ Thus, there appears to be no role for empiric sotalol for PVC suppression at this time.

Several other drugs, such as the angiotensin-converting enzyme inhibitors captopril, carvedilol (a third-generation beta-blocking agent with vasodilator properties, and the angiotensin II type I receptor antagonist losartan have been shown to reduce morbidity and mortality in patients with heart failure, including those who are post MI.^{56–60} The precise role of these agents in reducing SCD in post MI patients needs to be evaluated further.

Conclusions

Despite the overall reduction in mortality that is seen in patients with coronary artery disease, SCD continued to be the most common mode of death in patients who have sustained an MI. Patients with sustained ventricular arrhythmias or syncope due to an underlying arrhythmic etiology need to be evaluated and treated aggressively due to adverse prognosis. In asymptomatic postinfarction patients, several noninvasive tests including SAECG have an established value for risk stratification. However, these tests have a low positive predictive accuracy. Furthermore, the management strategies for asymptomatic post MI patients who are at high risk has not

yet been fully defined, and the standard antiarrhythmic drugs could potentially cause life-threatening side effects. Beta-adrenergic blocking agents have, however, been associated with a reduction in mortality in patients who have suffered an MI. Maximization of medical therapy in patients with reversible ischemia who may not be candidates for myocardial revascularization is also important. The role of the new drugs mentioned above and the ICDs used as a prophylactic therapy needs to be defined further as well.

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