

Prevention of Sudden Cardiac Death: The Role of the Implantable Cardioverter-Defibrillator

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Abstract

Sudden cardiac death, usually due to fatal ventricular tachyarrhythmias, results in the loss of 300,000–400,000 lives each year in the United States. Implantable cardioverter-defibrillator therapy has revolutionized both the secondary and, increasingly, the primary prevention of sudden cardiac death. In the last decade, subcutaneous pectoral implantation with transvenous lead placement has lessened perioperative risk considerably, raising the benefit/risk ratio for many candidates. As a consequence, the list of approved indications for implantable cardioverter-defibrillator therapy has expanded rapidly in recent years. Current devices offer tiered therapy utilizing bradycardia pacing, anti-tachycardia pacing, low-energy cardioversion, and high-energy defibrillation. Hybrid therapy, combining device, drugs and radiofrequency catheter ablation as required, has become the standard of care for reducing both appropriate and inappropriate shocks. As implantation rates continue to rise, so will the number of patients presenting with electrical storm. The dilemma of how our society will cope with the enormous projected costs of implantable cardioverter-defibrillator therapy has yet to be resolved.

Key Words: Sudden cardiac death, ventricular tachycardia, ventricular fibrillation, implantable cardioverter-defibrillator, tiered therapy, hybrid therapy, inappropriate shocks, electrical storm.

Introduction

SUDDEN CARDIAC DEATH is defined as unexpected death from a cardiac cause occurring within one hour of the onset of symptoms (1). Nearly 50% of all deaths attributable to cardiovascular disease are sudden in nature, accounting for the loss of 300,000–400,000 lives annually in the United States (2). Sudden cardiac death is usually due to malignant arrhythmia; 80–90% of such deaths are due to ventricular tachyarrhythmias, while the remainder may result from bradyarrhythmias, asystole, or pulseless electrical activity (3). Evidence from community-based studies indicate that only 4–33% of people with out-of-hospital cardiac arrest

survive to admission (4, 5). Consequently, implantable cardioverter-defibrillator (ICD) therapy has become an important option in both primary and secondary prevention of sudden cardiac death due to ventricular tachyarrhythmias.

Causes and Predictors of Sudden Cardiac Death

A number of diseases are associated with sudden cardiac death (Table 1). Epidemiologic data indicate that coronary artery disease (CAD) causes 80% of fatal arrhythmias (6), and the roles of myocardial ischemia or prior myocardial infarction (MI) in this regard are well established (7). Dilated cardiomyopathy and hypertrophic cardiomyopathy are responsible for an additional 10–15% of arrhythmic deaths (8). The other reversible and nonreversible diseases listed probably account for less than 5% of malignant arrhythmias (2).

Conventional, modifiable cardiovascular risk factors such as cigarette smoking, hypertension, diabetes mellitus, and dyslipidemia serve as easily identifiable markers of an increased risk of sudden cardiac death. However, their primary significance lies in their link to coronary artery disease, the predominant disease predisposing to sudden cardiac death, rather than as specific markers for immediate fatal

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TABLE 1
Diseases Associated with Sudden Death

Coronary artery disease (myocardial infarction/ischemia)
Nonischemic dilated cardiomyopathy
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Brugada syndrome
Long QT syndrome
Short QT syndrome
Complex congenital heart disease
Wolff-Parkinson-White syndrome
Valvular heart disease
Cardiac sarcoidosis
Myocarditis
Drug induced
Electrolyte/metabolic disturbances
Aortic dissection
Pulmonary embolism
Pulmonary hypertension

arrhythmia (2). Clinically, the degree of functional impairment, as categorized by the New York Heart Association classification, and the degree of left ventricular systolic dysfunction, as assessed by echocardiography, radionuclide scintigraphy, or radiocontrast ventriculography, are powerful predictors of the risk of death, whether it is arrhythmic or non-arrhythmic in nature (9–11). Invariably, an episode of aborted sudden cardiac death due to hemodynamically unstable sustained ventricular tachycardia or ventricular fibrillation unassociated with a reversible cause engenders the highest risk of sudden cardiac death (12, 13).

Standard 12-lead electrocardiography may reflect underlying structural heart disease or even help specify diseases of electrophysiological concern, including long QT syndrome (14), short QT syndrome (15), arrhythmogenic right ventricular cardiomyopathy (16), Brugada syndrome (17) and hypertrophic cardiomyopathy (18). Additional noninvasive testing, such as 24-hour Holter monitoring, can be useful in ascertaining the risk of sudden cardiac death, especially if nonsustained or sustained ventricular tachycardia (Fig. 1) is documented in certain high-risk subgroups, such as those with left ventricular systolic dysfunction and CAD (19).

Further methods of noninvasive testing have been evaluated. After MI, signal-averaged electrocardiography demonstrates high negative predictive value, but clinical utilization remains limited by its low positive predictive value (20–22). Studies of noninvasive tests focusing on the role of the autonomic nervous system, such as heart rate variability (23) and baroreflex sensitivity (24), have indicated relatively low accuracy as predictors of arrhythmic events. To date, other noninvasive tests evaluating electrocardiographic repolarization abnormalities, including QT-interval dispersion and T-wave alter-

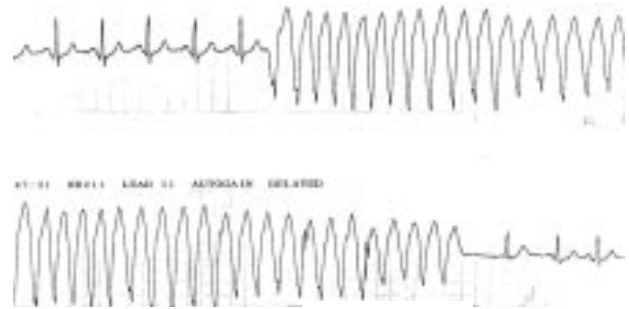


Fig. 1. Rhythm strip recording of sinus rhythm at 100 beats per minute with a 39 beat salvo of nonsustained ventricular tachycardia.

nans, have proven either inconsistent or lacking in applicability beyond specific high-risk groups (25).

Electrophysiological testing continues to occupy a role in risk stratification for sudden cardiac death. Induced sustained ventricular tachyarrhythmia by programmed electrical stimulation is a well-established marker of increased risk of ventricular tachyarrhythmias (26, 27). However, electrophysiological testing remains limited by the significant proportion of false negative results that occur (19). Nevertheless, it remains a useful tool for evaluating patients with impaired left ventricular function and syncope (28) or nonsustained ventricular tachycardia (19, 29).

ICD Therapy: Rationale and Indications

In 1980, Dr. Michel Mirowski revolutionized the management of ventricular arrhythmias when he demonstrated the efficacy of the automatic implantable defibrillator (30). With the implantable cardioverter-defibrillator (ICD), once ventricular tachycardia or ventricular fibrillation is detected, an electrical current is directed across a large portion of the myocardium to depolarize most of the ventricular tissue, thereby allowing an organized rhythm to return. Despite initial criticism and considerable controversy (31), the ICD has gained widespread acceptance and implementation, with an estimated 55,000 such devices now implanted in the United States annually. This dramatic acceleration in implantation is a direct reflection of the rapidly expanding list of approved indications for ICD therapy in recent years (Table 2) (32).

Secondary Prevention

In 1997, the Antiarrhythmics Versus Implantable Defibrillators (AVID) study provided definitive proof of the superiority of ICD therapy over drug therapy for those patients at highest risk of sudden cardiac death—those who had already experienced an aborted cardiac arrest (33). This landmark multi-

TABLE 2

Indications for Implantable Cardioverter-Defibrillator Therapy

Class I (general agreement that it is beneficial, useful, and effective):

1. Cardiac arrest due to VF or VT not due to a transient or reversible cause.
2. Spontaneous sustained VT in association with structural heart disease.
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant, sustained VT or VF induced at electrophysiologic study when drug therapy is ineffective, not tolerated, or not preferred.
4. Nonsustained VT in patients with coronary disease, prior MI, LV dysfunction, and inducible VF or sustained VT at electrophysiologic study that is not suppressible by a Class I antiarrhythmic drug.
5. Spontaneous sustained VT in patients without structural heart disease not amenable to other treatments.

Class IIa (weight of opinion is in favor of usefulness/efficacy): Patients with left ventricular ejection fraction of $\leq 30\%$ at least 1 month after MI and 3 months after coronary artery revascularization.

Class IIb (usefulness/efficacy is less well established by evidence/opinion):

6. Cardiac arrest presumed to be due to VF when electrophysiologic testing is precluded by other medical conditions.
7. Severe symptoms (e.g., syncope) attributable to ventricular tachyarrhythmias in patients awaiting cardiac transplantation.
8. Familial or inherited conditions with a high risk for life-threatening ventricular tachyarrhythmias such as long QT syndrome or hypertrophic cardiomyopathy.
9. Nonsustained VT with coronary artery disease, prior MI, and LV dysfunction, and inducible sustained VT or VF at electrophysiologic study.
10. Recurrent syncope of undetermined origin in the presence of ventricular dysfunction and inducible ventricular arrhythmias at electrophysiologic study when other causes of syncope have been excluded.
11. Syncope of unexplained origin or family history of unexplained sudden cardiac death in association with typical or atypical right bundle-branch block and ST-segment elevation (Brugada syndrome).

Adapted with permission from Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *J A Coll Cardiol* 2002; 40(9):1703–1719 (32).

LV = left ventricular VF = ventricular fibrillation
MI = myocardial infarction VT = ventricular tachycardia

center, unblinded, randomized controlled trial enrolled 1,016 patients resuscitated from near-fatal ventricular fibrillation or ventricular tachycardia (not due to reversible causes) with left ventricular ejection fraction (LVEF) $< 40\%$, and assigned them to either ICD therapy or antiarrhythmic drug therapy (empirically administered amiodarone in 95.8% of cases). The trial was stopped prematurely when ICD

therapy was shown to result in a significant survival advantage in comparison to antiarrhythmic drug therapy. The mortality rate in the ICD group was 24.6% vs. 35.9% in the antiarrhythmic group after 3 years of follow-up, yielding a relative risk reduction of 31%. The resulting average length of additional life associated with ICD therapy at 3 years was 2.7 months. However, one area of concern in the AVID study was the significant difference in beta-adrenergic blocker therapy between the ICD group (47.6%) and the antiarrhythmic group (18.9%), probably yielding some degree of survival advantage to the former. Similar results were reported in two smaller randomized trials, the Canadian Implantable Defibrillator Study (CIDS) (34) and the Cardiac Arrest Study Hamburg (CASH) (35). Details regarding the above-mentioned randomized control trials are provided in Table 3.

Primary Prevention

Unfortunately, only a small percentage of patients who suffer a cardiac arrest in the U.S. each year survive to benefit from an ICD for secondary prevention. Hence, ICD therapy for primary prevention of sudden cardiac death has become the focus of intense clinical investigation in recent years (Table 4). The first major study in this regard was the Multicenter Automatic Defibrillator Implantation Trial (MADIT), which included 196 patients with prior MI, LVEF $\leq 35\%$, nonsustained ventricular tachycardia (NSVT), and inducible sustained ventricular tachycardia upon electrophysiologic study not suppressible by intravenous procainamide (29). Follow-up over 5 years demonstrated a dramatic 41% relative risk reduction in mortality in the group randomized to ICD therapy as compared to the group given conventional therapy (including amiodarone). The Multicenter Unsustained Tachycardia Trial (MUSTT) included patients with CAD, LVEF $\leq 40\%$, NSVT, and inducible sustained ventricular tachycardia on electrophysiologic study (36). At five years, patients receiving ICD therapy experienced a mortality rate of 24% as compared to 55% for patients receiving antiarrhythmic therapy guided by electrophysiologic testing, and 48% for those patients treated with conventional therapy. More recently, the MADIT II study (37) compared 1232 patients with prior MI and LVEF $\leq 30\%$, without requiring documented NSVT or electrophysiologic testing, randomized either to ICD therapy or conventional medical therapy (including beta-adrenergic blockers and angiotensin-converting-enzyme inhibitors). After 20 months of follow-up, the mortality rates were 19.8% in the conventional therapy group and 14.2% in the defibrillator group. In

TABLE 3
Trials of ICD Therapy and Secondary Prevention of Sudden Cardiac Death

Trial	Design	Participants	RRR
AVID (33)	Multicenter RCT comparing ICD to amiodarone in those with prior VT or VF and LVEF < 40%.	1016 enrolled	31%
CIDS (34)	Multicenter RCT comparing ICD to amiodarone in those with VF or hemodynamically significant VT or syncope and inducible VT on EP study, and LVEF < 35%.	659 enrolled	20%
CASH (35)	Multicenter RCT comparing ICD to amiodarone or metoprolol in those who had been resuscitated from VT/VF.	288 enrolled	23%

EP = electrophysiologic

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

RCT = randomized controlled trial

RRR = relative risk reduction (total mortality)

VF = ventricular fibrillation

VT = ventricular tachycardia

essence, one life was saved among every 11 implants. Accordingly, the United States Food and Drug Administration further expanded its list of approved indications for ICD therapy.

Not all studies have shown clinical benefit with ICD therapy (Table 4). The Coronary Artery Bypass Graft (CABG) Patch Trial randomized 1,055 patients

with LVEF \leq 35%, no prior ventricular tachycardia/ventricular fibrillation, and abnormal signal-averaged electrocardiogram scheduled for CABG surgery to either concomitant epicardial ICD implantation or only conventional medical management—excluding antiarrhythmic agents (38). ICD therapy did not improve survival, probably reflecting the important ben-

TABLE 4
Trials of ICD Therapy in Primary Prevention of Sudden Cardiac Death

Trial	Design	Participants	RRR
MADIT (29)	Multicenter RCT comparing ICD to antiarrhythmic therapy in those with prior MI, LVEF \leq 35%, NSVT, and unsuppressible VT on EP study.	196 enrolled	41%
MUSTT (36)	Multicenter RCT comparing ICD to EP guided antiarrhythmic therapy or conventional therapy in those with CAD, LVEF \leq 40%, NSVT, and inducible VT on EP study.	704 enrolled	50%
MADIT II (37)	Multicenter RCT comparing ICD to conventional therapy in those with prior MI and LVEF \leq 30%.	1,232 enrolled	28%
CABG (38)	Multicenter RCT comparing ICD to conventional therapy in those undergoing surgical revascularization with LVEF \leq 35%, and abnormal SAECG.	1,055 enrolled	None
DEFINITE (39)	Multicenter RCT comparing ICD to conventional therapy in those with non-ischemic dilated cardiomyopathy, LVEF < 36%, and PVCs/NSVT.	458 enrolled	30%
COMPANION (40)	Multicenter RCT comparing ICD/CRT to CRT to conventional therapy with either ischemic or non-ischemic dilated cardiomyopathy, LVEF \leq 35%, and QRS \geq 120 ms.	1,520 enrolled	36%

RRR = relative risk reduction (total mortality)

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

VT = ventricular tachycardia

CAD = coronary artery disease

PVCs = premature ventricular contractions

RCT = randomized controlled trial

MI = myocardial infarction

NSVT = non-sustained VT

EP = electrophysiologic

SAECG = signal-averaged ECG

CRT = cardiac resynchronization

efit provided by definitive surgical revascularization in reducing myocardial ischemia and improving left ventricular systolic function.

Primary prevention trials have also been undertaken to study patients with non-ischemic cardiomyopathy. Recently, the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study was released (39). In it, 458 patients with non-ischemic cardiomyopathy, LVEF < 36%, NYHA I-III, and ventricular ectopy on Holter monitoring, were randomized to either conventional medical therapy or a single chamber ICD. After 29 months of follow-up, the DEFINITE study showed a significant 78.6% relative risk reduction in sudden cardiac death, but only a non-significant 30% relative risk reduction in overall mortality with ICD therapy ($p=0.08$). Previously, 2 smaller randomized trials, the Amiodarone versus Implantable Defibrillator in Patients with Non-ischemic Cardiomyopathy and Asymptomatic Non-sustained Ventricular Tachycardia (AMIOVIRT) study (40), and the Cardiomyopathy Trial (CAT) (41), had failed to show a mortality benefit with ICD therapy in the context of non-ischemic dilated cardiomyopathy. The relative lack of efficacy with ICD therapy in this group of patients may be due to the fact that the initiation of ventricular tachyarrhythmias in non-ischemic cardiomyopathy is often due to a focal autonomic mechanism rather than a reentrant mechanism (42). Hence, patients with non-ischemic cardiomyopathy may be more amenable to prophylaxis against sudden cardiac death with effective neurohormonal modulation alone (utilizing appropriate medical therapy). Data from the as-yet-unpublished Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) may help to further elucidate the role of prophylactic ICD therapy in patients with non-ischemic cardiomyopathy (43).

The results of the recently published Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial may provide the key to optimizing the efficacy of ICD therapy (44). In this trial, 1,520 patients with non-ischemic or ischemic (55%) cardiomyopathy, NYHA III-IV, LVEF $\leq 35\%$, and QRS ≥ 120 milliseconds, were randomized to optimal pharmacologic therapy alone or with cardiac resynchronization therapy (CRT—biventricular pacing) with either a pacemaker or ICD. After one year, CRT improved exercise tolerance and quality of life, and reduced mortality risk by 24%. More impressively, it reduced the relative risk of death by 36% (19.2% vs. 12.2%) when coupled with ICD therapy (Table 4). Therefore, it is likely that the benefits of CRT and ICD therapy are additive in patients with advanced heart failure and a prolonged QRS duration.

ICD Therapy: Implantation and Follow-up

ICD surgery in the 1980s and early 1990s required general anesthesia and prolonged hospital stays, and entailed a significant perioperative mortality rate (45). In that era, open thoracotomy was required for placement of epicardial patches tunneled to attach to the generator, the large size of which (> 200 cc) necessitated abdominal implantation.

In the 1990s, utilization of biphasic shock waveforms allowed for the development of active canisters (generators), which are smaller in size and do not require epicardial patches (46, 47). These smaller devices (~ 40 cc) can be implanted in the subcutaneous pectoral region, and the cephalic, axillary, or subclavian routes can be utilized (49) for transvenous right ventricular endocardial lead placement (Fig. 2). Accordingly, only local anesthesia and conscious sedation are required for device testing, hospital stays are short, and perioperative mortality rates are low (46–49).

The cardioverter-defibrillator lead is capable of bipolar sensing and pacing. It has at least one metal coil and is connected to the generator. A large charge of electricity, for shocking, can flow between this coil and the generator. The bulk of the generator consists of the battery (lithium silver vanadium oxide) that allows rapid discharge into a capacitor for shocks (50). Battery longevity ranges



Fig. 2. Chest X-ray (posterior-anterior view) demonstrating a left pectoral implantable cardioverter-defibrillator with leads in the right atrium and at the right ventricular apex.

from 4–10 years, depending upon usage. Long-term elective follow-up usually consists of office visits approximately every 3 months. Routine visits include a focused history, measurement of vital signs, physical examination and recording of the patient's current medical regimen (50). In addition, a manufacturer-specific computer programmer is used to analyze the device, to check battery, capacitor and lead status, and retrieve data pertaining to tachycardia episodes and therapies (including intracardiac electrograms).

Tiered Therapy and Inappropriate Shocks

The present generation of programmable ICDs feature “tiered therapy,” including anti-tachycardia pacing (ATP) for termination of monomorphic ventricular tachycardia, synchronized low-energy cardioversion, unsynchronized high-energy defibrillation and back-up bradycardia pacing. ATP therapies usually consist of “burst” or “ramp” pacing targeted to terminate ventricular tachycardia, usually due to a reentrant mechanism (Fig. 3). If the tachycardia is not successfully terminated after attempts at overdrive pacing, then a low-energy biphasic cardioversion (2–10 Joules) can be delivered. Ultimately, the ICD can deliver a high-energy biphasic shock (30–40 Joules) for the purpose of terminating ventricular tachycardia or ventricular fibrillation (Fig. 4). It is has become standard to forgo further ICD shocks following at least 5–6 sequential shocks for a refractory ventricular tachyarrhythmia (50).

One unique problem is that of preprogrammed ICD therapy delivery for benign or non-life-threatening tachyarrhythmias. Most commonly, sinus tachycardia or atrial tachyarrhythmia may result in a heart rate high enough to trigger detection and sub-

sequent ICD therapy delivery resulting in a painful, inappropriate shock (Fig. 5). Strategies to combat such undesirable scenarios include concomitant drug therapy (such as beta-adrenergic blockers or sotalol), software reprogramming (enabling automatic mode switch for atrial fibrillation or atrial flutter), upgrading of the device's hardware (single to dual chamber sensing), and radiofrequency catheter ablation.

Hybrid Therapy

Since reducing the risk of sudden cardiac death is the ultimate goal, adjunctive antiarrhythmic therapy may be beneficial. In particular, sotalol has been shown to reduce mortality and both appropriate and inappropriate shocks following ICD implantation, as compared to placebo (51). It may be necessary to reevaluate ATP therapies or defibrillation thresholds following the introduction of new antiarrhythmic agents, especially amiodarone (52). Contemporary software allows for sophisticated, noninvasive electrophysiologic testing designed to induce, pace terminate, and cardiovert or defibrillate tachyarrhythmias. As well, scar-related (reentrant) ventricular tachycardia mapping and ablation is becoming increasingly practical and efficacious (53). Such interventional electrophysiologic techniques can be helpful to patients experiencing multiple ICD shocks due to recurrent monomorphic ventricular tachycardia or to those prone to a slow, incessant monomorphic ventricular tachycardia unamenable to device detection and therapy delivery.

Conclusions

The role of the ICD in the epidemiologic period of delayed degenerative diseases will inevitably continue

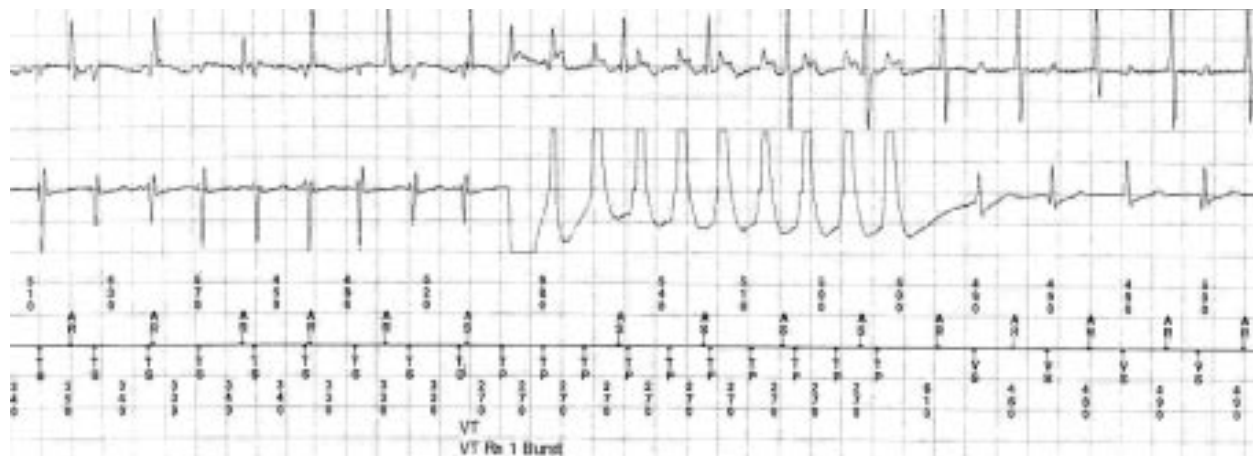


Fig. 3. Atrial (top) and ventricular (bottom) intra-cardiac electrograms indicating sinus tachycardia at approximately 115 beats per minute (top) and disassociated monomorphic ventricular tachycardia at 180 beats per minute (bottom). The ventricular tachycardia is successfully terminated by a 10 beat burst of rapid ventricular pacing.

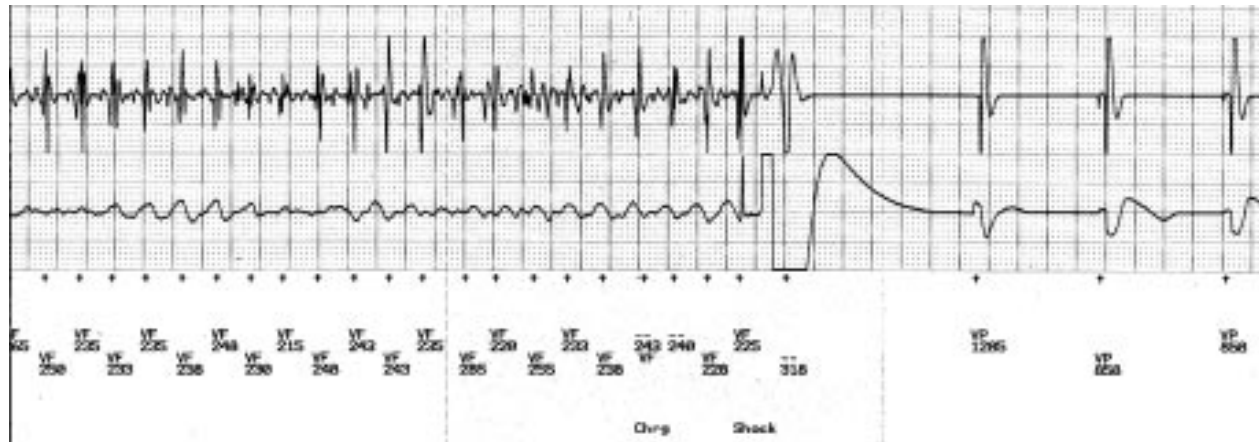


Fig. 4. Ventricular (top) and shock (bottom) intra-cardiac electrograms showing ventricular fibrillation successfully terminated by an internal biphasic shock (21 Joules) with resumption of ventricular pacing thereafter.



Fig. 5. Atrial (top) and ventricular (bottom) intra-cardiac electrograms indicating atrial tachycardia at 200 beats per minute (top) and variable 2nd degree atrio-ventricular block with an average ventricular response of 150 beats per minute (bottom) and the delivery of an “inappropriate” internal biphasic shock (28.1 Joules).

to grow and bring with it a number of medical, economic and social consequences. For appropriately selected patients, ICD therapy can prolong life for months or even years, but it does little to actually improve a patient’s quality of life. The evolving role of concomitant biventricular pacing for patients with symptomatic left ventricular systolic dysfunction and intraventricular conduction delay has the potential to both improve functional status and lower mortality (54).

As the number of patients receiving ICD treatment continues to rise, so does the daunting prospect of more ICD patients presenting with “electrical storms.” An electrical storm, defined as ≥ 3 shocks within a 24-hour period, can be difficult even for an experienced cardiac electrophysiologist to manage, and will pose an increasing challenge to our emergency rooms and coronary care units.

Finally, the cost of the ICD remains expensive (approximately \$30,000 per device). In 2005, ICD therapy is projected to account for approximately \$6.9 billion dollars, 0.4% of the U.S. national health care expenditure. This is a large sum for a nation already grappling with a sizable annual deficit and total debt. It has yet to be seen if our public institutions and private industry are capable of finding a solution that will be deemed affordable, practical, and fair to society as a whole.

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