Implantable cardioverter defibrillators and their role in heart failure progression

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Patients with an implantable cardioverter defibrillator (ICD) implanted for primary prevention have an increased mortality rate if they receive appropriate and/or inappropriate ICD shocks. The most common cause of increased mortality is worsening heart failure. ICD shocks cause direct myocardial injury, contraction band necrosis, and fibrosis, and could induce persistent inflammation. These changes likely contribute to the ventricular dysfunction in patients who have a significantly depressed ejection fraction initially. One-third of the patients with ICDs have psychiatric disorders. Studies have demonstrated that the patients have decreased quality of life, including emotional dysfunction, during the month following an ICD shock. Patients with anxiety and depression have an activated hypothalamus—hypophysis—adrenal axis, increased sympathetic activity, and decreased vagal tone. Chronic sympathetic stimulation could directly affect the myocardium and worsen cardiac dysfunction. Consequently, although ICD implantation is life-saving, it may contribute to heart failure progression. Completed trials need reanalysis to determine whether there are unique characteristics of patients receiving shocks that might lead to additional therapy. Furthermore, the interaction between psychiatric disorders and ICD therapy needs more study.

Keywords
Implantable cardioverter defibrillator • Arrhythmia • Heart failure

Implantable cardioverter defibrillators and heart failure

Heart failure is a common cause of morbidity and mortality. Approximately 60% of patients with ischaemic heart failure die from dysrhythmias, usually ventricular tachyarrhythmias.1 Randomized controlled trials such as CAST, EMiat, and CAMIAT demonstrated that anti-arrhythmic drug therapy clearly did not work in this population.2–4 Although β-blockers do reduce arrhythmic deaths and improve overall mortality, how much of this mortality benefit is due to their anti-arrhythmic effect is not clear.5

Currently, the implantable cardioverter defibrillator (ICD) is the recommended therapy for the primary and secondary prevention of ventricular arrhythmic deaths. The clinical use of ICDs escalated rapidly after the Multicenter Automatic Defibrillator Implantation Trial (MADIT) was published in 1996, even though this trial included only 196 patients.6 The MADIT II and SCD-HeFT trials extended the indications for the use of ICDs, and current guidelines recommend the use of ICD therapy in both primary and secondary prevention of sudden cardiac death as a Class I indication.7–11 After an average of 20 months follow-up of MADIT II participants, the mortality rates were 14.2% in the ICD group and 19.8% in the conventional medical therapy group (P = 0.016). This represented a 31% reduction in the relative risk of death, and the number of patients needed to treat with an implanted ICD to prevent one death over 2 years was 18. At 5 years, the number needed to treat was 13 in SCD-HeFT, 6 in MADIT II, and 2 in MADIT. Cardiologists now refer many patients with ischaemic heart failure and depressed ejection fractions for ICD therapy.8,12 However, do ICDs also have unintended effects on the natural history of ischaemic heart failure?

Human data: do implantable cardioverter defibrillator shocks worsen heart failure?

Implantable cardioverter defibrillators can sense supraventricular rhythm disturbances as lethal ventricular arrhythmia and may deliver shocks inappropriately. Almost one-third of the shocks (184 of 590) delivered to the 719 MADIT II participants were classified as inappropriate. At least one inappropriate shock occurred in 11.5% of the patients with ICDs, and 56 patients (7.8%) had only inappropriate shock(s).13 The most common

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reason for inappropriate shocks was atrial fibrillation/flutter (44%) followed by supraventricular tachycardia (36%) and abnormal sensing (19%). A history of atrial fibrillation, smoking, and a diastolic blood pressure higher than 80 mmHg were the independent risk factors for inappropriate shocks. Patients who received inappropriate shocks had a higher mortality [hazard ratio: 2.29, 95% confidence interval (CI): 1.11–4.71] than those who did not have inappropriate shocks. Hospitalization from heart failure was also higher in the ICD arm of the MADIT II population (19.9% vs. 14.9% over 20 months). This results in a number needed to harm of 20 (one excess hospitalization per 20 patients treated), suggesting that ICD therapy converts sudden death risk to a subsequent hospitalization for heart failure risk.

Poole et al. have evaluated the long-term (almost 4 years follow-up) prognostic significance of ICD shocks in SCD-HeFT participants. They demonstrated that patients with ICDs implanted for primary prevention have an increased mortality rate if they received appropriate and/or inappropriate ICD shocks. In this study, appropriate and inappropriate shocks were associated with a five-fold and two-fold increased risk of death, respectively. This risk increased by a factor of 11 in patients who received both shock types when compared with patients who received no shocks. Like the MADIT II results, the most common cause of increased mortality reported in the SCD-HeFT trial was worsening heart failure (42.9%). Sudden arrhythmia (ventricular tachycardia or ventricular fibrillation), non-cardiac events (e.g., stroke), and other cardiac events (e.g., acute coronary syndromes) were the other causes of death in these patients. Although the mortality benefit with ICDs occurs through the prevention of arrhythmic sudden cardiac death, these devices also appear to increase non-arrhythmic deaths in both trials.

The newer ICDs have more advanced sensing properties and can deliver more appropriate energy than the older models. However, regardless of the shock energy, ICDs still cause direct myocardial injury, contraction band necrosis, fibrosis, and possibly persistent inflammation. Serum cardiac troponin I elevations (3.8 ± 4.3 ng/mL) occur in 43% of patients independent of any concurrent acute coronary syndrome after spontaneous ICD shocks. Several episodes of ventricular fibrillation may be induced and terminated to test the correct sensing and defibrillation properties of the device during implantation. Therefore, 14% of patients have myocardial cell damage during their implantation of ICDs. Most clinicians currently induce ventricular fibrillation only once or twice during ICD implantation. However, the data regarding the number of shocks and troponin rise are conflicting, and Hurst’s study did not show any association between troponin rise and number of shocks in a multivariate analysis. Studies in patients undergoing defibrillator implantation demonstrated that shocks higher than 9 J reduce cardiac index by 10–15%, and this detrimental effect is proportional to the shock strength. In addition to the myocardial damage from the shock itself, endocardial leads may cause foreign body reaction and enhance myocardial fibrosis. Increased fibrosis can increase defibrillation thresholds, and higher energy defibrillations will be required during subsequent arrhythmic events. These fibrotic areas may also lead to the development of new arrhythmogenic re-entry circuits. Although the pathological changes in the myocardium affect <2% of the total myocardial mass, these changes likely contribute to the ventricular dysfunction in patients with an initial median ejection fraction of <25%.

Experimental data: do animal studies help us understand the effects of shocks on the myocardium?

Ultrastructural alterations of the myocardium following endocardial countershocks occur in animals. Myocardial cell necrosis, fibrosis, calcification, interstitial oedema, and macrophage infiltration were observed in the ventricular myocardium in areas adjacent to the ventricular electrodes in dogs. Schirmer et al. demonstrated that low-energy countershocks cause severe mitochondrial damage, especially in the right ventricle in dogs. They found prominent electron microscopic myocardial alterations, including swollen mitochondria, mitochondrial crest disruption, and loss in membrane integrity immediately after endocardial defibrillation. These structural changes in mitochondria likely alter myocardial cell energetics and would help explain how ICD shocks produce significant changes in the myocardium, which may impair systolic function and establish new foci for ventricular arrhythmias.

Oswald et al. compared the defibrillation injury caused by different types of defibrillator shocks in dogs. Biphasic shocks were less injurious to the myocardium, but both monophasic and biphasic shocks were significantly associated with depressed cardiac function, lower mean arterial pressure, and impaired cardiac output following the shock. Myocardial oxidative metabolism derived from myocardial lactate extraction was also suppressed. This finding strongly suggests that shock-induced dysfunction of myocardial cell respiration occurs.

Explanations: do implantable cardioverter defibrillator shocks activate the sympathetic nervous system?

Although the natural progression of heart failure will inevitably result in a cumulative increase in the number of both appropriate and inappropriate (secondary to the increased incidence of atrial fibrillation episodes) shocks, activation of the autonomic nervous system seems to contribute to the increased mortality in these patients. Both external and internal defibrillation shocks induce systemic sympathetic activation and increase overall sympathetic tone. Bode et al. investigated the effect of countershocks on cardiac and circulating catecholamines. In this study, systemic adrenaline levels increased three-fold following ICD shocks (10–34 J, 30 patients). This dramatic increase was even more significant in patients after external defibrillation shocks. Moreover, the cardiac noradrenaline uptake was found to be significantly increased when the arterial noradrenaline levels were compared with coronary sinus noradrenaline levels. This finding reflects the
enhanced myocardial uptake of catecholamines following an ICD shock. Furthermore, increased levels of systemic catecholamines persisted 10 min following the shock in another study.\textsuperscript{28} Catecholamines could cause direct myocardial cell damage through the activation of calcium channels producing calcium overload and myocardial dysfunction, through acute oxidative stress, or through the induction of an acute inflammatory process. Persistently elevated plasma catecholamine levels may also be associated with increased ventricular excitability and decreased threshold for future ventricular arrhythmias. This, in turn, may lead to more ICD shocks.

**Explanations: does activation of sympathetic nervous system influence the incidence and severity of psychiatric syndromes?**

**Epidemiology**

Implantable cardioverter defibrillator shocks cause severe pain. Patients who have received ICD shocks after implantation develop more anxiety, distress, and depression than those who have not had shocks.\textsuperscript{23} The acute distress following an ICD shock may even result in post-traumatic stress disorder.\textsuperscript{24} These patients feel sicker and closer to death regardless of their overall clinical condition. One-third of the patients with ICDs have psychiatric disorders.\textsuperscript{25} Mark et al.\textsuperscript{26} reported that patients have decreased quality of life, including emotional dysfunction, during the month following an ICD shock. Similarly, the randomized, controlled Coronary Artery Bypass Patch Trial demonstrated that quality of life outcomes in ICD patients were worse than the outcomes in the patients without ICD.\textsuperscript{27} The patients with ICD shocks had decreased physical and emotional role functioning and had lower levels of psychological well being in 6 months after their ICD placement. Frequent shocks, age <50, and female gender were risk factors for poor adjustment in ICD recipients in a national survey.\textsuperscript{25} One possible explanation for these findings is that the shocks may remind the patients that they are ill and were near death during the recent ICD firing. It is not surprising that these psychiatric consequences can lead to unfortunate complications, including the possibility of suicide. For example, a 20-year-old man from France ‘lay prostrate in the bed’ and contemplated suicide following 20 electrical shocks in one night.\textsuperscript{28}

**Explanation**

Psychiatric disorders, including depression and anxiety, influence ischaemic heart failure. Patients with chronic anxiety and depression have an activated hypothalamus—hypophysis—adrenal axis, increased sympathetic activity, and decreased vagal tone. Chronic sympathetic stimulation could directly affect the myocardium and increase cardiac dysfunction. Most patients with heart failure have a history of myocardial infarction (MI) as the aetiology of their heart failure. Post-MI depression increases morbidity and mortality in patients with recent MI.\textsuperscript{29} Furthermore, patients with ischaemic heart disease and depression or anxiety are more likely to develop malignant ventricular arrhythmias.

This association may be mediated by changes in the sympathetic nervous system, in vascular inflammation, and/or in platelet reactivity.\textsuperscript{30} Panic disorder and agoraphobia were found to be frequent side effects of ICD treatment.\textsuperscript{31} Although their efficacy is limited in the treatment of panic disorder as a monotherapy, ß-blocker therapy would be useful in these patients. The incidence of anxiety disorder was 6.9% even in patients who did not experience any shocks after ICD implantation (vs. 21% in patients who had ICD shock). In this study, new onset anxiety disorder developed in 16.7% of patients after ICD implantation. Other studies have also reported clinically diagnosable anxiety in 13–38% of patients following ICD implantation, and, regardless of the baseline psychological status, 24–87% of ICD recipients will have more anxiety-related symptoms after ICD implantation.\textsuperscript{25} This, in turn, will increase the number of appropriate ICD shocks since the Triggers of Ventricular Arrhythmias (TOVA) study demonstrated that more severe symptoms of depression predicted ventricular arrhythmias and, accordingly, appropriate ICD shocks.\textsuperscript{32}

Anxiety and panic attacks have acute episodic presentations and have the potential to initiate cardiac syndromes. In general, these attacks are more common in women with a history of cardiovascular disease, chest pain, and/or depression, and are associated with negative life events during the past year. Epinephrine is released from the heart at rest and during spontaneous attacks in patients with panic disorder.\textsuperscript{33} Radiotracer studies using epinephrine and norepinephrine with the collection of samples from the coronary sinus have demonstrated that patients with panic disorder have reduced extraction of norepinephrine and epinephrine during transit through the heart.\textsuperscript{34} This has been attributed to impairment in the norepinephrine transporter that limits catecholamine effects on the heart by uptake. This abnormality has the potential to increase cardiac responses to catecholamine surges during panic attacks and other stressful events. In addition, changes in catecholamine kinetics could have regional effects independent of high circulating levels. Finally, studies in patients with panic attacks have demonstrated that induced panic attacks cause myocardial perfusion defects in patients with known coronary disease.\textsuperscript{35} Severe stress with hyperadrenergic states can cause acute cardiac dysfunction in patients with normal coronary arteries (tako-tsubo syndrome, subarachnoid haemorrhage, and alcohol withdrawal) and in patients with coronary artery disease. These studies suggest an important interaction between psychiatric disorders and stress-induced sympathetic states and the worsening of heart failure after ICD implantation. The main ideas in the review are summarized in Table 1.

**Controversial points**

Although the association of ICD shocks with increased heart failure morbidity and mortality seems clear in the reports from the MADIT II trial and the SCD-HeFT trial, not all experts agree with this conclusion. Goldenberg et al.\textsuperscript{36} reported that inappropriate ICD shocks in the SCD-HeFT trial were not associated with a significant increase in risk of subsequent heart failure; therefore, the effects of shocks on the myocardium did not contribute to heart failure after ICD implantation. They concluded that the life-prolonging benefit of ICD therapy was associated with increased...
heart failure events as a feature of the natural history of these disorders. Healey and Connolly\textsuperscript{37} also downplayed the possible effects of myocardial shocks on myocardial function in an editorial for the *New England Journal of Medicine* written at the time of the publication of the subgroup analysis SCD-HeFT data which reported that both appropriate and inappropriate shocks were associated with heart failure morbidity. Recently, Bunch et al.\textsuperscript{38} reported that new onset atrial fibrillation during the first 3 months of implant was associated with significantly higher rates of death in a retrospective analysis. In this study, a history of atrial fibrillation was associated with higher prevalence of heart failure (52 vs. 36\%) and higher rates of heart failure hospitalization [hazard ratio: 2.14 (95\% CI: 1.29–3.54), \(P < 0.01\)]. These observations and commentaries all suggest that a subset(s) of these patients is at risk for heart failure progression.

Higher delivered energies likely cause more myocardial dysfunction and worse outcomes. Hence, ICD shock energy of the first and consecutive shocks may be another important factor influencing the outcome. The efficacy of limited shock testing, lower safety margins, and lower delivered energy devices for patient tolerability and lengthening battery life needs more study.

Controversy about the quality of life, anxiety, and psychiatric disorders in ICD patients also exists. A recent article published in the January 2009 issue of *Europace* found no evidence of increased long-term psychological morbidity in patients living with an ICD under advisory compared with patients with an ICD not under advisory, suggesting patients and physicians should avoid premature decisions of ICD replacement for psychological reasons.\textsuperscript{39} Similarly, health-related quality of life was not affected by ICD implantation among 458 patients in the Defibrillators in Non-ischaemic Cardiomyopathy Treatment Evaluation study.\textsuperscript{40} These findings underscore the necessity of a prospective randomized controlled trial investigating the impact of ICD implantation on heart failure progression and psychological outcomes. These outcomes should be analysed according to age, since it is likely that patients in different age quartiles may be affected differently from the psychological and mechanical (e.g. worsening of heart failure) consequences of ICD therapy.

### What are the therapeutic implications of this review?

(1) The medical management of these patients must be optimized to reduce the number of shocks, to prevent myocardial fibrosis, and to slow the progression of heart failure. Features such as anti-tachycardia pacing and the use of longer ‘number of intervals to detect’ reduce the number of ICD shocks. Hence, appropriate utilization of these features should be considered in all patients receiving ICDs. Angiotensin-converting enzyme inhibitors, β-blocking agents, spironolactone, and statins should be studied in properly controlled trials to determine their effects on disease progression. Cardiac resynchronization therapy might also be considered in patients with baseline QRS durations >0.12 s.

(2) Personality and psychological profiles should be assessed before ICD implantation. Patients who have a tendency to experience negative emotions should be reconsidered before device therapy, especially when the ICD indications are marginal as in, for example, patients with asymptomatic heart failure, ejection fraction >30\%, QRS intervals <120 ms, and ischaemic cardiac events older than 1 year.

(3) Detailed psychological aftercare and drug treatment for anxiety and depression should be considered in selected patients following ICD implantation.

(4) Although drug-related side effects often occur, amiodarone and β-blockers reduce the number of shocks. The treatment with β-blockers following ICDs implantation should be continued. In addition to their crucial effects on heart failure, malignant arrhythmias, and coronary artery disease, they may provide benefit in the treatment of hyperadrenergic state in panic disorders, which is highly prevalent in patients

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**Table 1: Consequences of implantable cardioverter defibrillator shocks**

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>Pain and stress</th>
<th>Doherty\textsuperscript{23} and Ladwig et al.\textsuperscript{24}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological symptoms</td>
<td>Anxiety (13–38%), panic disorder (10–62%), poor adjustment, depression, and agoraphobia</td>
<td>Doherty\textsuperscript{23}, Sears and Conti\textsuperscript{25}, and Kop et al.\textsuperscript{20}</td>
</tr>
<tr>
<td>Sympathetic nervous system</td>
<td>Catecholamine release, increase sympathetic tone, and increase cardiac noradrenaline uptake</td>
<td>Bode et al.\textsuperscript{21} and Yu et al.\textsuperscript{22}</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>Decrease 10–15%</td>
<td>Tokano et al.\textsuperscript{18}</td>
</tr>
<tr>
<td>Troponin</td>
<td>Release (up to 8.1 ng/mL)</td>
<td>Hasdemir et al.\textsuperscript{16}</td>
</tr>
<tr>
<td>Pathology</td>
<td>Inflammation, fibrosis, calcification, macrophage infiltration, myocyte necrosis, and interstitial oedema</td>
<td>Singer et al.\textsuperscript{15} and Hurst et al.\textsuperscript{17}</td>
</tr>
<tr>
<td>Systemic circulation</td>
<td>Increased level of circulating catecholamines (three-fold)</td>
<td>Bode et al.\textsuperscript{21} and Yu et al.\textsuperscript{22}</td>
</tr>
<tr>
<td>Ultrastructural studies</td>
<td>Mitochondrial swelling, loss of membrane integrity, and mitochondrial crest disruption</td>
<td>Schirmer et al.\textsuperscript{19}</td>
</tr>
<tr>
<td>Risk of death</td>
<td>Increase five-fold (appropriate shock)</td>
<td>Poole et al.\textsuperscript{14}</td>
</tr>
<tr>
<td></td>
<td>Increase two-fold (inappropriate shock)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase 11-fold (both shock types)</td>
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</table>
with ICDs. β-Blockers can potentiate the effect of conventional therapies in patients with treatment-resistant panic disorder.11

What do we need to know?

1. Implantable cardioverter defibrillators are life-saving, but these devices may contribute to heart failure progression. The primary question is whether or not electrical shocks increase disease progression through sympathetic effects on the myocardium and central nervous system. This question can be answered in part by reanalysis of the databases in the original trials using case-control studies of patients receiving shocks matched to patients not receiving shocks with propensity score comparison and survival analysis. A longitudinal ICD registry study could analyse the ejection fractions of the patients at the third year following ICD implantation prospectively.42 The comparison of systolic functional parameters between the ‘shocked’ or ‘not shocked’ group would provide useful information about this issue.

2. Databases should be analysed to determine the benefit of amiodarone therapy in patients with ICDs and its effect on heart failure progression among these patients. In spite of the favourable effects of amiodarone in mortality (GESICA) and left ventricular systolic function (CHF-STAT), an anticipated but significant increase in mortality was observed in Class III heart failure patients who were treated with amiodarone in SCD-HeFT trial.9,43,44 This finding may need more investigation.

3. The interaction between psychiatric disorders and ICD therapy needs more study in prospective trials. This information should provide better treatment strategies for psychological disorders in patients with ICDs and could increase the benefits with device therapy.

Conflict of interest: none declared.

References

28. Cevik C. Cevik et al.


