

# Apparent Protective Effect of Increased Left Ventricular Wall Thickness in an ICD Population

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## ABSTRACT

**Background:** Expanding indications for the implantable cardioverter defibrillator (ICD) call for further enhancement of patient selection for optimization of use. Because a subgroup of patients who receive ICDs may not receive therapies, we sought to identify clinical predictors of therapy-free survival in ICD patients.

**Methods:** We performed an analysis of a single-center, 13-year ICD implantation experience (1990–2002). The association between therapy-free survival and several clinical variables was evaluated.

**Results:** From a total of 562 patients included in the database, 98 patients (17%) received no shock therapies or antitachycardia pacing (group A). When compared with a randomly selected sample of 131 patients who did receive ICD therapies (group B), there were no significant differences in age, gender, frequency of coronary artery disease, or extent of left ventricular (LV) dysfunction. However, left ventricular hypertrophy (LVH; increased wall thickness by echocardiography) was significantly more common in group A versus group B (30% versus 18%; Pearson's chi-square = 4.69,  $P = .03$ ). The odds of patients in group A having LVH were 1.98 times higher versus group B (95% confidence interval for odds ratio: 1.06–3.71). Comparisons of calculated mean LV mass between the 2 groups were not significantly different (group A  $283 \pm 112$  gm versus group B  $271 \pm 108$ ,  $P = .58$ ). The overall mortality rate was 17% in group A and 22% in group B ( $P = .29$ ).

**Conclusions:** Increased LV wall thickness was a significant, independent predictor of therapy-free survival in this ICD population. Because LV mass was unchanged, this finding may reflect the importance of LV dilation and wall thinning (ie, eccentric remodeling) as a risk factor for recurrent ventricular arrhythmia in ICD patients.

**Key Words:** Implantable cardioverter-defibrillator, left ventricle, wall, dilatation, arrhythmia, remodeling, eccentric, concentric, recurrence.

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Expanding indications for implantable cardioverter-defibrillators (ICDs) have resulted in a steady increase in the pool of patients clinically eligible to receive devices. Between 1993 and 1999, the number of defibrillators implanted annually in the United States increased from 15,307

to 50,100, a 227% increase.<sup>1</sup> Estimates for the year 2000 indicated that 61,000 ICDs were implanted in the United States and 81,000 worldwide.<sup>1</sup> Recent clinical evidence<sup>2</sup> is likely to escalate the use of ICDs even further, with an exponential rise in the burden of long-term follow-up and device revisions.

Although the evidence from the ICD clinical trials indicates an overall beneficial effect on mortality, there are clearly subgroups of patients that are likely to derive maximum benefit or, conversely, patients whose survival is not affected by use of the ICD. To maximize benefit while using ICDs judiciously, the logical next step is to identify these subgroups. Because of variability in arrhythmia recurrence, some patients may never experience device therapies or have a low risk for future therapies.<sup>3</sup> We used a logistic regression model to examine the potential role of multiple clinical variables in predicting therapy-free survival after ICD implantation.

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## Methods

### Study Design

The ICD clinical database at Oregon Health & Science University was used to perform a retrospective analysis of potential clinical predictors of therapy-free survival in patients with implantable defibrillators. All patients who received ICDs between January 1990 and October 2002 were included in the analysis if they were currently followed at Oregon Health & Science University (seen within 6 months of analysis) or had died while being followed at our institution. Two groups of subjects from the ICD population were compared in this case control study—patients who had therapy-free survival (group A) versus those who had 1 or more ICD therapies after implantation (group B). Thus group A consisted of all subjects with a minimum of 1-year follow-up who never received any ICD therapy after device implantation. Group B consisted of 131 control subjects from the remainder of the patient population (ie, patients with a minimum 1-year follow-up who had received one or more device therapies after device implantation). Group B patients were selected randomly from the overall ICD population over a period of 12 years using a number system (every fourth patient in sequence), with proportional representation for all years. Investigators identified a list of clinical predictors that they hypothesized would differ between groups A and B. These clinical variables were age, sex, primary cardiac etiology, presence/absence of coronary artery disease, presence/absence of left ventricular dysfunction, and presence/absence of left ventricular hypertrophy (LVH). LVH was defined as left ventricular wall thickness of 12 mm or greater by echocardiography. A separate comparison was conducted of differences in antiarrhythmic drug therapy between the 2 groups. The Vaughn Williams classification of antiarrhythmic agents was used and consideration was given both to drug therapy at time of ICD implantation and during follow-up.

### Follow-up

As a routine, patients received follow-up in arrhythmia clinic 1 week, 1 month, and every 3 months after ICD implantation. At every visit, evaluation included patient history and device interrogation to determine occurrence of device therapies.

### Diagnosis of LVH

LVH was defined as left ventricular wall thickness of 12 mm or greater by echocardiography. In the overwhelming majority of cases analyzed (at least 90%), the cardiac echo was performed within 6 months of ICD implantation. In the remainder, diagnosis of LVH was made using the cardiac echo performed in closest proximity to ICD implantation. In the event of off-axis m-modes, wall thickness was measured using 2-dimensional images.

### Calculation of LV Mass

Left ventricular (LV) mass was calculated using echocardiographic parameters for 50 randomly selected cases in each group (total 100 cases) and comparisons made between groups A and B. The corrected ASE-cube method<sup>4</sup> was employed as follows:

$$\text{LV mass(g)} = 0.8\{1.04[\text{IVSd} + \text{LVIDd} + \text{PWTd}]^3 - \text{LVIDd}^3\} + 0.6 \text{ g}$$

where IVS = interventricular septal thickness, LVID = LV internal diameter, and PWT = posterior wall thickness (all in cm).

## Statistical Analysis

Data were collected in Excel spreadsheets and imported into SPSS v10.0, and merged together for analyses. Comparison of groups A and B were made on each of these variables individually using Pearson's chi-square test/Fisher's exact test and a logistic regression model. LV mass values and age for groups A and B were compared using the paired *t*-test.

## Results

### Clinical Predictors of Therapy-Free Survival

A total of 562 patients met criteria for analysis; 98 patients (17%) that remained free of device therapies after implantation constituted group A. Comparisons with group B are shown in **Table 1**. There were no significant differences in clinical characteristics between the 2 groups except for LVH. Approximately 30% of group A subjects had LVH, whereas only 18% of group B patients had LVH, a statistically significant difference (Pearson's chi-square = 4.69, *P* = .030). With logistic regression, the odds of having LVH were 1.98 times higher in group A versus group B (95% confidence interval for odds ratio: 1.06–3.71). Overall, there were no significant differences in the mortality rate between the 2 groups.

On reviewing the initial indications for device implantation, some patients had received “prophylactic ICDs” based on indicators of high risk, such as family history or as a course of enrollment in the Prevention of Sudden Cardiac Death in Patients with Congestive Heart Failure Trial (SCD-HFT) trial. Among patients with hypertrophic cardiomyopathy, 1 received a “prophylactic” ICD (group B). Among

**Table 1.** Comparison of Clinical Characteristics in Patients with Therapy-Free Survival (Group A) versus Those that Received ICD Therapies (Group B)

Variable	Group A (n = 98)	Group B (n = 131)	<i>P</i> Value
Age*	62 ± 15y	63 ± 16y	.90
Men†	73 (74%)	103 (79%)	.46
Coronary artery disease†	55 (57%)	81 (62%)	.44
Hypertrophic cardiomyopathy‡	4 (4%)	1 (1%)	.17
Idiopathic dilated cardiomyopathy†	24 (25%)	23 (17%)	.17
Long QT syndrome‡	4 (4%)	1 (1%)	.17
Idiopathic VF†	5 (5%)	9 (7%)	.62
ARVD‡	0	4 (3%)	.14
Miscellaneous conditions†	6 (5%)	14 (9%)	.23
LV dysfunction†	71%	71%	.97
Follow-up duration*	43 ± 26 mo	52 ± 39 mo	.04
LVH†	29 (30%)	23 (18%)	.03
Mortality rate‡	17%	22%	.29

ICD, implantable cardiac defibrillation; VF, ventricular fibrillation; ARVD, arrhythmogenic right ventricular dysplasia; LV, left ventricular; LVH, left ventricular hypertrophy.

\*Group A and B compared via independent samples *t*-test.

†Group A and B compared via Pearson's chi-square test.

‡Group A and B compared via Fisher's exact test (due to small cell sizes).

patients with idiopathic dilated cardiomyopathy, 8 received "prophylactic" ICDs—5 were in group A (3 enrolled in SCD-HFT) and 3 in group B ( $P = \text{NS}$  for these comparisons).

### LV Mass Comparison

The mean LV mass in group A was  $283 \pm 112$  g, compared with  $271 \pm 108$  g in group B ( $P = .58$ ).

### Comparison of Antiarrhythmic Drug Therapy

The only significant difference detected was for use of the class III antiarrhythmic agents amiodarone and sotalol (group A 13% versus group B 28%,  $P = .01$ ). Detailed comparisons are shown in Table 2. The time of initiation of class III antiarrhythmic agents in group B was also evaluated. Of the 40 patients on these drugs, therapy was initiated before ICD implantation in 20 and after device therapies in an equal number. Also 78% ( $n = 31$ ) patients were on amiodarone and only 22% ( $n = 9$ ) were on D,L-sotalol.

## Discussion

Patients with therapy-free survival (group A) constituted 17% of all ICD patients with at least 1 year of follow-up. They could not be distinguished from a control group of ICD patients who had received therapies (group B) on the basis of sex, mean age, presence/absence of coronary artery disease, or extent/absence of LV dysfunction. However, increased LV wall thickness emerged as a significant predictor of therapy-free survival. There was no significant difference in LV mass between randomly selected subsets of both groups.

Multicenter trials in the ICD population have focused largely on the impact of this intervention on overall survival.<sup>2,5-7</sup> However, recently, Halstrom and coworkers re-evaluated the Antiarrhythmics Versus Implantable Defibrillator trial population and identified a subgroup of patients at lower risk of arrhythmia recurrence.<sup>3</sup> At the end of 3 years of follow-up, 26.9% of all patients had event-free survival. This group consisted largely (78.9%) of patients who originally presented with isolated episodes of ventricular fibrillation and did not have cerebrovascular disease. In addition, the average LV ejection fraction was greater than 27%. The potential role of left ventricular hypertrophy as a clinical predictor of high/low risk of recurrent events in the ICD population has not been evaluated.

In the general population, there is a clear association between left ventricular hypertrophy and increased overall mortality.<sup>8-10</sup> An association has also been made between LVH and sudden death, but there were some important caveats. Using echocardiographic measures, Haider and coworkers observed a correlation between LVH and increased risk of sudden death.<sup>11</sup> However, because autopsy data were not analyzed, there was significant potential for abnormalities such as plaque rupture and coronary thrombosis being confounding variables.<sup>12</sup> As a consequence, the independent contribution of LVH to sudden death risk in the general population needs further assessment. The present ICD population, however, constitutes a select group. Devices were implanted following risk stratification for sudden death or survival from cardiac arrest. Unlike the general population, the majority of ICD patients have significant cardiac structural and functional abnormalities. In the present study population, coronary artery disease and LV dysfunction were present in 60% and 71% of overall patients, respectively. Consequently, it is difficult to extrapolate the potential role of LVH in the general population to this high-risk subgroup. In our ICD population, LVH was not a determinant of mortality. Instead, LVH correlated with fewer episodes of ICD therapies (ie, fewer episodes of recurrent arrhythmia).

Both LVH and dilatation can occur as a consequence of ventricular remodeling, which, in turn, is initiated by a primary event such as myocardial infarction.<sup>13-17</sup> Data from experimental models would suggest that either condition can promote the initiation of ventricular arrhythmias requiring device therapy.<sup>18,19</sup> However, LV dilatation may lead to a higher propensity for recurrent ventricular arrhythmia because of the additional involvement of mechano-electrical feedback.<sup>20,21</sup> Upon initiation of a ventricular arrhythmia, ventricular dilatation has also been implicated as an important contributing factor in the degeneration of the arrhythmia process.<sup>19,21</sup> Furthermore, elegant studies in the rat infarct model of heart failure also suggest that hypertrophy of residual myocardium after experimental myocardial infarction may, in fact, be protective. Litwin and coworkers demonstrated that induction of myocardial hypertrophy by chronic inhibition of long-chain fatty acid oxidation retarded the process of LV dilatation after myocardial infarction, and resulted in improved LV systolic function.<sup>22</sup> In the present study, the comparisons of LV mass may provide a possible explanation for the apparent protective effect of LVH. In general, LV mass may be increased to a similar extent in patients with dilated, thin walls (eccentric remodeling) as in patients with less dilatation, but thicker walls (concentric remodeling). Although there was a slightly higher mean LV mass in group A, this was not a statistically significant difference. This would suggest that apparent protective effect of LVH may in fact reflect decreased dilatation and better preservation of LV wall thickness in patients with therapy-free survival. LV dilatation and wall thinning i.e. eccentric remodeling, may have been a stronger risk factor for recurrent arrhythmia in this patient population.

**Table 2.** Comparison of Antiarrhythmic Drug\* Use in Therapy-Free Versus Therapy Groups

Antiarrhythmic Therapy	Therapy-Free (n = 98)	Therapy Group (n = 131)	
Class I	2 (2%)	9 (7%)	$P = .12$
Class II	43 (44%)	67 (51%)	$P = .35$
Class III	13 (13%)	37 (28%)	$P = .01$
Class IV	6 (6%)	8 (6%)	$P > .99$

\*Vaughn-Williams classification.<sup>24</sup>

### Potential Limitations

The diagnosis of LVH was made by echocardiography for all patients in both groups, except for 2 subjects in group B in whom echocardiography data were not available. However, because both patients had LVH on 12-lead electrocardiogram, their exclusion would merely underscore the present findings. Individual events in the control group were not evaluated for occurrence of inappropriate therapies, which may occur with up to 20% of third-generation devices.<sup>23</sup> Again, if these patients were to be excluded from the comparison, it would only further strengthen the predictive ability of variables in group A. We observed a significantly increased use of amiodarone and sotalol in group B. Because drug therapy during the latest follow-up was also included in the analysis, this is an expected consequence of the recurrent arrhythmia and ICD therapies that occurred in the group B. Furthermore, among group B patients, an equal number of patients were initiated before implantation versus initiation after recurrent arrhythmia (see Results). Because the majority of the patients were on amiodarone (78%, D,L-sotalol 22%), proarrhythmia as a cause of recurrent therapy is unlikely.

### Conclusions

In this ICD population, 17% of patients experienced therapy-free survival after implantation. In terms of clinical characteristics, these patients were distinguishable only by the presence of increased LV wall thickness, which was a significant predictor of therapy-free survival. LV mass measurements suggest that increased wall thickness may, in fact, be a marker for decreased extent of eccentric LV remodeling in patients who had therapy-free survival. Investigations using larger clinical databases will be needed to further clarify the relationship between patterns of LV remodeling and therapy-free survival.

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