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A Restrictive Inflow Pattern Does Not Predict Implantable Cardioverter-Defibrillator Therapy in Primary Prevention

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ABSTRACT

Background: Current guidelines for the use of implantable cardioverter-defibrillators (ICDs) are broad and significantly increase the cost of caring for patients with heart failure. In an effort to identify the specific subset of patients who benefit from this therapy, the predictive value of numerous echocardiographic parameters have been studied. Severe diastolic dysfunction has been shown to predict adverse events in a group of patients who received an ICD for secondary prevention, but has not been tested in those who receive ICDs for primary prevention.

Hypothesis: We tested the hypothesis that a restrictive mitral inflow pattern on echocardiography will predict the risk of appropriate therapy in this patient population.

Methods: This retrospective study identified 145 consecutive patients who met primary prevention criteria for ICD implantation and had an echo performed no more than 1 year prior to receiving the ICD. A restrictive pattern was defined as a mitral inflow E/A$>$2 or a deceleration time $<$150 ms.

Results: A restrictive pattern was present in 69 patients (40.7% of the group). Appropriate ICD therapy occurred in 8 (11.5%) subjects with a restrictive pattern and 14 (18.4%) with a nonrestrictive pattern over 680 days of average follow-up ($P =$ not significant). Cox regression analysis showed the presence of a restrictive pattern was not helpful in predicting time to first ICD therapy.

Conclusions: In a population of patients who received ICDs for primary prevention, echocardiographic findings of severe diastolic dysfunction were not helpful in targeting the use of ICDs to those at highest risk.

Introduction

Arrhythmias account for up to 51% of deaths in those with a low ejection fraction (EF) untreated with implantable cardioverter-defibrillators (ICDs).[1] The Multicenter Automatic Defibrillator Implantation Trial (MADIT-11)[2] and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[3] trials demonstrated that ICDs can significantly reduce mortality from sudden cardiac death when implanted prophylactically in patients with an EF less than 30% to 35%. This broad selection criterion has led to a dramatic increase in ICD implantations over the last 5 years. The expense of these devices considerably increases the cost of heart failure care.[4] There is growing interest in determining how to identify the subset of patients who will benefit from ICD implantation. While some models of prognosis based on clinical and echocardiographic criteria are able to predict overall mortality in patients with systolic heart failure, these have proven to be more predictive of pump failure; most fail in predicting sudden death specifically.[5]

A high E/E′ as measured by tissue Doppler and a restrictive pattern detected by pulse wave Doppler of the mitral inflow both correlate with overall mortality in patients with a low ejection fraction.[6–8] It is not clear if these parameters indicate an increased risk of death from pump failure, arrhythmia, or both. One study suggests that in a subgroup of patients, a restrictive mitral inflow pattern and, to a lesser extent, a high E/E′ on tissue Doppler are independent risk factors for ICD discharges.[9] This study was small, and it was composed mainly of a subgroup of patients at very high risk (74% had ICD implantation for secondary prevention and 30% were on oral antiarrhythmic agents). It remains unclear if there is an association between arrhythmic events and diastolic parameters among patients who receive ICDs for primary prevention. This question is the focus of our study.

Methods

Patient Selection

After approval from the institutional review board, we conducted a retrospective study of all patients over age 18 at the University of Michigan who had an EF <35% and received an ICD for primary prevention of sudden cardiac death between March 21, 2002 (the date of publication of MADIT-II) and July 1, 2005. Also, subjects had to have at least 2 months of electrophysiology follow-up (the time of first ICD interrogation) within the University

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of Michigan system. Patients with a history of ventricular arrhythmias, syncope, hypertrophic cardiomyopathy, or congenital heart disease were excluded. Of these 267 subjects, we identified 145 consecutive patients who also received an echocardiogram during which diastolic parameters were measured no more than 1 year prior to the ICD implantation.

Echocardiography

Various measurements from the echocardiograms were obtained. Left ventricular end-diastolic and end-systolic diameters were measured in the parasternal long axis view. Left atrial volume was measured at end-systole in the apical 4-chamber view. The peak E wave and A wave velocities as well as E wave deceleration times were measured from the pulse wave Doppler spectra of mitral valve inflow. All recorded beats were measured, and a mean was calculated to obtain the E to A ratio and deceleration times. The EF was calculated using Simpson's method to determine left ventricular end-diastolic and end-systolic volumes. When a good quality 2-chamber view was available, a biplane method was used. If the endocardial borders in this view were not visualized or if it was foreshortened, EF was calculated from the apical 4-chamber view alone. Mitral regurgitation was graded semiquantitatively. The maximum regurgitant jet area was also measured.

Statistical Analysis

In patients with sinus rhythm, a restrictive filling pattern was defined as an E to A ratio >2 or a deceleration time <150 ms. Because of atrial fibrillation or paced rhythms, 36 of the 145 subjects did not have discernable A waves on mitral inflow patterns. In these cases only the deceleration time was used to define a restrictive pattern. The primary endpoint was an appropriate ICD discharge therapy which was defined as the initiation of either a shock or antitachycardia pacing for confirmed ventricular tachycardia (VT) or ventricular fibrillation. Cox regression analysis was used to identify independent predictors of the first ICD discharge or death as primary endpoint. All statistical analysis was completed using SPSS version 14 (Chicago, IL). A P value of <.05 was used to define statistical significance. Continuous variables are expressed as mean ± SD.

Results

The follow-up period was 680±419 days. During this time, 22 (15.2%) subjects had a primary event. First therapies consisted of ICD discharge in 15 subjects and antitachycardia pacing in 7. An event occurred in 8 (11.5%) of those with a restrictive pattern vs 14 (18.4%) without a restrictive pattern (P = not significant). The baseline characteristics of the studied patient sample are shown in Table 1. Those with a restrictive pattern were more likely to be receiving a loop diuretic and to have a slightly lower serum sodium.

Table 1. Baseline Characteristics of the Group of Those With a Restrictive Pattern Compared to the Group with a Nonrestrictive Pattern

	Restrictive Pattern n = 69	Nonrestrictive n = 76	*P* Value
Age	59 ± 11y	61 ± 12 y	.301
Male gender	81%	79%	.836
Medication use			
Aspirin	74%	68%	.583
β-Blockers	91%	86%	.193
ACE inhibitors	88%	87%	.806
Loop Diuretics	88%	67%	.003
Spironolactone	42%	45%	.867
Digoxin	49%	61%	.246
Antiarrhythimcs	12%	12%	1.000
Class			
1 or 2	30%	46%	.363
3 or 4	70%	54%	.363
Ischemic	75%	65%	.145
Valve disease	13%	13%	1.000
Prior bypass surgery	39%	46%	.407
Prior infarction	51%	51%	1.000
Prior PTCA	26%	22%	.698
Diabetes	39%	37%	.864
Hyperlipidemia	80%	78%	.840
COPD	7%	9%	.768
QRS duration	136±33 ms	137±33 ms	.909
Sodium	139±4 mg/dl	140±3 mg/dl	.042
Creatinine clearance	83±27 ml/min	98±63 ml/min	.088
Hematocrit	39±5	38±5	.223

Continuous variables are expressed as mean ± Standard Deviation.

The results of the univariable regression analysis are shown in Table 2. None of the clinical or echocardiographic variables we investigated were significant in predicting an event. There was no difference in the rate of events between those who had a restrictive pattern vs those who did not. No other echocardiographic measurements including left ventricular size, left atrial volume, EF, or presence of significant mitral regurgitation predicted events.

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Table 2. Predictive Value of Echocardiographic and Clinical Variables on Event-free Survival by Univariable Analysis

Variable	*P* Value
Restrictive pattern	.143
Mitral regurgitation area	.781
Left atrial volume	.259
Ejection Fraction	.425
Left ventricular end-systolic volume	.861
Left ventricular end-diastolic volume	.800
Gender	.529
Age	.616
β-Blockers	.442
ACE inhibitors	.235
Loop diuretics	.850
Spironolactone	.661
Digoxin	.712
Aspirin	.616
Diabetes	.852
Ischemic	.131
Chronic Obstructive Pulmonary Disease	.719
Sodium	.969
Creatinine clearance	.218
Hematocrit	.612
QRS duration	.912
Atrial fibrillation	.236

Discussion

Multiple studies have clearly shown that severe diastolic dysfunction is associated with increased mortality among patients with a low EF.[6–8] It is unclear if severe diastolic dysfunction is associated with an increase in mortality from pump failure, arrhythmic death, or both. The study by Bruch et al[9] suggested that a restrictive mitral inflow pattern predicts ICD therapy and death in patients with systolic heart failure. The patient group they studied, however, was largely comprised of patients requiring ICDs for secondary prevention, and many of them were already on oral antiarrhythmic therapy. In contrast, the current study was comprised entirely of patients who received ICDs for primary prevention, and we found no association between a baseline restrictive mitral inflow pattern and subsequent appropriate ICD tachyarrhythmia therapy, suggesting that severe diastolic dysfunction in these patients is not associated with arrhythmic events.

If severe diastolic dysfunction predicts overall mortality in a general sample of heart failure patients and also predicts arrhythmic events in a secondary prevention sample, why did it fail to predict arrhythmias in our primary prevention sample? One possibility is that among our group of primary prevention patients, a larger proportion of treated arrhythmias may have been nonlife-threatening, compared to the arrhythmias treated in secondary prevention patients in the study by Bruch et al.[9] ICDs also treat episodes of VT, particularly slow VT, that would otherwise abort on their own before causing death or syncope.[10] As such, it is possible that the degree of overtreatment was greater in our sample than in that studied by Bruch et al.[9] A larger, longer study that examines the relationship between the degree of diastolic dysfunction and actual arrhythmic mortality may provide further information.

A second possible explanation for the negative results of our study is that it examined a lower risk population and was not adequately powered to detect a difference at these low rates. Of note, however, our study's larger sample size and longer follow-up duration resulted in a similar event risk to the study conducted by Bruch et al.[9] As such, the sample size does not explain the differences observed between the 2 studies.

In the current study, no other echocardiographic measurement was helpful in predicting ICD events. This result is consistent with previous studies in which left ventricular size and EF have failed to consistently predict mortality or arrhythmic events.[7,11] Although mitral regurgitation and left atrial volume have been previously associated with overall mortality,[12] we are unaware of any studies that have focused on a specific relationship with ventricular arrhythmias.

A limitation of our study was the inclusion of patients who had ICDs implanted with and without cardiac resynchronization (CRT, or biventricular pacing). Of the 145 patients in our study, 58 (38%) had CRT capability. Biventricular pacing can lead to reverse remodeling that may alter several echocardiographic parameters including left ventricular size, left atrial size, the degree of mitral regurgitation, and the mitral inflow pattern. Left ventricular reverse remodeling may explain why biventricular pacing decreases death and arrhythmias in patients with cardiomyopathy.[13] In the Cox regression analysis, however, biventricular pacing was not predictive of events. Eliminating these patients from the analysis also failed to identify any association between echo parameters and events.

The search for an accurate model to predict sudden death in patients with systolic heart failure remains elusive. While electrocardiographic measurements like QRS duration and T-wave alternans may enhance sudden death risk stratification, additional tools are needed.[14–16] This

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study suggests that current echocardiographic parameters may not be helpful in further risk stratifying such patients. Specifically, in a population with no known history of arrhythmic events, a restrictive mitral inflow pattern was not helpful in identifying those patients who received appropriate ICD antitachycardia therapy.

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