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Population-Based Analysis of Sudden Cardiac Death With and Without Left Ventricular Systolic Dysfunction

Two-Year Findings from the Oregon Sudden Unexpected Death Study

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OBJECTIVES We sought to evaluate the contribution of left ventricular (LV) dysfunction toward occurrence of sudden cardiac death (SCD) in the general population, and to identify distinguishing characteristics of SCD in the absence of LV dysfunction.

BACKGROUND Patients who manifest warning symptoms and signs are more likely to undergo evaluation before SCD. Although prevalence of LV dysfunction in this subgroup may overestimate the prevalence in overall SCD, this is the only means of assessment in the general population.

METHODS All cases of SCD in Multnomah County, Oregon (population 660,486; 2002 to 2004) were prospectively ascertained in the ongoing Oregon Sudden Unexpected Death Study. We retrospectively assessed LV ejection fraction (LVEF) among subjects who underwent evaluation of LV function before SCD (normal: ≥55%; mildly to moderately reduced: 36% to 54%; and severely reduced: ≤35%). Of a total of 714 SCD cases (annual incidence 54 per 100,000), LV function was assessed in 121 (17%).

RESULTS The LVEF was severely reduced in 36 patients (30%), mildly to moderately reduced in 27 (22%), and normal in 58 (48%). Patients with normal LVEF were distinguishable by younger age (66 ± 15 years vs. 74 ± 10 years; $p = 0.001$), higher proportion of females (47% vs. 27%; $p = 0.025$), higher prevalence of seizure disorder (14% vs. 0%; $p = 0.002$), and lower prevalence of established coronary artery disease (50% vs. 81%; $p < 0.001$).

CONCLUSIONS In this community-wide study, only one-third of the evaluated SCD cases had severe LV dysfunction meeting current criteria for prophylactic cardioverter-defibrillator implantation. The SCD cases with normal LV function had several distinguishing clinical characteristics. These findings support the aggressive development of alternative screening methods to enhance identification of patients at risk. (J Am Coll Cardiol 2006;47:1161–6) © 2006 by the American College of Cardiology Foundation

Severe left ventricular (LV) dysfunction confers significantly increased risk of sudden cardiac death (SCD) and is currently the major indication for primary prevention with the implantable cardioverter-defibrillator (ICD) (1–4). In the absence of severe LV dysfunction, ICD implantation for increased risk of SCD is limited to a small subset of conditions, such as hypertrophic obstructive cardiomyopathy, the long QT and Brugada syndromes, and idiopathic ventricular fibrillation (5). Large cohort studies have identified several other risk predictors, such as family history, diabetes mellitus, obesity, and heart rate profile during exercise (6–10), indicating that determinants of SCD are likely to be diverse as well as multifactorial.

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In fact it has been postulated that patients with severe LV dysfunction, such as those studied in the prospective prophylactic ICD trials, may represent a minority of the sudden death population at risk (11–14). However, the distribution of LV function among cases of SCD has not been evaluated in a U.S. subpopulation. A suitable approach would be prospective and population based, with SCD cases being ascertained from multiple sources such as first responders and medical examiners as well as area hospitals (13,15). Determination of the extent and distribution of LV dysfunction among SCD cases in the general population is also a logical first step in the identification of novel predictors of SCD risk among subjects who do not have LV dysfunction.

The Oregon Sudden Unexpected Death Study is an ongoing investigation of SCD among all residents of a large U.S. community (15). To evaluate the prevalence of LV dysfunction among SCD cases in the general population, we

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Abbreviations and Acronyms

ARVD = arrhythmogenic right ventricular dysplasia
CAD = coronary artery disease
ICD = implantable cardioverter-defibrillator
LV = left ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction
SCD = sudden cardiac death

performed a retrospective analysis of left ventricular ejection fraction (LVEF) among patients who underwent LV function evaluation before SCD. To identify distinguishing characteristics of SCD in the absence of LV dysfunction, we performed clinical comparisons between SCD cases with evidence of LV dysfunction and those with normal LV function.

METHODS

Study population. All residents of Multnomah County, Oregon (population 660,486), who experienced sudden cardiac death between February 1, 2002, and January 31, 2004, were evaluated. Cases were identified from multiple sources: the county emergency medical response system, the medical examiner, and area hospitals. Detailed methods have been published earlier (15). In order to be included in this analysis, medical records were required with sufficient detail such that LV function before SCD could be established.

Case ascertainment. The county emergency medical service, the medical examiner, and all public and private hospitals participated in the study. Cases were identified by emergency medical technicians, the office of the medical examiner, and emergency department physicians, and physicians of record referred these cases to investigators for screening. Missed cases were captured during weekly audits of the ambulance run-sheets and medical examiner death reports. Medical records were obtained from one or more of the following sources: 1) emergency medical responders; 2) medical examiner; 3) hospital of record; 4) primary care physician. After all available medical records were accessed, investigators performed a detailed evaluation of each case, which included analysis of the circumstances of death, known medical history and any information from the index hospitalization or autopsy. Cases were categorized as SCD by a majority consensus of three cardiologists. Deaths were categorized as sudden if they met the World Health Organization criteria (16). Witnessed SCDs were those in which cardiac arrests happened within 1 h of symptom onset. Unwitnessed SCDs were those in which patients were found dead within 24 h of having last been seen alive and in a normal state of health. All patients were included, regardless of whether they underwent resuscitation. Patients were excluded if death was not unexpected (e.g., terminal cancer) or if non-cardiac etiologies of sudden death were identified (e.g., trauma, drug overdose, or pulmonary embolism).

Definitions. Left ventricular function was categorized by the quantitative assessment of LVEF or qualitatively reported LVEF as follows: normal: ≥55%; mildly or moderately reduced: 36% to 54%; and severely reduced: ≤35%. Direct quantitative measurements of EF were used only if confirmed as accurate in the echocardiographer's assessment.

Patients were categorized as having hypertension, previous cerebrovascular accident, sleep apnea, or seizure disorder if indicated in the medical record. Patients were categorized as having diabetes or hyperlipidemia if directly indicated in the medical record or if diabetes or cholesterol medications were noted. Coronary artery disease (CAD) was defined as coronary artery stenosis of >50% or documentation of previous myocardial infarction (MI), coronary artery bypass grafting, or percutaneous coronary intervention. Acute MI at the time of arrest referred to: 1) documented acute MI in the medical record; 2) fresh infarction or clot identified on autopsy; 3) typical acute injury or infarct pattern on electrocardiogram (ECG); or 4) a combination of elevated troponin/serum creatine kinase-MB fraction (CK-MB) and either ECG or clinical evidence for infarction. Ischemic symptoms were defined as pain in the chest, shoulder, arm, epigastrum, neck, or jaw or abrupt onset of dyspnea.

Assessment for potential bias. Comparisons of age, gender, socioeconomic profile, and characteristics of cardiac arrest were performed between patients with and without assessments of LV function in order to assess for potential selection bias. Geographic-based socioeconomic indicators were determined by identifying the 2000 Census Bureau Census Tract for each subject based on home address. For the purpose of comparisons, the values of several preselected parameters (17) associated with each tract were assigned to all subjects residing in the tract, and mean values were obtained.

Statistical analysis. All statistical analyses were performed using SPSS 13.0 for Windows (SPSS Inc., Chicago, Illinois). Continuous variables were expressed as mean values ± standard deviation. Significance between groups was determined using two-sided independent-sample Student *t* tests for continuous variables and Pearson chi-square test (or Fisher exact test if expected cell count is <5) for discrete variables.

RESULTS

Distribution of LV function among SCD cases evaluated before cardiac arrest. During the two-year period, 714 residents of Multnomah County experienced SCD (annual incidence 54 cases per 100,000 residents). The mean age was 66 ± 19 years, and 40% were female. Overall, 48% of SCD cases were witnessed and 63% underwent attempted resuscitation. Medical records from emergency medical responders or the medical examiner were available in 704

Table 1. Comparisons Between SCD Cases That Underwent Evaluation of LV Function and All Remaining Cases of SCD

	LVEF Known (n = 121)	LVEF Unknown (n = 593)	p Value
Age (yrs)	70 ± 13	66 ± 19	0.02
Female	44 (36%)	238 (40%)	0.44
Witnessed	61 (50%)	279 (47%)	0.50
Resuscitation attempted	80 (66%)	370 (62%)	0.44
SES characteristics*			
Median income	$41,500 ± 12,800	$42,200 ± 12,800	0.59
Poverty (all ages)	13 ± 5.5%	13 ± 7.7%	0.53
Poverty (elderly)	10 ± 6.2%	10 ± 7.7%	0.97
Median home value	$158,600 ± 39,600	$164,800 ± 62,200	0.38
High education (Bachelor's degree)	25 ± 15%	27 ± 16%	0.42

*SES variables are based on Census Tract data. Analysis omits seven patients owing to incomplete information regarding residence.

LVEF = left ventricular ejection fraction; SCD = sudden cardiac death; SES = socioeconomic; VT = ventricular tachycardia.

cases (98%). A total of 121 cases (17%) underwent an assessment of LV systolic function before SCD. There were no significant demographic differences between those with an assessment of LVEF and those without, aside from a small difference in age (Table 1). Mean age of patients with an LVEF assessment was 70 ± 13 years, 44 (36%) were female, and 80 (66%) underwent attempted resuscitation. The LVEF was assessed by echocardiogram in 107 (88%), by contrast left ventriculography in 13 (11%), and by radionuclide ventriculography in 1 (1%). The exact date of LV function assessment was known in 117 cases, and the majority of evaluations were conducted within two years of SCD (n = 74; 63%). Of the 121 cases that underwent assessment of LV function, 58 patients (48%) had normal LVEF, 27 (22%) had mild to moderately reduced LVEF, and 36 (30%) had severely reduced LVEF.

Indications for ICD implantation based on current criteria. None of the 714 SCD cases underwent ICD implantation before cardiac arrest. Among the subgroup that had evaluation of LV function, severely reduced LVEF was observed in 36 patients (30%) and would have been the most common indication for prevention of SCD with a prophylactic ICD. Other indications included previous cardiac arrest without severely reduced LVEF (n = 4) and high-risk genetic conditions (n = 2). Had all information been available for all individuals before SCD, the majority of cases (n = 79; 65%) would not have qualified for ICD implantation for prevention of SCD based on current guidelines.

Distinguishing characteristics of patients with normal LV function. As shown in Table 2, patients in the normal LV systolic function subgroup were significantly less likely to have documented CAD. Patients with normal LV function also had a significantly younger mean age, higher proportion of women, and higher proportion of seizure disorder. All eight patients with a history of seizure disorder had normal LV function. Average age was 60 ± 12 years, and five of these patients were female. One of these patients also had a diagnosis of arrhythmogenic right ventricular dysplasia (ARVD). This patient's seizure disorder was attributed to an intracranial arteriovenous malformation for which surgical resection was performed. For the overall subgroup of patients with seizure disorder, the most recently used antiepileptic medications were phenytoin (n = 2),

Table 2. Clinical Characteristics of SCD Cases That Underwent Evaluation of LV Function

	Reduced EF			
	Severe (n = 36)	Mild/Moderate (n = 27)	Normal EF (n = 58)	p Value*
Age (yrs)	74 ± 11	73 ± 9.1	66 ± 15	<0.01
Female	9 (25%)	8 (30%)	27 (47%)	0.03
Attempted resuscitation	23 (64%)	19 (70%)	38 (66%)	1
CAD	27 (75%)	24 (89%)	29 (50%)	<0.01
Prior SCD	2 (6%)	1 (4%)	3 (5%)	1
DM	11 (31%)	9 (33%)	19 (33%)	1
Hypertension	25 (69%)	19 (70%)	35 (60%)	0.27
Hyperlipidemia	21 (58%)	15 (56%)	23 (40%)	0.06
Seizure disorder	0	0	8 (14%)	<0.01
Prior CVA	4 (11%)	5 (19%)	9 (16%)	0.85
Sleep apnea	4 (11%)	3 (11%)	6 (10%)	0.89

*p value for difference between any reduction in EF and normal EF.

CAD = obstructive coronary artery disease; CVA = cerebrovascular accident; DM = diabetes mellitus; EF = ejection fraction; LV = left ventricular; SCD = sudden cardiac death.

Table 3. Diagnosis of Myocardial Infarction or Ischemic Symptoms Among SCD Cases That Underwent Attempted Resuscitation

	Reduced EF (n = 42)	Normal EF (n = 38)	p Value
STEMI	0	2 (5%)	0.22
Non–STEMI	1 (2%)	4 (11%)	0.19
Ischemic symptoms	3 (7%)	3 (8%)	1
Any of above	4 (10%)	7 (18%)	0.25

Only subjects in whom resuscitation was attempted were analyzed.
EF = ejection fraction; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction.

carbamazepine (n = 3), phenobarbital (n = 1), gabapentin (n = 1), and unknown (n = 1). Two patients had electroencephalograms documented and both were abnormal, but neither had epileptiform discharges present. Each of the four witnessed cases in our analysis had a sudden cardiac arrest with no seizure-like activity observed either preceding or during the event.

On comparing the medication lists of patients with reduced LV function with those of the normal LV function group, no significant differences were identified for antiarrhythmic, antipsychotic, and antidepressant medications. However, a significantly greater proportion of the normal LV function group had an antiepileptic medication prescribed (19% vs. 3%; $p < 0.01$). The indication for prescribing antiepileptics for the two patients in the reduced EF group was neuropathic pain, not seizure disorder.

Detailed clinical characteristics of subsets. There were 51 patients (42%) older than 75 years. Left ventricular dysfunction was significantly more prevalent among patients older than 75 years (severely reduced LVEF: 41% of older group vs. 21% of younger group; p = 0.019). Among the 80 patients (66%) who had resuscitation attempted, 7 (9%) had occurrence of recognized acute MI and 13 (16%) had either acute MI or ischemic symptoms before the arrest. The rates of MI and ischemic symptoms did not vary based on LV function (Table 3). Of the seven patients with recognized acute MI, death occurred within 1 h of the onset of symptoms in five.

A total of 112 patients (93%) had an echocardiogram performed, of which 41 were inpatient and 71 outpatient echocardiograms. The most common reasons for hospitalization among patients with inpatient echocardiograms were chest pain or acute MI (n = 10), congestive heart failure (n = 7), and chronic obstructive pulmonary disease (n = 3). For all echocardiograms, one or more indications were available in 80 patients. Common reasons listed included evaluation of LV function (n = 28), dyspnea or congestive heart failure (n = 18), and murmur and valvular disease (n = 11). Predisposing conditions for SCD were present in a minority of these patients, with severe aortic stenosis in five patients and likely hypertrophic cardiomyopathy in one patient (septal wall thickness 19 mm). The remainder of the patients with normal LV function (including the one with ARVD diagnosed by other means) did not have indicators of SCD risk on the echocardiogram.

DISCUSSION

Earlier cohort studies as well as the primary and secondary prevention trials for SCD have established severe LV dysfunction as the best available risk predictor for SCD (1–4,18,19), but U.S. population-based evaluations have not been conducted. The present community-based study demonstrated that of the patients who had LV function assessed before cardiac arrest, 52% had some decrease in LV systolic function and 30% had severely decreased LV systolic function. Therefore, based on current LVEF guidelines for SCD prevention, only 30% would have qualified as candidates for a prophylactic ICD. Overall, considering LV dysfunction as well as other high-risk conditions, 65% of these patients would not have met the criteria for ICD implantation. Patients with SCD and normal LVEF were younger, more often female, more likely to have a seizure disorder, more likely to be taking antiepileptic medications, and less likely to have an established diagnosis of CAD compared with those with an abnormal LVEF.

The frequency of LV dysfunction in SCD from a community-based study in Maastricht, the Netherlands, has been reported (20,21). Among 200 cases of SCD with an assessment of LV function available, 101 (51%) had normal LVEF, defined as >0.50, and 38 (19%) had severely reduced LVEF, defined as ≤0.30. If the LVEF criteria from this study were applied to the present study, 53% of our cases would have had normal LVEF and 26% would have had severely reduced LVEF. Therefore, our results in a U.S. population show similar trends for distribution of severe LV dysfunction. In addition to the geographic location, there are several important differences in how the two studies were conducted. The Netherlands study was limited to cases 20 to 75 years old, whereas our study included all ages. Because the frequency of SCD increases with age, older patients can account for a significant proportion of cases. Indeed, in our study, patients over 75 years of age constituted 38% of the total SCD cohort during this two-year period. In addition, the present study collected and analyzed detailed information on comorbidities, permitting evaluation of potential alternative clinical risk predictors of SCD. Finally, we were able to evaluate for potential bias between the subgroups with and without evaluation of LV function.

The findings from the present study confirm the need to identify SCD risk predictors other than severe LV dysfunction in the general population. Severe LV dysfunction, the current major risk predictor of SCD, was identified in only 30% of SCD cases. Even if all of the other risk predictors, such as history of resuscitated cardiac arrest, the long QT or Brugada syndromes, hypertrophic cardiomyopathy, and ARVD, were taken into account, only 35% of SCD cases

would have been identified as being at high risk for SCD. Therefore, in a hypothetical ideal situation in which all of these cases were to be evaluated before cardiac arrest, the majority (65%), based on prevailing knowledge, would not have met criteria for SCD prevention with the ICD (1,22,23).

However, our findings identify other potential predictors that may enhance risk stratification for SCD in the general population. The logical first step in the search for alternative risk predictors is a clinical comparison with SCD cases that had normal LV systolic function (48% of evaluated cases in the present study). This comparison showed a lower rate of previously diagnosed coronary artery disease in the normal LV function group. In general, there is a strong association between SCD and significant CAD, and prevailing knowledge would suggest that acute myocardial ischemia is likely to be the overall dominant contributor to SCD (12,15, 24,25). In an earlier autopsy evaluation during the first year of this community-based study, 75% of overall adult SCD cases had associated significant CAD (15). Given the unexpected and dynamic nature of cardiac arrest, it can be difficult to establish whether or not acute myocardial ischemia was the precipitating event. Therefore, the lower prevalence of previously diagnosed CAD in the normal LV function group could indicate a higher prevalence of unrecognized CAD, with SCD being the first and fatal manifestation. Continued emphasis on reduction of established risk factors for coronary artery disease is likely to remain valuable for prevention of SCD (6,26).

There were other distinguishing features among patients with normal LVEF (Table 1). Fourteen percent of subjects had a known history of seizure disorder, and this condition was found exclusively among subjects with normal LV function. Sudden unexpected death in epilepsy (27–31) is well recognized as a cause of death in patients with seizure disorder. In population-based studies, increased seizure frequency, duration of seizure disorder, and greater use of anticonvulsant or psychotropic medications have all been associated with this condition (29,32). With findings of cardiac autonomic abnormalities (33) and of periods of asystole in patients who were monitored during seizures (34), a case has also been made for simultaneous and related occurrence of seizures and heart rhythm disorders. Finally, in a subgroup of patients with missed primary cardiac arrhythmogenic disorders the clinical presentation of a ventricular arrhythmia can mimic a seizure (35), which remains a distinct possibility in the patient with ARVD and seizure disorder in the present study. Overall, a higher proportion of subjects with normal LV function were female as well as younger in age. An earlier study from Albert et al. (36) that evaluated gender differences among cardiac arrest survivors, observed that females were less likely to have CAD. However, the same study found that CAD status was the most important predictor of cardiac arrest in women, and LV dysfunction the most important predictor in men (36). From a separate autopsy-based study, we have previously reported a higher rate of unexplained SCD among younger women compared to men (37). In general, disease conditions in younger age groups are more likely to have genetic (as opposed to environmental) influences (38), and the possibility exists that genetic factors may also contribute to risk of SCD (39).

Study limitations. Because this study was dependent on the performance of LV function evaluation before SCD, the analysis was performed in a subgroup of total SCD cases. In general, this is an inherent limitation of population-based studies, especially in an investigation of SCD. In as many as 50% of cases, SCD can be the first manifestation of heart disease. Although prospective cohorts can circumvent this limitation, the numbers of subjects studied in existing cardiovascular cohorts may yield limited numbers of SCD cases per year. Nonetheless, in the present study, medical records from emergency medicine responders or the medical examiner were available in 98% of subjects, and LV function evaluation was performed before SCD in a significant subgroup. Because symptomatic patients with greater severity of pre-existing heart disease are more likely to have LVEF evaluated, any bias in our results is likely to reflect an overestimation of the prevalence of LV dysfunction among SCD cases in the general population. Due to potential demographic and socioeconomic differences between Multnomah County and the rest of the country, caution should be exercised in generalizing results of this study to other communities with significantly different characteristics.

Conclusions. In this large U.S. subpopulation followed for two years, approximately one-half of the SCD cases that underwent evaluation before cardiac arrest had LV dysfunction, and one-third had severe LV dysfunction. Younger age, female gender, seizure disorder, specific medications, and lower likelihood of recognized CAD were identified as distinguishing characteristics of patients with normal LV systolic function and SCD. Left ventricular dysfunction is a significant determinant of SCD risk in the general population, but a renewed emphasis on identifying alternative SCD risk predictors in the general population is warranted.

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