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Women Have Lower Prevalence of Structural Heart Disease as a Precursor to Sudden Cardiac Arrest: the Oregon Sudden Unexpected Death Study

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Abstract

Objective—Utilization of a community-based approach to identify gender-related differences in risk factors for sudden cardiac arrest (SCA).

Background—There are significant gender-based differences in prevalence and manifestation of SCA. Any differences related to predictors of SCA in women vs. men are likely to have implications for risk stratification and prevention.

Methods—The Oregon Sudden Unexpected Death Study is an ongoing prospective investigation of SCA in the Portland, Oregon metropolitan area (pop. 1,000,000). All cases meeting criteria for SCA were ascertained using multiple sources. Medical records were reviewed to identify clinical conditions that may contribute to SCA risk and comparisons made between male and female SCA cases using Pearson's chi-square tests for categorical variables, t-tests for continuous variables and multivariate logistic regression analysis.

Results—During 2002-2007, 1568 adult SCA cases were identified (women 36% vs. men 64%; $p<0.0001$) and women were older (mean age 71±14 vs. 65±14, $p<0.0001$). There were no significant gender differences in prevalence of obesity, dyslipidemia, history of COPD/asthma, left ventricular (LV) hypertrophy or history of myocardial infarction (MI). In multivariate analysis, women were significantly less likely to have severe LV dysfunction [OR 0.51 (0.31 – 0.84)] or previously recognized CAD [OR 0.34 (0.20 – 0.60)] compared to men.

Conclusions—Women were significantly less likely than men to have a diagnosis of structural heart disease (LV dysfunction or CAD) prior to SCA. These findings suggest that fewer women may be eligible for prophylactic ICD placement based on current guidelines and therefore may not have

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equal opportunity for prevention. Enhancement of SCA risk stratification may have even higher importance for women.

Keywords

Death, sudden; gender; ejection fraction; coronary artery disease; risk stratification; population

INTRODUCTION

Sudden cardiac arrest remains a major public health problem, claiming at least 250,000 lives in the US on an annual basis (1,2). There are significant gender-related differences in prevalence and manifestation of SCA. The condition manifests more commonly and at younger ages in men, implying a protection conferred by female gender (1,3). Prevalence of coronary artery disease (CAD), the diagnosis most commonly associated with SCA, is significantly lower in female SCA (4,5). A recent autopsy study in the age-group 35-44 years found significantly higher rates of unexplained sudden deaths in women compared to men (6). Female SCA cases are more likely to present with pulseless electrical activity or asystole compared to males (1,7). Since rates of successful resuscitation are significantly lower in pulseless electrical activity/asystole vs. ventricular tachycardia/fibrillation (2% vs. 25% respectively; (1,8)), there are implications for survival from SCA in women.

Due to these significant gender-based differences, the possibility that women may have a different SCA risk profile from men merits consideration. Available comparisons of SCA risk predictors between the genders would suggest that coronary disease-related risk factors are common to both men and women (4). However, an earlier analysis of the Oregon Sudden Unexpected Death Study performed in a small number of patients suggested that women who suffer SCA may have a lower prevalence of severe LV dysfunction (9), the major risk stratification variable currently utilized in clinical practice. Given the reported lower rates of CAD and higher rates of unexplained sudden death among female SCA cases, we hypothesized that gender-specific risk factors would be identified among cases of SCA in the general population. As part of the ongoing prospective, population-based Oregon Sudden Unexpected Death Study we performed a larger, comprehensive comparison between women and men of all available clinical risk predictors of SCA.

METHODS

Case ascertainment

Detailed methods regarding the ongoing Oregon Sudden Unexpected Death Study have been published earlier (3,9,10). Cases of SCA in the Portland Oregon metropolitan area (population approx. 1 million) were identified between February 1, 2002 and January 31, 2007 using multiple sources. During 2002-2005, cases of out of hospital SCA were identified from emergency medical services (approx. 70%), the medical examiner's office (approx. 25%) and local emergency rooms (approx. 5%). During 2005-2007, ascertainment was limited to SCA cases with attempted resuscitation or those that were investigated by the medical examiner.

SCA was defined as a sudden unexpected pulseless condition occurring within 1 hour of symptom-onset (witnessed events) or within 24 hours of having last been observed alive and symptom-free (unwitnessed) (11). Furthermore, the location of SCA had to be in an out-of-hospital or emergency room setting. A diagnosis of SCA was assigned following in-house adjudication by three physicians who evaluated circumstances of cardiac arrest and all available clinical data. Survivors of SCA were included. Subjects with chronic terminal illnesses (e.g. cancer), known non-cardiac causes of sudden death (e.g. pulmonary embolism, cerebrovascular accident), traumatic deaths and overdoses were excluded. This study was

approved by the Institutional Review Boards of Oregon Health and Science University as well as all other participating hospitals and health systems.

Data collection

SCA cases included in the analysis of demographics and arrest circumstances were at least 35 years old at the time of event; analysis of clinical characteristics were restricted to the majority subset with medical records available. Records were retrospectively reviewed for demographic information as well as detailed clinical history of CAD, left ventricular mass/hypertrophy (LVM/LVH), hypertension, smoking, diabetes, dyslipidemia, obesity and other comorbidities. When available and unrelated to the SCA event, electrocardiograms (ECG), echocardiograms, coronary angiograms, and laboratory data were reviewed as well as all available autopsy data. Information regarding LV systolic function (LV ejection fraction) was obtained from echocardiogram, LV angiogram, or multi-gated acquisition scan performed prior and unrelated to SCA.

Definitions of clinical variables

LV systolic function was classified using ejection fraction (EF) as follows: normal (EF ≥55%), mild-moderate LV dysfunction (EF = 36-54%), and severe LV dysfunction (EF ≤35%). Left ventricular mass (LVM) was calculated from echocardiograms prior to arrest using the American Society of Echocardiography modified equation (12), and LVM was indexed to body surface area (BSA). LVH was defined as LVM/BSA >134 g/m^2 for men and >110 g/m2 for women (13). Definite CAD was defined as ≥ 50% stenosis of a major coronary artery on angiogram or postmortem examination; history of percutaneous coronary intervention or coronary artery bypass grafting; physician report of myocardial infarction; pathologic Q waves on ECG; or myocardial infarction history determined by any two of the following three: ischemic symptoms, ECG changes, or positive troponins/creatinine kinase-MB. The QT interval was obtained from a standard 12-lead pre-arrest ECG, with measurements conducted manually using calipers, and corrected using Bazett's formula (QTc). Gender-specific categories of QTc were also used: [males ≤430 (normal), 431-450 (borderline), >450 (abnormal); females ≤450 (normal), 451-470 (borderline), >470 (abnormal)].

Hypertension was defined by clinical history of hypertension, diabetes mellitus (DM) by clinical history of DM or use of anti-diabetic medications. Dyslipidemia was defined by clinical history or use of lipid-lowering medications. Response time was defined as the time from dispatch of emergency medical personnel to their arrival on the scene. Return of spontaneous circulation following resuscitation was defined as a return of a palpable pulse in conjunction with a systolic blood pressure of at least 60 mmHg. Survival to hospital discharge was defined as discharge to home or a non-critical care facility.

Statistical analysis

Statistical analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC). Demographic and clinical characteristics of male and female SCA cases were summarized using frequencies for categorical variables and means with standard deviations for continuous variables, and gender differences were examined using Pearson's chi-square tests for categorical variables or t-tests for continuous variables. Gender differences were also evaluated adjusted for age using the Cochran-Mantel-Haenszel test for categorical variables and analysis of covariance for continuous variables. Multiple logistic regression was performed using variables found to be significant in univariate comparisons. For all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Subject demographics and circumstances of sudden cardiac arrest

During the five year period of ascertainment, 1568 SCA cases were identified (Table 1). The majority of cases were male (1012 men, 64% vs. 556 women, 36%; p<0.0001) and women were older (mean age 71±14 vs. 65±14, p<0.0001; Table 1). Information on presenting arrhythmia at the time of arrest was available in 706 (70%) men and 356 (64%) women (Table 1). Ventricular fibrillation or ventricular tachycardia (VF/VT) were more commonly observed among men and pulseless electrical activity (PEA)/asystole among women (p<0.0001). Gender differences observed in the presenting rhythm remained significant after adjusting for age (p = 0.0004). Women were more likely to have a return of spontaneous circulation during resuscitation (women 25% and men 21%, p = 0.04). However there were no significant gender differences in the proportion of arrests that were witnessed, in response time, or in rates of survival to hospital discharge (≥0.25) (Table 1).

Gender-based comparisons of clinical characteristics

Of the total 1568 cases, 1258 had medical records available [805 men (80%) and 453 women (81%)]. Men were more likely to be active or former smokers compared to women (42% vs. 36%, and 36% vs. 24%, respectively; p<0.0001) (Table 2). Previously documented CAD was lower in women vs. men (40% vs. 49%; p = 0.001), but there were no differences with respect to history of MI (29% versus 26%; p = 0.19) (Table 2). Hypertension and DM were more common among women (73% versus 62%; p = 0.0001 and 40% versus 34%; p = 0.03, respectively). Only 18 subjects (1.1% of the total, n =1568) had implantable cardioverter defibrillators (ICDs) implanted prior to the event, 14 (1.4%) men and four (0.7%) women (p = 0.23). There were no gender differences in the prevalence of history of prior cardiac arrest, dyslipidemia, obesity, history of chronic obstructive pulmonary disease (COPD) or asthma, history of seizure, or presence of left ventricular hypertrophy (p ≥ 0.10).

Records documenting LV function were available in 307 (38%) men and 178 (39%) women (Table 2). Women were significantly more likely to have normal LV systolic function compared to men (49% vs. 35%) and men were more likely to have severe LV systolic dysfunction than women (35% vs. 21%, p = 0.001). Corrected QT interval was significantly longer in females compared to men (457 ± 39 vs. 444 ± 45 msec; p = 0.003).

After adjustment for age, all clinical comparisons in Table 2 remained consistent, except history of MI, which became significant (p=0.05), and the gender-specific QTc interval categories, which lost significance (p=0.16).

In the multivariate logistic regression analysis, all 1258 subjects had information on age, CAD, hypertension, history of myocardial infarction and diabetes mellitus. LV systolic function was available for 485 of the 1258 cases. Table 3 presents the results of the logistic model (n=485). Women were significantly less likely to have CAD [OR 0.34 (0.20 – 0.60)] and severe LV dysfunction [OR 0.51 (0.31 – 0.84)] compared to men (Table 3). Hypertension, history of myocardial infarction and diabetes mellitus were no longer significantly different by gender. In a model including QTc (n=223 subjects with complete data), longer QTc remained associated with female gender, and the other associations remained consistent but confidence intervals were wider.

DISCUSSION

In this population-based analysis, gender-based comparisons of potential risk factors for SCA identified two distinct clinical factors that were unique to women who suffer SCA. Women were significantly less likely than men to have severe LV dysfunction as a precursor to SCA.

In addition, there was a significantly lower likelihood of women having an established diagnosis of CAD prior to SCA. These findings coincided with trends toward higher prevalence of DM and hypertension in women. There were no significant gender differences in the mean body mass index or prevalence of obesity, dyslipidemia, history of COPD/asthma, or left ventricular hypertrophy. After correction for age, significant gender differences disappeared for the gender-specific QTc categories which account for underlying male-female differences in the QTc interval, but remained for QTc measured continuously. This may imply that when the underlying longer QTc in women is taken into account, QTc does not appear to differentiate female from male SCA patients. With regard to presenting arrhythmia at the time of cardiac arrest, VF/VT was more commonly observed among men and PEA/asystole among women.

The lower rate of severe systolic LV dysfunction in females who suffer SCA is a finding with potentially important implications. Risk stratification based on degree of LV systolic dysfunction remains the major current and clinically utilized method of SCA risk stratification. The vast majority of patients who undergo ICD implantation have some form of cardiomyopathy with evidence of severe LV systolic dysfunction (LVEF≤35%). From community-based studies, we and others have previously reported that only 25-30% of SCAs occur in subjects who have severely reduced LV systolic function (3,9,10,14,15). Using the existing guidelines for ICD implantation, we are likely to miss the opportunity to effectively risk stratify almost 70-75% of individuals who will suffer from SCA, and the current findings suggest that this number could be even higher for women.

The significantly lower prevalence of recognized CAD among women who suffer SCA is a novel finding in a population-based setting. There are several possible explanations. The fact that these results are consistent with published findings among hospitalized survivors of SCA (16) would suggest that this reflects lower prevalence of significant CAD among female SCA cases. However, the possibility that women without CAD are more likely to be successfully resuscitated from SCA cannot be ruled out. Other potential explanations are that consideration of traditional risk factors may lead to underrecognition of CAD in women (17); or that physicians pursue a less aggressive management approach to CAD in women than in men (18); and/or there are higher rates of microvascular CAD (as opposed to epicardial CAD) among women (19). While this phenomenon clearly warrants further investigation, CAD remains the condition most commonly associated with SCA. Symptoms related to CAD often prompt health care provider visits and an opportunity for risk stratification and initiation of drug therapy. Therefore it is also likely that the lower prevalence of recognized CAD among women impedes effective risk stratification and prevention of SCA in women.

It is of interest that a recent analysis of a Medicare population sample (1991-2005) reported that men were significantly more likely to undergo ICD implantation for both primary and secondary prevention of SCA (hazard ratio 3.15, 95% C.I. 2.86 to 3.47, and hazard ratio 2.44, 95% C.I. 2.30 to 2.59, respectively) (20). This same gender disparity has also been reported in two other database analysis studies (21,22). A subgroup analysis of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) (23) also reported lower rates of enrollment in women. However, women and men experienced a similar survival benefit from implantable cardioverter-defibrillator therapy. Therefore, development of methods that enhance SCA risk stratification in women should become an even higher priority. This need is underscored by our additional findings regarding the proportion of female SCA cases being higher than expected. In 2004, in contrast to earlier studies that have reported a 25:75 female:male ratio (24,25), we observed that 40% of all cases were female (3,10). Over a period of five years, these findings have been consistent in the Ore-SUDS with an average prevalence of 36%. While the reasons for this changing trend need to be evaluated in detail, one possibility is it corresponds to the altered sex distribution in prevalence of and mortality from CAD (26).

If prevalence of severe LV systolic dysfunction in women is low and corresponds to lower rates of diagnosed coronary disease, what are the mechanisms of SCA in the majority of women? The established association between CAD risk factors such as smoking, hypertension and diabetes is common to both women and men (4). However, there appear to be distinct differences in how SCA manifests in women. In a postmortem study, a subgroup of younger women tended to have plaque erosion with relatively little coronary arterial narrowing and less plaque calcium (27). Furthermore, the majority of women (69% in an earlier prospective study (4)) tend to have no history of cardiac disease prior to SCA (5). This could be consistent with higher rates of vulnerable plaque rupture without pre-existing severe stenosis. There are other potential mechanisms. Based on higher rates of diastolic heart failure among women in the community, it has been suggested that women who suffer SCA could have higher prevalence of LV diastolic dysfunction (with preserved LV systolic dysfunction) vs. men (28,29). Our findings that hypertension and DM, however, were more common in women compared to men (73 vs 62%, p=0.0001 and 39% vs 34%, p=0.03, respectively) would support the diastolic dysfunction hypothesis. There is evidence that common as well as rare gene variants may contribute to SCA and that at least some of these may be distributed more commonly among women. In community based studies, common variants in the SCN5A gene can increase susceptibility to SCA among women (30), but not in men (31). The majority (approximately 70%) of all reported cases of the familial or acquired long QT syndromes are women. Consistent with prior observations, the QTc was significantly longer in females (32). Women were more likely to manifest with pulseless electrical activity compared to men, had higher rates of return of spontaneous circulation, but there were no differences in rates of survival to hospital discharge.

Limitations

Based on their design, population-based studies of SCA have some limitations that relate mostly to the fact that all subjects analyzed may not have uniform information available. This is directly attributable to the fact that a large proportion of patients may have SCA without prior warnings or health care provider visits for cardiac testing. While prospective cohort studies could circumvent this limitation, the incidence of SCA is such that the large size of cohort required renders this approach unfeasible. However, in the present study availability of medical records were comparable in men and women (80% vs. 81%). Also, documentation of LV function was available in 307 (38%) men and 178 (39%) women, further decreasing the likelihood of gender bias in this regard. Nonetheless it remains possible that if the entire population were screened with echocardiograms, the overall prevalence of LV dysfunction may be different. Also, while subjects included in our analysis constituted the vast majority of SCA cases in the region, limiting ascertainment to individuals that underwent attempted resuscitation or were investigated by the medical examiner during the last two years of this five-year study may impact the generalizability of the findings to all SCA cases.

CONCLUSIONS

In this population-based analysis, the proportion of women with SCA was higher than anticipated (36% women, 64% men). However, prevalence of severe LV systolic dysfunction and previously established CAD were significantly lower in women vs. men. This could, in part, explain the lower rates of ICD implantation in women. Although the underlying pathophysiology and risk factors for SCA in women are generally assumed to be similar to men, these findings suggest that women may have unique risk predictors. Since fewer women may be eligible for ICD implantation based on LV ejection fraction criteria alone, the identification of novel SCA risk predictors for women becomes an important priority.

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Abbreviations and definitions

CAD	Coronary artery disease
COPD	Chronic obstructive pulmonary disease
DM	Diabetes mellitus
ECG	Electrocardiography
EF	Ejection fraction
ICD	Implantable cardioverter defibrillator
LV	Left ventricle
PEA	Pulseless electrical activity
SCA	Sudden Cardiac Arrest
VF/VT	Ventricular fibrillation/Ventricular tachycardia

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Table 1

Demographics and arrest circumstances of men and women age ≥ 35 with SCA, Portland OR metropolitan area, 2/2002 – 1/2007 (n = 1568)

	Men	Women	P value*
Total number	1012 (64.5%)	556 (35.5%)	<0.0001
Age (mean in yrs ± SD)	64.9 ± 14.5	71.0 ± 14.5	<0.0001
Age categories (%)			
35-54 yrs	294 (29.0%)	97 (17.4%)	<0.0001
55-74 yrs	436 (43.1%)	205 (36.9%)	
75+ yrs	282 (27.9%)	254 (45.7%)	
Presenting rhythm			
VF/VT	335 (47.4%)	117 (32.8%)	<0.0001
PEA	167 (23.7%)	101 (28.4 %)	
Asystole	193 (27.3%)	126 (35.4 %)	
Other†	11 (1.6%)	12 (3.4 %)	
Missing‡	306	200	
ROSC (%)	210 (20.8%)	141 (25.4%)	0.04
STHD (%)	74 (7.3%)	47 (8.4%)	0.42
Witnessed status			
Witnessed	515 (51.3%)	262 (48.2%)	0.25
Not witnessed	489 (48.7%)	281 (51.8%)	
Missing‡	8	13	
Response time (mean ± SD)	6.4 ± 3.3 (n = 716)	6.5 ±3.0 (n = 379)	0.77

*P value from Pearson chi-square test for categorical variables and *t-test* for continuous variables.

†Other presenting rhythms include: paced rhythm, third degree heart block, bradycardia.

‡For variables with missing values, proportions and p-values are calculated using the non-missing data as the denominator.

PEA= pulseless electrical activity; ROSC = return of spontaneous circulation; SCA = sudden cardiac arrest; VF/VT = ventricular fibrillation/ ventricular tachycardia; STHD = survived to hospital discharge; SD = standard deviation.

Table 2

Clinical characteristics of men and women age ≥ 35 with SCA and physician records available, Portland OR metropolitan area, 2/2002 – 1/2007 (n=1258)

	Men	Women	P value*	P value† (Age-Adjusted)
Total number (% of total subjects)	805 (64.0%)	453 (36.0%)	<0.0001	-
Age (mean in yrs ± SD)	66.3 ± 14.3	71.3 ± 14.3	<0.0001	-
BMI (mean ± SD)	29.6 ± 8.2 (n = 617)	29.4 ± 10.1 (n = 314)	0.73	0.60
Obesity (%)‡	232 (37.6%)	120 (38.2%)	0.85	0.28
Missing§	188	139		
Smoking (%)				
Active	235 (41.8%)	107 (36.4%)	<0.0001	<0.0001
Former	203 (36.1%)	71 (24.1%)		
Nonsmoker	124 (22.1%)	116 (39.5%)		
Missing§	243	159		
Documented CAD (%)	396 (49.2%)	180 (39.7%)	0.001	0.0005
History of MI (%)	234 (29.1%)	116 (25.6%)	0.19	0.05
History of prior cardiac arrest (%)	22 (2.7%)	8 (1.8%)	0.28	0.26
Hypertension (%)	500 (62.1%)	330 (72.8%)	0.0001	0.002
Diabetes mellitus (%)	272 (33.8%)	180 (39.7%)	0.03	0.02
Dyslipidemia (%)	302 (37.5%)	154 (34.0%)	0.21	0.18
COPD/Asthma (%)	219 (27.2%)	143 (31.6%)	0.10	0.12
History of seizure (%)	44 (5.5%)	29 (6.4%)	0.49	0.17
Left ventricular hypertrophy (%)	92 (44.7%)	61 (49.2%)	0.42	0.41
Missing§	599	329		

	Men	Women	P value*	P value† (Age-Adjusted)
LV systolic dysfunction (%)//				
Normal function	108 (35.2%)	87 (48.9%)	0.001	0.001
Mild-moderate dysfunction	90 (29.3%)	54 (30.3%)		
Severe dysfunction	109 (35.5%)	37 (20.8%)		
Missing§	498	275		
Gender-specific QTc categories (%)¶				
Normal	110 (40.9%)	89 (49.7%)	0.05	0.16
Borderline	58 (21.6%)	24 (13.4%)		
Abnormal	101 (37.5%)	66 (36.9%)		
Missing†	536	274		
QTc (mean ± SD) #	444.3 ± 45.4 (n = 269)	456.7 ± 38.8 (n = 179)	0.003	0.002

*P value from Pearson chi-square test for categorical variables and *t-test* for continuous variables.

†P –value adjusted for age using Cochran-Mantel-Haenszel test for categorical variables and analysis of covariance for continuous variables.

‡BMI ≥ 30.

§For variables with missing values, proportions and p-values are calculated using the non-missing data as the denominator.

//LV systolic dysfunction defined as: normal (EF ≥ 55%), mild-moderate dysfunction (EF = 36-54%), severe dysfunction (EF ≤ 35%).

¶QTc categories defined as: Males ≤430 ms (normal), 431-450 ms (borderline), >450 ms (abnormal); Females ≤450 ms (normal), 451-470 ms (borderline), >470 ms (abnormal).

#Corrected using Bazett's formula.

BMI = body mass index; CAD = coronary artery disease; BMI = body mass index; CAD = coronary artery disease; MI = myocardial infarction; QTc = corrected QT interval; SCA = sudden cardiac arrest; BMI = body mass index; CAD = coronary artery disease; SD = standard deviation.

Table 3

Multivariate odds ratio estimates of clinical predictors of women vs. men age ≥ 35 with SCA, Portland OR metropolitan area, 2/2002 – 1/2007 (n = 485)

	OR (95% CI)
Characteristics	
Age	1.02 (1.00 – 1.04)
CAD	0.34 (0.20 – 0.60)
History of MI	1.46 (0.84 – 2.53)
Hypertension	1.31 (0.81 – 2.12)
Diabetes mellitus	1.25 (0.84 – 1.85)
LV systolic dysfunction*	
Normal function	Reference
Mild-moderate dysfunction	0.91 (0.57 – 1.45)
Severe dysfunction	0.51 (0.31 – 0.84)

*LV systolic dysfunction defined as: normal (EF ≥ 55%), mild-moderate dysfunction (EF = 36-54%), severe dysfunction (EF ≤ 35%).

CAD = coronary artery disease; CI = confidence interval; LV = left ventricle; MI = myocardial infarction; OR = odds ratio; SCA = sudden cardiac arrest.