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Survival Advantage from Ventricular Fibrillation and Pulseless Electrical Activity in Women Compared to Men: The Oregon Sudden Unexpected Death Study

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Abstract

Objective—Studies evaluating a possible survival advantage from sudden cardiac arrest (SCA) in women have produced mixed results possibly due to a lack of comprehensive analyses. We hypothesized that race, socioeconomic status (SES) and elements of the lifetime clinical history influence gender effects, and need to be incorporated within analyses of survival.

Methods—Cases of SCA were identified from the ongoing, prospective, multiple-source Oregon Sudden Unexpected Death Study (population approx. one million). Subjects included were age 18 years who underwent attempted resuscitation by EMS providers. Pearson's chi-square tests and independent samples *t*-tests or analysis of variance were used for univariate comparisons. We evaluated gender and race differences in survival adjusted for age, circumstances of arrest, disease burden and socioeconomic status using a logistic regression model predicting survival.

Results—A total of 1296 cases had resuscitation attempted (2002–2007) (mean age 65years, male 67%). Women were older than men (68 vs. 63years, $p<0.0001$) and were more likely to have return of spontaneous circulation (41% vs. 33%, $p=0.004$). Women were more likely to present with PEA and asystole ($p<0.0001$) and overall, PEA was more common among African Americans ($p=0.04$). Higher survival to hospital discharge was observed in women compared to men presented with VF/VT (34% vs. 24%, $p=0.02$) or with PEA (10% vs. 3%, $p=0.007$). In a multivariate model adjusting for age, race, presenting arrhythmia, arrest circumstances, arrest location, disease burden and SES, women were more likely than men to survive to hospital discharge [OR 1.85; 95% CI (1.12–3.04)].

Conclusions—Despite older age, higher prevalence of SCA in the home and higher rates of PEA, women had a survival advantage from ventricular fibrillation and pulseless electrical activity.

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Keywords

sudden cardiac arrest; survival; women; pulseless electrical activity; ventricular fibrillation; resuscitation

1 INTRODUCTION

Out-of-hospital sudden cardiac arrest (SCA) is a major public health issue [1] with average survival rates in North America continuing to remain below 5% [2]. Successful resuscitation is dependent on the “links in the chain of survival” : early activation of the EMS response, early CPR, early defibrillation and advanced life support [3] and the Utstein data elements have traditionally been used for a more detailed evaluation of determinants of survival. However, we have recently observed that there are likely to be additional determinants of survival beyond the Utstein elements [4], with selected populations reporting recent increases in survival rates [5–7].

There are important gender and race-related differences in the presentation and outcome of out-of-hospital sudden cardiac arrest [8]. Women with SCA are more likely than men to be found at home [9] and to manifest with pulseless electrical activity (PEA) and asystole (as opposed to ventricular fibrillation) [10, 11]. Although women may have better resuscitation rates than men [10, 12, 13], all of these studies evaluated either return of spontaneous circulation (ROSC) or survival to hospital admission as outcomes. The only published study that used the established meaningful endpoint (survival to hospital discharge) actually found opposite results, with lower survival in women compared to men [11]. It is possible that the latter analysis was not comprehensive enough since other predictors such as race, socioeconomic status and the lifetime clinical history were not incorporated. Race is a significant predictor of survival from SCA with lower survival rates among African American population [14, 15]. Socioeconomic status [16], prior heart disease and functional status [17] were reported to be significant confounders of this association. We have previously reported important effects of socioeconomic status (SES) on SCA incidence that also need to be considered [18, 19]. We therefore hypothesized that inclusion of lifetime clinical history as well as race and SES in an analysis of survival determinants would influence the relationships between gender, race and survival. Accordingly we performed a comprehensive study of survival determinants in the ongoing Oregon Sudden Unexpected Death Study (Oregon-SUDS).

2 METHODS

2.1 Study population

Cases of out-of-hospital sudden cardiac arrest (SCA) were identified from the ongoing population-based Oregon-SUDS (population approximately 1,000,000). Details on case ascertainment have been published previously [20–24]. In brief, emergency medical services (EMS) are provided by a two-tier, advanced life support (ALS) first response system. Cases of SCA were identified through EMS, the Medical Examiner’s (ME) office or 16 local hospitals. Each patient with cardiac arrest was subjected to a comprehensive evaluation using ME investigation, autopsy, EMS report, and medical records information. After a process of in-house adjudication, cases of cardiac arrest were included in the study. SCA was defined as sudden unexpected loss of the pulse within an hour of symptom onset if witnessed or within 24 hours of observed alive and without symptoms for unwitnessed cases [25]. Cases with non-cardiac etiology of SCA, trauma, terminal illness or drug overdose were excluded. Cases 18 years or older with resuscitation attempted by the emergency medical services personnel from 2002–2007 were included in this analysis.

This study was approved by the Institutional Review Boards of participating hospitals and health systems.

2.2 Resuscitation, demographics and clinical characteristics

Presenting arrhythmia was defined as the initial rhythm identified from review of the actual presenting electrocardiographic rhythm strip when available (59% of cases). When the rhythm strip was not available, the presenting arrhythmia was identified from the first responder report. Response time was calculated as the time from dispatch of EMS personnel to their arrival at patient side. Return of spontaneous circulation (ROSC) was defined as a return of a palpable pulse in conjunction with a systolic blood pressure of at least 60 mmHg. Demographics, arrest circumstances and clinical characteristics were identified from medical records, first responder and Medical Examiner reports. Age was analyzed as a continuous as well as a categorical variable using age 50 years as cutoff [26]. The “disease burden” was calculated based on the Charlson Comorbidity Index [27]. The disease burden was then categorized as no co-morbidity, 1–3 co-morbidities and 4 or more co-morbidities. Median household income (US Census 2000) was identified from residential census tract and used to ascertain socioeconomic status.

2.3 Statistical analysis

Gender and racial differences in circumstances of arrest and outcomes were identified using Pearson’s chi-square tests for categorical variables and independent samples t-tests or analysis of variance with Tukey-Kramer post-hoc tests for continuous variables. Nonparametric tests were used for analysis of median income. Significant variables from univariate analysis were entered in two multiple logistic regression models to identify significant factors associated with presenting arrhythmia and survival. In order to adjust for circumstances of arrest and clinical and socio-economic status, response time, witnessed status, arrest location, disease burden and median household income were retained in the regression models regardless of their significance level. For all analyses, $p < 0.05$ was considered statistical significant. All statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

3 RESULTS

3.1 Demographics, arrest characteristics and outcome of study group

A total of 1296 cases of SCA with resuscitation attempted by EMS personnel from February 2002 to January 2007 were enrolled in the study. Mean age was 65 ± 16 years and 67% were male. The race distribution of SCA cases was: White 86.3%, African American 7.3%, Hispanic 2.3%, Asian 2.8% and other races such as Native American Indian, Alaskan Native, Hawaiian and Pacific Islander 1.4%. Presenting arrhythmia was ventricular fibrillation/tachycardia (VF/VT) in 48.0%, pulseless electrical activity (PEA) in 26.2%, asystole in 23.4% and other rhythms such as paced rhythm or atrioventricular block in 2.4%. Sixty-eight percent of SCA were witnessed, majority of cases arrested at home (64%) and 27% of all cardiac arrests had bystander CPR. Return of spontaneous circulation (ROSC) was observed in 36% and 14% survived to hospital discharge (STHD).

3.2 Gender differences in circumstances of arrest and outcome

Among SCA cases with resuscitation attempted, females were older than males (68 years vs. 63 years, $p < 0.0001$), more likely to present with PEA or asystole ($p < 0.0001$), more likely to arrest at home (69% vs. 61%, $p < 0.0001$) and to have ROSC ($p = 0.004$) (Table 1). There were no gender differences in witnessed status, bystander CPR, response time and survival to hospital discharge in univariate analyses ($p = 0.13$).

Given the profile of women with SCA (older age, initial rhythm of PEA rather than VF/VT, in-home arrest, and a higher disease burden), the observation that survival rates were similar to men, was unexpected. Therefore, we examined gender differences in survival stratified by age, presenting arrhythmia, arrest location and disease burden (Table 2). Among patients < 50 years of age, women were more likely to survive to hospital discharge compared to men (25.5% vs. 13.4%, $p = 0.04$), whereas no gender differences were found in survival among patients ≥ 50 years (15.1% vs. 13.2%, $p = 0.39$). Women < 50 years of age had somewhat better survival compared to women ≥ 50 years (25.5% vs. 15.1%, $p = 0.06$), but there was no survival difference in men < 50 years versus men ≥ 50 years (13.4% vs. 13.2%, $p = 0.95$). Furthermore, women were more likely to survive than men within arrhythmia subgroups (VF/VT 33.6% vs. 23.5%, $p = 0.02$ and PEA 10.4% vs. 3.1%, $p = 0.007$, respectively). Women also had a survival advantage among subjects that arrest at home ($p = 0.01$) or in public places ($p = 0.02$).

3.3 Racial differences in circumstances of arrest and outcome

There were significant differences in age and presenting arrhythmia based on race. African Americans and Hispanics had an arrest at a younger age compared to White or Asian cases ($p < 0.0001$). White and Hispanic cases were more likely to present with VF/VT, African Americans presented more with PEA, and Asians were more likely to have VF/VT or asystole as presenting arrhythmia ($p = 0.04$). African Americans were more likely to have a somewhat lower median household income ($p = 0.06$) and a higher disease burden ($p = 0.01$). No significant differences among race categories with respect to other arrest circumstances or outcomes, including survival to hospital discharge, were found in univariate analyses.

3.4 Determinants of presenting arrhythmia

Female gender [OR 1.48 (1.05 – 2.09)] and African American race [OR 2.10 (1.20 – 3.69)] were significant determinants of PEA as presenting arrhythmia versus VF/VT in multivariable analyses. Female gender was also a significant determinant of asystole [OR 1.79 (1.22 – 2.63)] versus VF/VT. Witnessed arrest, presence of bystander CPR and arrest in public locations were more likely to be associated with VF/VT than PEA or asystole ($p = 0.03$).

3.5 Determinants of survival from SCA

In a multivariable analysis, women were more likely to survive to hospital discharge compared to men [OR 1.85 (1.12 – 3.04)] (Table 3). Cardiac arrests that were witnessed and occurred in public locations were positively associated with survival to hospital discharge. On the other hand, cardiac arrests that presented with PEA or asystole were negatively associated with survival. African American race was associated with a worse survival ($p = 0.05$).

4 DISCUSSION

In this population-based study of out of hospital cardiac arrest, women suffered a cardiac arrest at an older age than men, and were more likely to present with PEA or asystole and to arrest at home, all established determinants of worse survival. However, women were significantly more likely to have return of spontaneous circulation. When survival was examined within each presenting arrhythmia (VF/VT or PEA), women were also more likely to survive compared to men. In a multivariable analysis, after adjusting for circumstances of arrest, disease burden, race and median household income, female gender was independently associated with higher likelihood of survival from hospital discharge. This is the first comprehensive evaluation of gender differences in survival from SCA by incorporation of

variables such as race, socioeconomic status and the lifetime clinical history, elements that had not been considered in earlier analyses. The findings indicate that in addition to ROSC and survival to hospital admission, survival to hospital discharge is also better in women presenting with VF and PEA, compared to men. The disparate findings from the only other study with survival to hospital discharge as an endpoint [11] could be explained by differences in analysis methodology (PEA and asystole were treated as one group) as well as the comprehensive nature of the present analysis.

Why do women have a survival advantage over men when it comes to sudden cardiac arrest? The specific reasons responsible for this phenomenon are likely to require further evaluation but there are several possibilities. It has been reported that women who suffer a cardiac arrest are less likely to have underlying coronary artery disease [28] or a diagnosis of structural heart disease [22] and these could be contributing factors. It is also possible that higher estrogen levels in women are protective and influence SCA outcome. For example, women of reproductive age (13–49 years) have a better survival from SCA compared to men and women of other ages and this phenomenon could be explained by the cardioprotective effects of endogenous estrogen [26]. In the present study, we have found that women < 50 years were more likely to survive to hospital discharge compared to men or women ≥ 50 years of age. Recently, we have identified a novel genomic locus that has protective effects against SCA [29]. It is possible that genetic variations that are gender-specific (i.e. found on the X-chromosome) may play a role in the pathophysiology and outcome of cardiac arrest. Additionally, we observed no significant gender differences in the availability of bystander CPR, witnessed cardiac arrest or the response time. We have recently reported that the clinical correlates of PEA are multifactorial but also gender- and race-specific [24].

Earlier studies that evaluated race and survival have also reported mixed results. Some report lower survival among African Americans [14, 15], but more recent studies have found no significant association after adjusting for SES and prior cardiac and functional status [16, 17, 30]. The incorporation of lifetime clinical history (i.e., disease burden) in our study showed a trend, of borderline significance, toward lower survival in African Americans. These findings correlate with significantly higher frequency of PEA among African Americans in the present study as well as in a separate analysis that we have published [24] and lower proportion of VF [14, 16, 17], both scenarios that decrease likelihood of survival. In our study population, the majority of subjects were white (86%) with African Americans representing only 7%. Therefore, the borderline significance in the survival from SCA could be explained by small numbers of African Americans in this population. Either way, the reasons for higher prevalence of PEA among African Americans need to be investigated in further detail. Consistent with earlier studies [4, 31–33], we report that out-of-hospital SCAs that were witnessed, occurred in public places, and presented with VF were associated with better survival.

There are some limitations associated with this analysis. Survival information was unknown for 3.5% of subjects with a slightly higher proportion in men compared to women (4.0% vs. 2.3%). However, this was not statistically significant ($p=0.11$). In addition, when a conservative scenario was considered by assuming that all subjects with unknown information survived the cardiac arrest, female gender remained a significant determinant of survival. In-hospital course and management of the disease may provide more insights regarding potential mechanisms of gender differences in survival but this information was not available for this analysis. Additionally, the race distribution in our population is mainly White non-Hispanic and therefore the findings of this study need to be replicated in a larger multi-ethnic study of SCA.

5 CONCLUSIONS

In this comprehensive population-based study, despite older age, higher prevalence of SCA in the home and higher rates of PEA, women had a survival advantage from ventricular fibrillation and pulseless electrical activity. Further detailed studies of clinical as well as genetic determinants of survival from SCA are warranted, preferably in larger, multi-ethnic populations.

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Table 1

Gender differences among SCA cases with resuscitation attempted by first responders (n = 1296)

Categories	Male n = 865	Female n = 431	P value*
Age (yr)	63.2 ± 15.3	68.1 ± 15.8	< 0.0001
Race			0.42
White	717 (86.7%)	351 (85.4%)	
African Am	57 (6.9%)	33 (8.0%)	
Hispanic	19 (2.3%)	9 (2.2%)	
Asian	20 (2.4%)	15 (3.7%)	
Other	14 (1.7%)	3 (0.7%)	
Unknown	38	20	
Presenting rhythm			< 0.0001
VF/VT	440 (54.8%)	153 (38.0%)	
PEA	197 (24.5%)	127 (31.5%)	
Asystole	166 (20.7%)	123 (30.5%)	
Other/unknown	62	28	
Witnessed status			0.67
Witnessed	527 (61.4%)	255 (59.6%)	
Witnessed EMS	59 (6.9%)	27 (6.3%)	
Not witnessed	272 (31.7%)	146 (34.1%)	
Unknown	7	3	
Arrest location			< 0.0001
Home	523 (60.8%)	296 (69.2%)	
Public locations	209 (24.3%)	44 (10.3%)	
ED/outpatient clinic/care fac.	86 (10.0%)	70 (16.4%)	
Other	42 (4.9%)	18 (4.2%)	
Unknown	5	3	
Bystander CPR	243 (28.1%)	105 (24.4%)	0.15
ROSC	285 (33.0%)	177 (41.1%)	0.004
STHD			0.13
Yes	110 (13.2%)	69 (16.4%)	
No	720 (86.8%)	352 (83.6%)	
Unknown	35	10	
Response time (min)	6.5 ± 3.2 (n = 759)	6.6 ± 3.0 (n = 392)	0.43
Response time > 4 min	590 (68.2%)	311 (72.2%)	0.15
Median income [†]	40300 (32700–48300) (n = 695)	40000 (35400–45800) (n = 384)	0.26

Categories	Male n = 865	Female n = 431	P value*
Disease burden			0.06
No co-morbidity	164 (19.0%)	64 (14.8%)	
1 – 3 co-morbidities	451 (52.1%)	219 (50.8%)	
4 co-morbidities	250 (28.9%)	148 (34.3%)	

*Results presented as n (%) or mean $\pm$ SD. Significant differences ($p < 0.05$) among groups based on Pearson chi-square test for categorical variables and *t-test* for continuous variables. For variables with missing values, proportions and p-values are calculated using the non-missing data as the denominator.

†Median (interquartile range), p value from Wilcoxon rank sum test.

SCA, sudden cardiac arrest; VF/VT, ventricular fibrillation/tachycardia; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; STHD, survival to hospital discharge.

Table 2

Gender differences in survival to hospital discharge (n = 1251)

Categories	Male	Female	P value*
Survival stratified by age			
Age < 50 years (n=215)	22 (13.4%)	13 (25.5%)	0.04
Age ≥ 50 years (n=1036)	88 (13.2%)	56 (15.1%)	0.39
Survival stratified by presenting arrhythmia			
VF/VT (n=562)	97 (23.5%)	50 (33.6%)	0.02
PEA (n=319)	6 (3.1%)	13 (10.4%)	0.007
Asystole (n=284)	0 (0.0%)	3 (2.5%)	0.07
Survival stratified by arrest location			
Home (n=796)	41 (8.1%)	40 (13.8%)	0.01
Public locations (n=237)	48 (24.6%)	18 (42.9%)	0.02
ED/outpatient clinic/care fac. (n=150)	12 (14.8%)	9 (13.0%)	0.76
Other (n=60)	8 (19.0%)	1 (5.6%)	0.26
Survival stratified by disease burden			
No co-morbidity (n=200)	24 (17.1%)	13 (21.7%)	0.45
1 – 3 co-morbidities (n=653)	49 (11.1%)	27 (12.7%)	0.56
4 co-morbidities (n=398)	37 (14.8%)	29 (19.6%)	0.21

*Results presented as n (%). Significant differences (p ≤ 0.05) among groups based on Pearson chi-square test.

VF/VT, ventricular fibrillation/tachycardia; PEA, pulseless electrical activity.

Table 3

Multivariate odds ratio estimates of survival from SCA

Categories	OR (95% CI)* n = 869
Age	0.98 (0.97 – 1.00)
Female	1.85 (1.12 – 3.04)
Race	
White	1.0 (ref)
African American	0.34 (0.12 – 1.00)
Hispanic	0.42 (0.05 – 3.74)
Asian	0.94 (0.19 – 4.64)
Presenting arrhythmia	
VF/VT	1.0 (ref)
PEA	0.25 (0.14 – 0.46)
Asystole	0.05 (0.01 – 0.20)
Witnessed by EMS/bystander	3.81 (1.82 – 7.94)
Bystander CPR	1.43 (0.89 – 2.32)
Arrest location	
Home	1.0 (ref)
Public locations	2.17 (1.27 – 3.69)
ED/outpatient clinic/care facility	1.23 (0.57 – 2.66)
Vehicle/other	0.58 (0.16 – 2.09)

* Adjusted for response time, disease burden and median household income

SCA, sudden cardiac arrest; VF/VT, ventricular fibrillation/tachycardia; PEA, pulseless electrical activity.