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Out-of-hospital cardiac arrests and cardiopulmonary resuscitation. Is there a difference between genders?

Paro cardiaco extrahospitalario y resucitación cardiopulmonar. ¿Hay diferencia de género?

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Palabras clave:
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ABSTRACT

Sudden Cardiac Death (SCD) is almost twice as common in men as in women. The leading cause in both groups is Coronary Artery Disease (CAD), but most women who present with SCD have no prior history of heart disease, are asymptomatic, or have been considered low-risk subjects for SCD. Prevention of SCD in women is more difficult, although control of risk factors for CAD has been demonstrated to reduce the incidence of SCD. Women suffering from SCD are generally older, have more comorbidities, and are less likely to die in public spaces. They also receive less bystander Cardiopulmonary Resuscitation (CPR) than men. They usually present with an initial non-shockable rhythm and are less likely to survive an Out-Of-Hospital Cardiac Arrest (OHCA) and be discharged from the hospital. The present work reviews significant differences concerning risk factors, treatment, and outcomes that must prompt collective actions to reduce the mortality burden of cardiac arrest in women.

RESUMEN

La muerte súbita cardiaca (MSC) es casi el doble de frecuente en hombres que en mujeres. La principal causa en ambos grupos es la enfermedad arterial coronaria (EAC), pero la mayoría de las mujeres que presentan MSC no tienen antecedentes de cardiopatía, son asintomáticas o se han considerado sujetos de bajo riesgo de MSC. La prevención de la MSC en mujeres es más difícil, aunque se ha demostrado que el control de los factores de riesgo de la EAC reduce la incidencia de MSC. Las mujeres que sufren MSC suelen ser mayores, presentan más comorbilidades y tienen menos probabilidades de fallecer en espacios públicos. También reciben menos reanimación cardiopulmonar (RCP) por parte de testigos que los hombres. Generalmente presentan un ritmo inicial no desfibrilable y tienen menos probabilidades de sobrevivir a un paro cardiaco extrahospitalario (PCEH) y ser dadas de alta del hospital. El presente trabajo revisa las diferencias significativas en cuanto a factores de riesgo, tratamiento y resultados que deben impulsar acciones colectivas para reducir la carga de mortalidad por paro cardiaco en mujeres.

Abbreviations:
B-CPR = Cardiopulmonary Resuscitation Bystander
CA = Cardiac Arrest
CAD = Coronary Artery Disease
CPR = Cardiopulmonary Resuscitation
ECG = electrocardiogram
EMS = Emergency Medical System
LVH = Left Ventricular Hypertrophy
OHCA = Out-Of-Hospital Cardiac Arrest
ROSC = Return of Spontaneous Circulation
SCD = Sudden Cardiac Death
VF = Ventricular Fibrillation

INTRODUCTION

Sudden Cardiac Death (SCD) is a significant health problem worldwide, with approximately 350,000 cases in the USA and 275,000 in Europe and experiencing Out-Of-Hospital Cardiac Arrest (OHCA).[1,2] and more than 120,000 in women.[1-5] Lately, the decline in SCD incidence among women has been less compared with men and could represent up to 40% of SCDs.[6]

Even though significant Coronary Artery Disease (CAD) is the leading cause of SCD in

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women, non-ischemic SCD in women occurs more frequently than in men. Women with SCD are less likely to have a history of CAD, structural heart condition, or left ventricular dysfunction than men. Although the prevalence of SCD in men is half to 2-3 times higher than in women, major clinical risk factors are very similar for both, but also substantial differences exist in outcomes, treatment, and predictors.[7-9]

Despite SCD incidence rates being higher for the male population, it is still a leading cause of death in both genders; SCD in women is increasing, with a different pattern. Understanding how males and females are different in the context of SCD is critical to ensure that preventive strategies are effective for both males and females in the future.

Considering that many of these elements usually depend on society and the location of the OHCA, it is understandable that there are differences, some of them significant, according to the population studied and/or in different areas of the world, in which it is presented.

We analyze gender differences across various aspects of SCD and OHCA, including epidemiology, age, clinical presentation, cause, risk factors, ECG and autopsy findings, treatment and prevention, and outcomes.

Each year, approximately 350 thousand deaths in the USA and 275 thousand in Europe are secondary to OHCA[1,2] of which 120 thousand occur in women[3-5] with an annual incidence of 30 to 97.1 per 100 100,000 inhabitants, depending on the population studied.[6] The annual survival is very low, varying between 7.6% and 12% when we talk about OHCA, compared to figures of 24.8% when the event occurs in the hospital.[7] We do not have information on SCD, OHCA, and Cardiopulmonary Resuscitation (CPR) in women in Mexico. There are only a few studies that have investigated symptoms prior to SCD in women and have found that around 50 to 70% of victims seek medical attention before the SCD event.[8-11]

Presentation of clinical aspects and coronary artery disease

It is important to mention that the spectrum of SCD in women is not so typical and out of the ordinary compared with men, with a more atypical presentation of cardiac diseases, and occurs more often without the knowledge of a previous CAD. For both men and women, the most common underlying risk factor for SCD is the presence of significant CAD. For this reason, the causes, etiology, and pathologies associated with SCD in women are more difficult to recognize, diagnose, predict, and even prevent. Data indicate that sex differences are likely to exist in coronary risk factors and the pathophysiology and clinical manifestations of CAD, despite being the main cause of death in the world; data on the cause of death among women with CAD and SCD are still limited. The rate of SCD in women has been considerably lower than in men, with an annual rate estimated to be almost half in women than in men, with the main differences in middle age around premenopausal women and early postmenopausal years.[1,12,13]

The age of presentation of an SCD event in men is generally eight years younger than in women. Differences in life expectancy between genders could explain this, as women live almost five years longer than men, and this difference in age presentation may be related to estrogen and cortisol levels. It is noteworthy that the majority of SCD events are secondary to coronary heart disease, which in turn has substantially reduced mortality by almost half during the same period.[14] Haukilahti et al., in 5,869 subjects with SCD, most patients were male (78.9%) compared to women (21.1%), $p < 0.001$. The majority of subjects with CAD and SCD were men (79.8%) compared to women (20.2%), $p = 0.005$. Women with non-ischemic etiology of SCD were more common, 28.3%, than men, 24.3% ($p = 0.005$).[15] The presence of an SCD event in women is commonly one of the first manifestations of CAD. CAD risk factors also predict SCD risk in women. Therefore, prevention of atherosclerosis, ventricular arrhythmias, and some other risk factors may reduce the incidence of SCD in women.[1]

In addition, different traditional risk factors for developing CAD and SCD in women are presented. Some other risk factors also present concerning SCD are increased sympathetic activity, heart failure with preserved left

ventricular systolic function, increased body mass index and abdominal fat, depression, and/or use of antidepressants. Prediction and prevention of SCD is an area of active investigation, but current guidelines for preventive intervention apply to a tiny portion of the population at risk.[16,17] It is also crucial to mention that it is common to present events of undetected myocardial infarction and underlying left ventricular hypertrophy detected by 12-lead rest electrocardiogram (ECG) in women. Around 30% of women with SCD have normal ECG before the event, so it is essential to understand that a normal ECG in women does not rule out an underlying risk for SCD, even in a non-ischemic SCD event. Autopsy findings indicate that women who present non-ischemic SCD have a higher prevalence of myocardial fibrosis than men. Long corrected QT interval, myocardial infarction, and congestive heart failure are independent risk factors in women with non-ischemic SCD and atrial fibrillation, diabetes, glomerular filtration rate of less than 40 mL/min/1.73 m^2, reduced LVEF, and physical inactivity are independent predictors of SCD in women with ischemic SCD.[18,19]

Women have a lower prevalence of structural heart disease, which reduces the chance of identifying predictor risk factors for SCD in these patients. The cause of SCD by gender found during an autopsy is shown in *Figure 1*. It must be taken into account that these causes may vary depending on the population and the place of the study.[15,20]

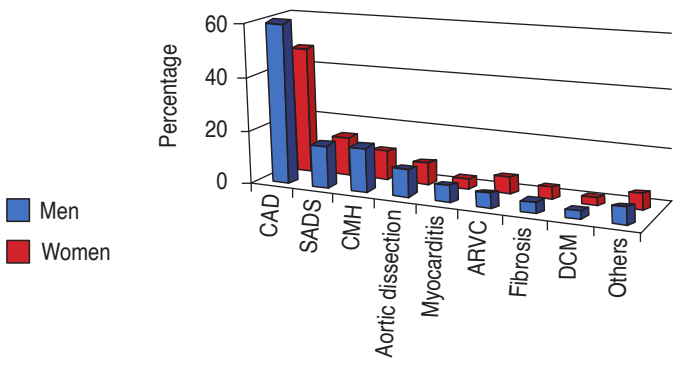

Figure 1: Causes of death in autopsy in SCD according to sex (percentage).
Modified from: Skjelbred T et al.[20]
ARVC = arrhythmogenic Right Ventricle Cardiomyopathy. CAD = Coronary Artery Disease. CMH = hypertrophic cardiomyopathy. DCM = Dilated Cardiomyopathy. SADS = Sudden Arrhythmic Death Syndrome. SCD = Sudden Cardiac Death.

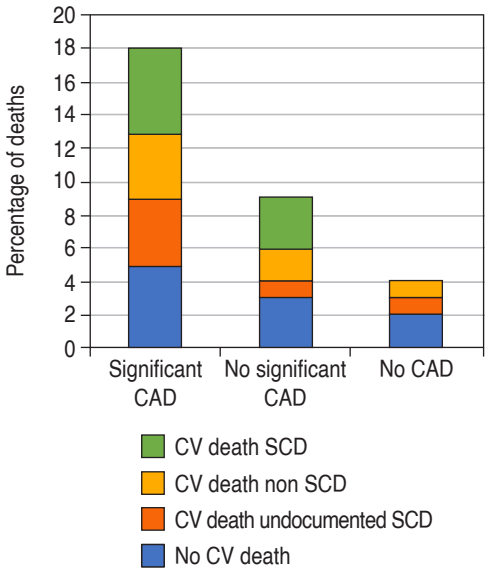

Figure 2: Mortality in women by coronary artery disease severity.
Modified from: Mehta PK, Johnson BD, Kenkre TS et al. Sudden cardiac death in women with suspected ischemic heart disease, preserved ejection fraction, and no obstructive coronary artery disease: a report from the women's ischemia syndrome evaluation study. J Am Heart Assoc. 2017; 6 (8): e005501. doi: 10.1161/JAHA.117.005501.
CAD = Coronary Artery Disease. CV = cardiovascular.

Mortality in women with SCD, according to the CAD severity, is shown in *Figure 2*. Predicted (marginal) probabilities of survival for male and female victims of OHCA versus age are shown in *Figure 3*.

Context

Approximately 83% of the OHCA are unwitnessed in women and 85% in men, with a higher incidence of ischemic SCD in men than in women. SCD occurred during exercise more often in men than in women, and even more so for those with ischemic SCD. OHCA in women occurred indoors more often than in men, 92 versus 82%, respectively, especially in women with non-ischemic SCDs, and also occurred more often between midnight and 6 am than in men, when the event happened more often during the daytime. Women with CAD and SCD also have a lower risk of lethal ventricular

arrhythmias compared to men.[21,22] Given these results, we must observe with caution in greater detail the factors that have been shown to truly affect survival during an OHCA event, such as OHCA presence by a witness, Cardiopulmonary Resuscitation Bystander (B-CPR) shockable rhythm upon arrival of the Emergency Medical System (EMS), and Return of Spontaneous Circulation (ROSC) at the site of cardiac arrest.[23] Some other demographic differences factors, like race, gender, and socioeconomic status, have also been shown to impact the survival of the OHCA.[5,24,25]

Patient sex has also been proven to influence OHCA survival, with the incidence in men threefold higher than in women.[26] The data that report worse survival in the OHCA for women most of the time are related to worse pre-hospital factors, like less B-CPR, less witnessed Cardiac Arrest (CA), less EMS CPR, and some other reports of less administration of medications (intravenous) and received fewer attempts of endotracheal intubations.[27,28]

Cultural and religious factors concerning gender, their effect on the treatment to be performed, and the sensation of feeling aggressive management of compressions in the CA, especially under certain conditions, contribute to the different results between genders. The difference in CPR between genders during OHCA is related to multiple factors, including physiological, biological, and social differences.[29-31]

The general population perceives fears about inappropriate touching, possible accusations of sexual assault, and fear of causing injury or harm as inhibiting B-CPR for women. It has been proven that education may reduce these differences during B-CPR.[32,33] Since many of these factors change based on the different societies and cultures worldwide where OHCA is produced, it is logical to observe different results.[34]

Blom MT et al. found that women with OHCA are less likely to receive B-CPR than men (69.2% vs 73.9%; $p < 0.001$). Women have lower chances than men to be resuscitated and survive OHCA.[35]

Dispatcher-assisted CPR is associated with more favorable neurological survival in men than in women and could be related to delays in initiation of chest compression CPR maneuvers, on occasions associated with the shame of uncovering a woman's breast, and being subject to possible complaints of harassment, because this generally occurs in public places, the victim will expose their chest and breast in public as well as the psychological factors of how it harms a woman, etc.[36]

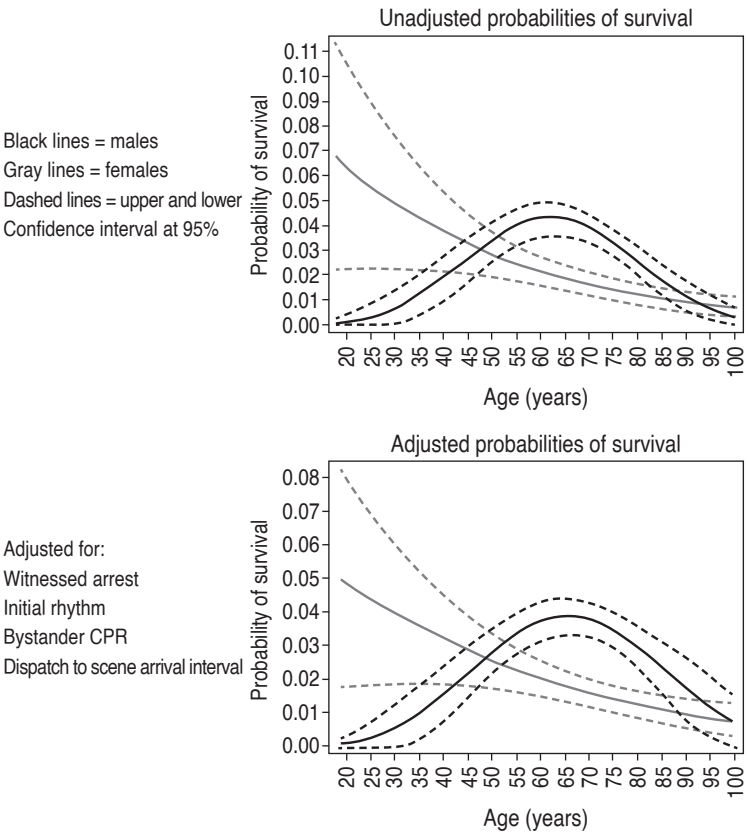

Figure 3: Predicted (marginal) probabilities of survival for male and female victims of OHCA versus age.
Modified form: Safdar B et al.[62]
CPR = Cardiopulmonary Resuscitation. OHCA = Out-of-Hospital Cardiac Arrest.

Age

Post-menopausal women, when experiencing OHCA, are, on average, eight years older than their male counterparts, a finding that is consistent in many studies. This trend could be related to differences in overall life expectancy, with females living nearly five years longer than males. It has been argued that these age differences between genders could be related

to disparities in estrogen and cortisol levels. Estrogen decreases the CA death pathway by reducing the anti-apoptotic mechanisms.[37] The drop of estrogen levels commonly seen in pre-menopause, and the loss of that positive effect on the heart-protective effect results in an increased incidence of cardiac events, including SCD.[38] Given the beneficial role of estrogen trying to reduce the death cascade in CA victims, has been proposed a role for intravenous estrogen as a stabilizing cell drug in women victims of CA.[37]

Young women

In young women less than 35 years old, males have a higher incidence of SCD than women at 1.8 versus 0.7 cases per 100,000 persons.[39]

SCD in specific groups

Pregnancy: approximately 1 in 30,000 pregnancies are complicated by maternal cardiac arrest.[40] Previous studies done in pregnant women found the causes of SCD are unexplained (54%) and cardiomyopathies (14%), including dilated, peripartum, hypertrophic, and arrhythmogenic, as the more relevant, and other causes like aortic dissection, valvular heart disease, and congenital heart disease in adults.[41] However, obesity-related cardiomyopathy has also been associated with an increased risk of SCD during pregnancy, and some autopsy findings showed that 43% of women who died from SCD were obese (43%) or overweight (16%).[42]

Eclampsia. The mortality in patients with eclampsia is secondary to cerebrovascular disease, pulmonary edema, and acute kidney injury, leading to CA. However, eclampsia has been reported as a rare entity, but it has finally been recognized as a cause of SCD.[43]

SCD in sports. In general, it has an incidence of approximately 1 in 50,000 to 80,000 young athletes,[44] and in most of the studies, males have a consistently greater risk of SCD (10 times more) compared with women.[45,46] The common cause of SCD in athletes less than five years of age is secondary to congenital heart disease, mainly hypertrophic cardiomyopathy, followed by anomalous coronary arteries. Compared with athletes over 35, most SCD events are related to CAD.[47] Racial factors may play a role in SCD in athletes, with a higher incidence in black athletes.[48] Gender differences within this subgroup have not yet been investigated. The atherosclerosis risk in community studies, including black and white athletes, found an increased risk associated with race, more pronounced in women than in men.[49]

ECG findings

The 12-lead ECG plays a vital role in risk stratification for SCD, but women are more likely to have a normal ECG than men prior to an SCD event. It is essential to remember that a normal electrocardiogram in women does not rule out an underlying risk for SCD, even in non-ischemic SCD, because almost 35% of women with SCD have normal ECGs before the SCD event.[15]

Left Ventricular Hypertrophy (LVH). The value of LVH in a 12-lead rest ECG as a marker of ischemic SCD appears greater in women than in men, with an incidence of around 22.8% in women with LVH on ECG, compared with 10.2% in men. In patients with non-ischemic SCD, LVH and repolarization abnormalities are more common in women, 10.2% of cases versus 4.6%. The Cornell index, as an ECG marker for LVH, is more frequent and has higher values in women (17.9%) than in men (10.6%).[15,19]

Silent myocardial infarction. Women with SCD have a history of the presence of silent with any abnormal Q-waves, and therefore, non-reperfused acute myocardial infarctions detected by ECG are almost twice as frequent as in men.[15]

Idiopathic monomorphic ventricular tachycardia (VT). It originates most commonly from the right ventricular outflow tract (RVOT-VT) and is more common in women.[50] Studies have found that women tend to have frequent ventricular tachycardia initiation in the premenstrual period compared with men, whereas RVOT-VT is more commonly triggered by exercise or stress.[51]

Autopsy

SCD in women is more frequently associated with non-ischemic heart disease than in

men, and primary myocardial fibrosis is more commonly found in women with SCD.[15] The cause of death in autopsy in SCD according to sex (percentage) is shown in *Figure 1*.

Arrhythmias

Ventricular Fibrillation (VF) is less common (about half) as a first rhythm in women with CA. VF and VT are more commonly the initial arrhythmia in men, and pulse less electrical activity and asystole are more common among women.[28] Women with an initial shockable rhythm are present in a smaller number of patients (mainly ventricular tachycardia) but have a better prognosis than men. However, unlike men, who show more pulseless electrical activity and ventricular fibrillation, women also present more asystole as the initial rhythm. Some of the reports that indicate a better prognosis related to initial shockable rhythms in women occur more frequently in young, NON-perimenopausal women and are therefore related to non-ischemic SCD at these ages. From this, it has been suggested that the differences observed in these initial rhythms among young women without ischemic heart disease may be related to the stage of the menstrual cycle at the time of OHCA.[52-57] This may partially explain why women have a lower survival rate, since the presence of a VF event would imply a reversible and treatable arrhythmia and potentially abort the CA event. The gender difference in the initial rhythm during OHCA is shown in *Figure 4*.

Lack of treatment

In general, women with SCD during CPR and EMS intervention receive less advanced respiratory support, intravenous adrenaline, and fewer defibrillations per encounter.[34] The CONCORDANCE acute coronary syndrome registry in Australia found that women are less likely to receive invasive management, revascularization, or preventative medication after being discharged from the hospital.[57] Women at high risk of SCD are less likely to receive implantable cardiac defibrillators.[58]

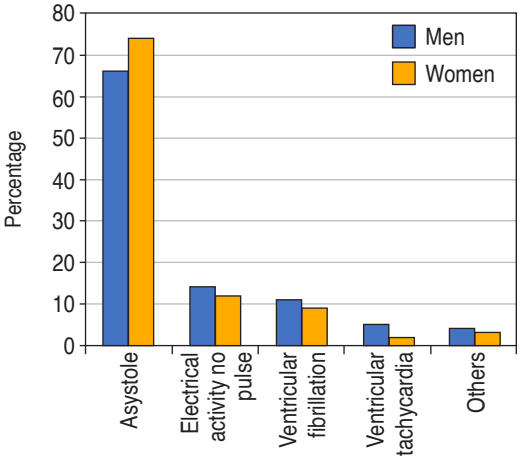

Figure 4: Differences by gender in the initial rhythm during out-of-hospital cardiac arrest.

OHCA survival and hospital discharge

It is another perspective to analyze SCD in women. Compared to men, women were less likely to receive bystander CPR (67.9% versus 72.7%), even in the subset of a witnessed CA; some studies demonstrated higher rates of ROSC during OHCA.[34] Overall survival to hospital discharge is significantly lower for resuscitated women (12.5% versus 20.1%) than men, probably related to a lower survival rate after ROSC when admitted to the hospital. This lower survival rate for women could be explained by their lower rate of having an initial shockable rhythm, a powerful survival predictor after OHCA. The in-hospital mortality of women who survive an OHCA and who are transferred to the hospital and admitted to intensive care units is higher than that of men,[59] also coupled with a worse prognosis and higher mortality at hospital discharge at 30 days after OHCA.[60] In the Opals registry, which analyzed more than 10,000 patients who presented an event of SCD and OHCA, the ratio of men to women victims of SCD was 2 to 1, with older women, having fewer initial shockable events and a smaller number of patients who received B-CPR ($p < 0.01$). *Figure 3* indicates gender differences in the initial rhythm detection during OHCA.[61] The overall survival of women with an OHCA event is lower than that of men, and this proportion decreases as age increases. Unlike men, the probability of survival varies

with age, increasing in men between 18 and 65 years of age and decreasing afterward, with a greater possibility of survival before perimenopause. Women have a lower chance of surviving an OHCA event that is directly related to age, but in young adult men who are victims of OHCA, this survival is lower when compared to men over 65 years of age; this trend is reversed. Men between 18 and 47 years have a lower probability of being discharged from the hospital after an OHCA compared to women of the same age, who have a higher percentage of survival during reproductive age. However, the survival rate to hospital discharge is generally lower in women, even when they present ROSC in an OHCA, 12.5% vs 20.1%,[19] compared to men, undoubtedly due to previously explained factors.[56]

CONCLUSIONS

Gender differences affect almost all SCD spectra, including epidemiology, age, clinical presentation, cause, risk factors, mechanisms of ECG and autopsy findings, treatment, prevention, and outcomes. In summary, although the prevalence of SCD in women is almost 30 to 50% less than in men, major clinical risk factors are present and similar for both genders; substantial differences exist in outcomes and predictors. Information must be provided to the general population and patients about the risk factors for the development of SCD, which are common in both genders, specifying, in women, those that differ and how to recognize them. It is not easy to understand why women receive fewer CPR maneuvers and treatment during CA events and post-ROSC therapies.[62] There are not enough community campaigns trying to raise awareness about the importance of CPR in the general population,[63] but also specifically in women with SCD. This could be beneficial and improve outcomes. Much is still left to be learned about gender-related differences in SCD between women and men. However, we believe that what is most important is to remove prejudices about factors that are not physiological, biological, or genetic and cannot be ethical[64] and that only respond to taboos or concepts of society concerning the difference in gender and race, regardless of the health problem, but specifically speaking of the SCD.

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