Title

When the Female Heart Stops: Sex and Gender Differences in Out-of-Hospital Cardiac Arrest Epidemiology and Resuscitation

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Highlights:

- **Sex is an important biological variable, which impacts the pathophysiologic development of heart disease and cardiac arrest**
- **Women have worse outcomes after cardiac arrest and are *less likely* to receive evidence-based interventions in pre-hospital and hospital settings**
- **Gender may also affect the care delivered to female victims of cardiac arrest, for example lower rates of bystander CPR in public locations**
- **Sex and gender should be considered as important determinants of disease when caring for women who suffer cardiac arrest in both the acute and post-acute phases**

Abstract

Sex and gender differences are emerging as clinically significant in the epidemiology and resuscitation of out-of-hospital cardiac arrest (OHCA) victims. Female patients tend to be older, arrest in private locations, and have fewer initial shockable rhythms (ventricular fibrillation/ventricular tachycardia). Despite standardized algorithms for management of OHCA, women are less likely to received evidence-based interventions including advanced cardiac life support (ACLS) medications, percutaneous coronary intervention and targeted temperature management. While some data suggest a protective mechanism of estrogen in the heart, brain, and kidney, its role is incompletely understood. Female victims suffer higher mortality from OHCA, prompting the need for sex-specific research.

Introduction

In recent years, sex and gender based research has grown exponentially and has shown repeatedly that women and men manifest disease in fundamentally different ways. Researchers have found not only pathophysiologic differences between women and men, but also disparities in the delivery of medical care that have clinical relevance in many diseases. The first and most well studied is cardiovascular disease.

Heart disease continues to be the leading cause of death in women in the United States.[1] Out-of-hospital cardiac arrest (OHCA) is the most common form of death from cardiac disease, and is also the leading cause of disability adjusted life years.[2,3] Important sex and gender based differences have been shown in the pathogenesis and treatment of ischemic heart disease, congestive heart failure, and cardiac arrhythmias.[4]

In ischemic heart disease, women have a higher burden of non-obstructive microvascular disease and endothelial dysfunction, in contrast to the obstructive, large vessel plaques classically associated with acute coronary syndromes in men.[5] Women also tend to develop coronary artery disease (CAD) 10-15 years later in life than men, and present with non st elevation myocardial infarction (NSTEMI) more often than st elevation mi (STEMI).[5] Women, particularly young women, have higher mortality both acutely and long term following an acute myocardial infarction.[6,7] As with the development of CAD, female victims of OHCA tend to be older and with other co-morbidities, making them more susceptible to pulseless electrical activity (PEA) & asystolic rhythms of cardiac arrest. The macrovascular CAD in men results in proportionally higher primary cardiac origin of ventricular tachycardia/ventricular fibrillation (VT/VF). While it is unclear how the epidemiologic and pathophysiologic differences in heart disease translate to cardiac arrest, it is evident that cardiac arrest characteristics show significant variation by sex.

Created in 2004, the American Heart Association’s (AHA) Go Red for Women campaign aims to increase awareness of heart disease and stroke in women. This campaign, combined with the National Institute of Health’s 2015 requirement to include sex as a biologic variable in all grant applications, has increased research and education in heart disease in women specifically. While sex differences in cardiovascular diseases have been studied for decades, sex differences in OHCA have only recently gained attention. In this article, we will review current knowledge about cardiac arrest, with particular attention to the association of sex and gender with prehospital, in-hospital, post-arrest care and outcomes for women with OHCA. We will also review important influences of estrogen on molecular mechanisms surrounding OHCA and provide recommendations for future research. It is our hope that information about patients’ sex and gender will be considered as important variables in the disease process, particularly when resuscitating victims of cardiac arrest, and in the provision of unbiased therapies that have been shown to impart better neurologic outcomes after cardiac arrest

Prehospital Setting

The overall incidence of treated OHCA in the United States is 52.1 persons per 100,000 population,[8] but incidence and arrest characteristics vary dramatically by sex. OHCA is more common in men than women.[9-12] In the Framingham Heart Study, which followed a cohort of study participants over a course of 26 years, approximately one-third of individuals who suffered a cardiac arrest in this time frame were women.[13] On average, women with OHCA are older than men and less likely to have VT or VF as their initial arrest rhythm.[9,11] Women are also less likely than men to suffer their OHCA in a public location.[9] Although the reasons for this are unclear, there are data to suggest that women delay seeking medical care when suffering an acute MI.[14-16]

Rapid, high-quality prehospital care, including cardiopulmonary resuscitation (CPR) beginning with bystanders and continuing to emergency medical services (EMS) personnel is critical to survival and good neurologic recovery in OHCA.[17] Women and men experience similar bystander CPR rates overall.[9] However, when stratified by location, women are less likely than men to receive bystander CPR in public locations but equally likely to receive bystander CPR in private locations.[12] This disparity likely represents an effect of gender, and recent evidence suggests this may be due to a combination of misperceptions about women in medical distress, perceived frailty of the female body, and social norms regarding the appropriateness of exposing or touching unknown women's chests.[18] Bystanders may perceive the risk of injury from CPR to be greater for female than male patients. CPR classes also use male mannequins and focus on technical aspects of CPR, rather than the psychosocial aspects of providing CPR.

Standardized protocols for the care of patients with OHCA assume the majority to be cardiac in origin, although they do include a provision for reversible causes (eg. hypoxia, hypothermia). Despite this, EMS providers differ in their approach to treatment of OHCA in women and men. After adjustment for patient and arrest characteristics including age, witnessed arrest, public location, bystander CPR, and first known rhythm of ventricular tachycardia/fibrillation, women experienced delays in OHCA recognition and intervention. In several studies, women were less likely than men to receive guideline-recommended procedures and medications.[9,19,20] For example in one trial, women were less likely to receive successful intravenous or intraosseous access (OR 0.78, 95% CI 0.71−0.86) but equally likely to receive a successful advanced airway (OR 0.94, 95% CI 0.86−1.02).[9] Women were less likely to receive epinephrine (OR 0.81,95% CI 0.74−0.88), atropine (OR 0.86, 95% CI 0.80−0.92), and lidocaine or amiodarone (OR 0.68, 95%

CI0.61−0.75), even after adjusting for intravenous and intraosseous access, prehospital return of spontaneous circulation, and endotracheal intubation.[9] Importantly, these data come primarily from well-developed EMS systems participating in a clinical trial. The Hawthorne effect associated with the clinical trial likely optimized protocol compliance in these EMS agencies, therefore the true magnitude of sex differences may be underestimated. While most studies attempt to control for protocol changes over time, it is possible that temporal and regional EMS protocol differences may contribute to some of the effects seen through the study periods.

Luckily these trends are modifiable. In one statewide study from North Carolina, women were less likely to receive bystander CPR and first-responder defibrillation at baseline.[21] Following a statewide, multifaceted intervention to improve care and outcomes for OHCA patients, rates increased substantially and were comparable in men and women. Unfortunately, these improvements in prehospital care for women did not translate into improved outcomes at hospital discharge,[21] highlighting the importance of standardized care in all links in the “chain of survival.” This includes rapid recognition of cardiac arrest with activation of the EMS system, early CPR and defibrillation, and advanced life support and post cardiac arrest care.[22]

Hospital Setting

As was previously outlined, women who suffer OHCA tend to be older in age, arrest from non-shockable initial rhythms, have un-witnessed events and receive lower rates of bystander CPR.[12,23-26] Despite the aforementioned factors, studies have shown that women survive to hospital admission at similar to improved rates in comparison to men.[25,27,28] While there is conflicting data with regard to survival and neurologically intact survival, several studies have found that women are less likely to survive to hospital discharge.[29,30] In-hospital mortality after out of hospital cardiac arrest is higher in women versus men (64% vs. 61.4%, $p<0.001$) even when analyzing a cohort of patients who have arrested due to ventricular dysrhythmia (pulseless ventricular tachycardia/ventricular fibrillation) (49.4% vs. 45.6%, $p<0.001$).[31] A recent study by Bosson *et al* confirmed that women had higher mortality, worse neurologic outcomes and received less post-arrest intervention in unadjusted models, however after adjusting for these notable differences, sex was not associated with worse outcomes in comparison to men; thus the survival difference we see by sex may be a function of inadequate application of evidence based interventions.[11] Outcome data also varies widely by age, which may explain the conflicting data across all age groups. Understanding sex differences in critical care treatments and interventions for cardiac arrest patients may help us understand sex differences in survival outcomes.

Currently, practice guidelines for all cardiac arrests are uniform between the sexes. Algorithmic advanced cardiac life support (ACLS) should be provided for all patients who present in cardiac arrest. In 2015, the AHA released a novel algorithm for maternal resuscitation emphasizing manual left uterine displacement and perimortem cesarean if resuscitative efforts are unsuccessful after 4 minutes.[32] This marks the first sex specific alternative to standard ACLS measures for individuals in cardiac arrest.

Post-arrest treatment bundles have been developed to impart best outcomes for patients who suffer OHCA.[33] Within this bundle of care, it is recommended that patients with presumed cardiac etiologies of arrest, most specifically an initial rhythm of VF or pulseless VT should receive early invasive cardiac testing. Similar to women who suffer myocardial infarction,[34,35] women who have cardiac arrest secondary to VF/VT are less likely to receive coronary angiography (OR 0.75; 95% CI 0.74-0.77) and percutaneous coronary intervention (PCI) (OR 0.71; 95% CI 0.69-0.73) in comparison to men (adjusted analysis).[31]

Targeted temperature management (TTM), a neuro-protective strategy utilizing therapeutic hypothermia, has been shown to impart better neurologic recovery and is now a level 1 AHA indication for comatose survivors of cardiac arrest, regardless of initial rhythm.[36] Recent literature has shown that women who suffer a cardiac arrest receive less TTM when compared to men (0.90; 95% CI 0.86-0.94), even when controlled for initial rhythm.[31] Similarly, Bosson, *et al.*, found that 33% of women received TTM, in contrast to 40% of men.[11] Further investigation is necessary to explore potential differences in hemodynamic optimization as an additional critical intervention that might potentially explain differences in outcome from cardiac arrest.

An integral aspect of post-arrest management is neuro-prognostication. Guidelines endorse delayed neuro-prognostication, recognizing that 72 hours after return of spontaneous circulation (ROSC) is the earliest time that neurologic testing becomes accurate.[36] Despite this guideline, early prognostication occurs[37] and can be associated with decisions to withdraw life sustaining therapy. Female sex is associated with withdrawal of life sustaining therapy (WLST) in post-cardiac arrest patients[38] and most notably, female sex is associated with higher incidence of “early” (less than 72 hours after ROSC) WLST for neurologic reasons.[39] While these trends have been observed, understanding the role of patient preference or prior wishes cannot be established from these large registry based studies. To that end, the potential role of implicit gender bias may contribute to the differences seen when exploring decisions to limit or withdraw life-sustaining therapies in women compared to men.

Women have been noticeably underrepresented in recent intervention trials to improve outcomes from cardiac arrest. In several landmark randomized control trials (RCTs) exploring temperature management for neuroprotection, women were under-represented in the treatment arms; in Bernard *et al* women represented 42%; HACA: 23% and Nielsen *et al*.: 17% of the study participants.[40-42] An example of a concerning trend is exhibited by the HYPERION trial, a RCT to explore the utility of TTM in patients with cardiac arrest from initial non-shockable rhythm, which excludes breastfeeding women from enrollment. Ensuring adequate enrollment of female study participants is necessary to understand how sex and gender affect cardiac arrest outcomes and therapies.

Sex Hormone Influences

Despite decades of research and revised guidelines, survival from OHCA with good neurological outcomes remains quite low at 7.6%.[17] Outcomes may remain poor due to the paucity of mechanistic, basic science understanding. Sex influences how a patient develops, presents with coronary artery disease, and how they respond to treatment. Yet our understanding of the cascade of events is incomplete, with gaps in our understanding of sex-based influences on gene transcription, cell singling, and cell death mechanisms in cardiac arrest.

Estrogen, and particularly its most abundant form Estradiol (E2), is the most potent steroid hormone with both protective and deleterious effects on the spectrum of cardiovascular disease.[43] There is growing evidence that E2 activation of genomic actions, via mitochondrial homeostasis, contributes to sex differences in disease.[44] In a rat model, strong evidence demonstrates that E2 regulates cardiac mitochondrial function and provides protection against damaging oxidative stress, whereas depletion leads to progressively worsening dysfunction of cardiac mitochondria and increased levels of lipid perioxidation and free radical formation.[45] Animal studies have also shown a protective effect of estrogen in the brain by reducing neural injury, while testosterone increased neural injury.[46] Noppens *et al* showed that E2 exerted neuroprotective effects mediated particularly via estrogen receptor beta in specific brain regions.[47] Estrogen has also been shown to have a protective effect in the kidney. Mice given E2 after cardiac arrest resuscitation showed improvement in creatinine and volume of necrotic tubules in young male mice and in aged male and female mice, but not in young female mice, who were believed to be protected by endogenous estrogens.[48]

As discussed above, TTM is the only approved treatment to counter the effects of global ischemia and neuronal injury in cardiac arrest. Interestingly, animal models of cardiac arrest in juvenile mice indicate that although TTM confers synaptic plasticity in both sexes, male mice required a deeper level of TTM for equivalent protection.[49] Such findings highlight the need for sex-specific personalized therapy.

The stroke and sepsis literature confirm that there is a dichotomous response noted between male and female animals that involves both sex steroid specific processes and other intrinsic non sex-hormone processes.[51,52] In sepsis, female sex hormones augment immune mediated responses, whereas male sex hormones have been shown to be immunodepressive, thus advocating that hormonal status should be taken into account when treating sepsis.[45] Similar exploration is necessary in cardiac arrest in order to improve survival and minimize the public health burden of sudden cardiac death.

Research Priorities

Despite observational data in animals and humans that demonstrate estrogen's benefit in stroke and cardiovascular disease, clinical trials such as the Women's Health Initiative have failed to show that exogenous estrogens provide protection for women in cardiovascular disease.[53] With age, the protective mechanisms and beneficial effects of estrogen are reduced and ultimately reversed. Therefore, it is crucial that future animal studies include aged animal models to better understand the interaction of estrogen loss and aging on cardiomyocytes. If we are to make larger strides in neurological intact survival from cardiac arrest, further investment is needed in proteomics studies to investigate the sex and gender influences on molecular processes, biomarkers, clinical outcomes, and therapeutic responses. [50]

Research has been limited given that there are fewer women in the databases that are generally used to study cardiac arrest. Performing studies designed a priori to investigate sex as a biological variable and pooling data across databases may help mitigate this limitation. Future cardiac arrest animal and clinical trials need to consider treatments that modify the sex hormone profile and its effect on neurological outcomes. Prior consensus statements have noted the dearth of information on sex differences in both acute coronary syndromes and cardiac arrest resuscitation, and outlined clinically relevant research questions and priorities, which include many of the themes addressed here.[5,54] Overall, a more complete understanding of the underlying sex differences in injury response in the brain and heart is an important step toward personalized medicine and effective therapeutic interventions in patients of both sexes.

Conclusions

It is clear in the data discussed above that sex and gender are a important factors to consider in the treatment of patients with OHCA. Women are less likely to receive evidenced-based interventions and have worse outcomes following cardiac arrest. The reasons for these differences are complex and involve effects of both biologic sex and gender influences in the pathophysiology of disease, treatment rendered, and response to treatment. Sex-specific research has improved outcomes for women with acute coronary syndromes and acute myocardial infarction and has fostered sex specific treatment considerations. A similar research focus can do the same in cardiac arrest resuscitation. Understanding and embracing sex and gender based differences in OHCA is key for providing appropriate and personalized resuscitative care both in and outside the walls of the hospital, to ultimately improve survival for both men and women.

As we move toward a more individualized approach to caring for patients, it is our hope that information about one’s sex and gender will be considered as important determinants of disease, particularly when resuscitating victims of cardiac arrest.

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