

Editorial

Sex and Gender Differences in Cardiovascular Resuscitation, Recovery, and Survival



Sex and gender researchers have the challenging task of working backward. It is now appreciated that the biomedical evidence collected up until the last decade was primarily based on research utilizing male models (ie, male animals and male humans). Because of this approach, most of our understanding of disease states, such as cardiovascular disease, stroke, and susceptibility to infections, is based on evidence derived from healthy middle-aged men that has been applied to the general population, including children, women, and the elderly.¹

The problem? This approach led to a deficiency in the understanding of the role of biological sex, including sex chromosomes and hormones, on health and disease states and how this affects the delivery of medical care for men and women. Outcomes data suggest that women have been adversely affected. Women have higher mortality rates than men after a myocardial infarction.² Women are more likely to have poorer outcomes than men after aortic surgery.³ Women have worse outcomes than men when admitted with community-acquired pneumonia.⁴ Women are twice as likely to experience a stroke after surgery than men.³ These sex differences seem endless, yet the factors underlying disparate outcomes remain unknown.

To understand what causes these discrepancies, one must work backward from the outcome and ask: Are women less likely to receive lifesaving medication? Are women less likely to undergo the necessary diagnostic testing as men with the same condition? Is it harder to recognize women's presentation and symptoms when care providers are looking for male patterns of disease? Are there important differences in communication based on societal and cultural gender roles? Or are there cellular and hormonal differences in pathophysiology of disease states between men and women that are not well understood? Are treatments as effective in women as they are in men? As evidence continues to evolve, we must also consider how sex may interact with other factors such as age, race, socioeconomic class, and gender to influence health outcomes.⁵

Let us consider the third leading cause of death in the United States behind cancer and heart disease: cardiac arrest.⁶ This condition is an important cause of morbidity and mortality that strikes more than 450,000 people each year, killing the vast majority of those individuals. Male athletes experience a greater number of sudden cardiac death during exercise, with some estimates as high as 80% compared with women.⁷

Wide disparities in cardiac arrest outcomes have been documented, many due to variations in patient demographic characteristics and health status and system-level factors affecting the quality and availability of care, such as rates of cardiopulmonary resuscitation knowledge and comfort in performance among bystanders. For instance, women who experience an out-of-hospital cardiac arrest (OHCA) receive bystander cardiopulmonary resuscitation less often than men due to general public fears regarding inappropriate touching, accusations of sexual assault, and fear of causing injury in women.⁸ Moreover, women presenting to the hospital with cardiac arrests are then less likely to undergo therapeutic procedures, including coronary angiography, percutaneous coronary interventions, and targeted temperature management.⁹ Despite trends in improving survival after cardiac arrest over 10 years, women continue to have higher in-hospital mortality compared with men.

Sex and gender differences in physiology, disease risk, and health outcomes have been increasingly recognized; however, data are still lacking regarding the influence of sex and gender on cardiac arrest epidemiology, treatment, and outcomes. This Specialty Update in *Clinical Therapeutics* is dedicated to Sex and Gender Differences in Cardiovascular Resuscitation, Recovery, and Survival. Each invited article examines conditions that require intensive



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resuscitation, the moments that make the difference in life and death, to shine a light upon important differences between men and women.

OHCA affects >350,000 individuals annually in the United States, with women making up one third of this number.¹⁰ In the study “Sex Differences in ‘Do Not Attempt Resuscitation’ Orders After Out-of-Hospital Cardiac Arrest and the Relationship to Critical Hospital Interventions,” Perman and colleagues¹¹ explored the knowledge that women who experience OHCA have similar rates of survival to hospital admission as men; however, women are less likely to survive to hospital discharge. The study authors found that female survivors of cardiac arrest are significantly more likely than men to have a Do Not Attempt Resuscitation (DNAR) order established within the first 24 h of in-hospital treatment. The establishment of a DNAR is associated with patients undergoing fewer procedures than individuals who do not have a DNAR established. Given that patients who have a DNAR receive less aggressive intervention after cardiac arrest, it is possible that an early DNAR may contribute to sex differences in survival to hospital discharge.

Another serious condition that often requires intensive resuscitation measures is sepsis, the body's inflammatory response to infection. Sepsis affects >1.5 million patients annually in the United States and accounts for >500,000 emergency department visits yearly.¹² “Clinical and Demographic Parameters of Patients Treated Using a Sepsis Protocol” by Ward and colleagues¹³ attempts to clear up the conflicting results in the literature regarding sex and gender differences in sepsis mortality. This multisite study assesses differences in demographic characteristics, clinical variables, and therapy between men and women treated for sepsis in a hospital setting. Female subjects were more likely to have a genitourinary cause for sepsis and less likely to arrive by ambulance, but there were no differences in in-hospital mortality when analyzed according to sex.

Finally, “When the Female Heart Stops: Sex and Gender Differences in Out of Hospital Cardiac Arrest Epidemiology and Resuscitation” by Jarman and colleagues¹⁴ (including myself) with expertise in resuscitation present a review of the literature regarding the significance of sex and gender in the epidemiology and resuscitation of OHCA victims. The overall incidence of treated OHCA in the United States is 52.1 persons per 100,000 population.¹⁵ Female patients tend to be older, experience cardiac arrest in private locations, and have fewer initial shockable rhythms such as ventricular fibrillation/ventricular tachycardia. Despite standardized algorithms for the management of OHCA, emergency medical services providers differ in their approach to the treatment of OHCA in women and men, with women receiving fewer evidence-based interventions (including advanced cardiac life support medications, percutaneous coronary intervention, and targeted temperature management).

This Specialty Update for Women's Health and Gender Medicine highlights sex- and gender-based health disparities in conditions that have high public health significance; that is, the medical care surrounding resuscitation in acutely ill patients. Recognizing the areas in which the delivery of evidence-based optimal medical care falls short based on sex and gender can lead to the development of effective quality improvement interventions.

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