Commentary

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

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ABSTRACT

Sex- and gender-based differences are emerging as clinically significant in the epidemiology and resuscitation of patients with out-of-hospital cardiac arrest (OHCA). Female patients tend to be older, experience arrest in private locations, and have fewer initial shockable rhythms (ventricular fibrillation/ventricular tachycardia). Despite standardized algorithms for the management of OHCA, women are less likely to receive evidence-based interventions, including advanced cardiac life support 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 patients experience higher mortality from OHCA, prompting the need for sex-specific research. (Clin Ther. 2019;41:1013−1019) © 2019 Published by Elsevier Inc.

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INTRODUCTION

In recent years, sex- and gender-based research has grown exponentially and has found 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 among these 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 cause of cardiac disease—related death and 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 nonobstructive 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 do men, and present with non−ST elevation myocardial infarction (MI) more often than ST elevation MI.[5] Women, particularly young women, have higher mortality both acutely and in the long term following an acute MI.[6,7] As with the development of CAD, female

patients with OHCA tend to be older and have comorbidities, making them more susceptible to pulseless electrical activity and asystolic rhythms of cardiac arrest. The macrovascular CAD in men results in proportionately 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 the characteristics of cardiac arrest show significant variation by sex.

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

Prehospital Setting

The overall prevalence of treated OHCA in the United States is 52.1 persons per 100,000 population,[8] but the prevalence and characteristics of arrest vary dramatically by sex. OHCA is more common in men than in women.[9–12] In the Framingham Heart Study, which followed up a cohort of study participants over a course of 26 years, approximately one third of individuals with cardiac arrest in that 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

experience OHCA in a public location.[9] Although the reasons for this finding are unclear, data suggest that women delay seeking medical care when experiencing an acute MI.[14–16]

Rapid, high-quality prehospital care, including cardiopulmonary resuscitation (CPR) administered first by bystanders and continued by emergency medical services (EMS) personnel, is crucial in survival and neurologic recovery in OHCA.[17] Women and men experience similar rates of bystander-administered CPR overall.[9] However, when stratified by location, women are less likely than men to receive bystander-administered CPR in a public location but similarly likely to receive it in a private location.[12] This disparity likely represents an effect of gender, and recent evidence suggests that this finding 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 for injury from CPR to be greater in female than in male patients. CPR classes also use male mannequins and focus on the technical aspects of CPR, rather than the psychosocial aspects of providing CPR.

Standardized protocols on the care of patients with OHCA assume the majority of cardiac arrests to be cardiac in origin and do not take into account patient sex, although the protocols do include a provision for reversible causes (eg, hypoxia, hypothermia). Despite this, EMS providers differ in their approaches to the treatment of OHCA in women versus men. After adjustment for patient and arrest characteristics, including age, witnessed arrest, public location, bystander-administered CPR, and first known rhythm of VT/VF, 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 (odds ratio [OR] = 0.78; 95% CI, 0.71−0.86) but similarly likely to receive successful advanced airway management (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% CI, 0.61−0.75), even

after adjustments 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 by these EMS agencies; therefore, the true magnitude of sex-based differences may have been underestimated. While most studies attempt to control for protocol changes over time, it is possible that temporal and regional differences in EMS protocols may have contributed to some of the effects seen through the study periods.

However, these trends are modifiable. In one statewide study from North Carolina, women were less likely to receive bystander-administered CPR and first-responder–administered defibrillation at baseline.[21] Following a statewide, multifaceted intervention to improve care and outcomes in patients with OHCA, rates increased substantially and were comparable in men and women. Unfortunately, these improvements in prehospital care in 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 experience OHCA tend to be older, arrest from nonshockable initial rhythms, have non witnessed events, and have lower rates of bystander-administered CPR.[12,23–26] Despite the aforementioned factors, studies have shown that women survive to hospital admission at similar to higher rates in comparison to men.[25,27,28] While data on survival and neurologically intact survival are conflicting, 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 among a cohort of patients who have experienced arrest due to ventricular dysrhythmia (pulseless VT/VF) (49.4% vs 45.6%; $P < 0.001$).[31] In a recent study by Bosson et al,[11] women had higher mortality, had worse neurologic outcomes, and received less postarrest

intervention in unadjusted models. However, after adjustment for these notable differences, sex was not associated with worse outcomes in comparison to men; thus, sex-related differences in survival may be a function of inadequate application of evidence-based interventions. Outcomes data also vary widely by age, which may explain the conflicting data across all age groups. Understanding sex-based differences in critical care treatments and interventions in patients with cardiac arrest may help us to understand sex-based differences in survival outcomes.

Currently, practice guidelines on cardiac arrest are uniform between the sexes. Algorithmic advanced cardiac life support should be provided in all patients who present in cardiac arrest. In 2015, the American Heart Association released a novel algorithm for maternal resuscitation, emphasizing manual left uterine displacement and perimortem cesarean section if resuscitative efforts are unsuccessful after 4 min.[32] This addition marks the first sex-specific alternative to standard advanced cardiac life support measures in cardiac arrest.

Postarrest treatment bundles have been developed to impart optimal outcomes in patients who experience 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, receive early invasive cardiac testing. Similar to women who experience MI,[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 (OR = 0.71; 95% CI, 0.69–0.73) in comparison to men (adjusted analysis).[31]

Targeted temperature management (TTM), a neuroprotective strategy utilizing therapeutic hypothermia, has been shown to impart better neurologic recovery and is now a level 1 American Heart Association indication for comatose survivors of cardiac arrest, regardless of initial rhythm.[36] Recent literature has shown that women who experience cardiac arrest receive less TTM when compared to men (OR = 0.90; 95% CI, 0.86–0.94), even after control for initial rhythm.[31] Similarly, Bosson et al[11] found that 33% of women received TTM, in contrast to 40% of men. Further investigation is necessary to explore potential differences in hemodynamic optimization as an additional critical care intervention

that might potentially explain differences in outcomes after cardiac arrest.

An integral aspect of postarrest management is neuroprognostication. Guidelines endorse delayed neuroprognostication, recognizing that 72 h after the return of spontaneous circulation is the earliest time that neurologic testing becomes accurate.[36] Despite this guideline, early prognostication occurs[37] and can be associated with decisions on the withdrawal of life-sustaining therapy. Female sex is associated with withdrawal of life-sustaining therapy in post–cardiac arrest patients[38] and, most notably, female sex is associated with a higher prevalence of early (<72 h after return of spontaneous circulation) withdrawal of life-sustaining therapy for neurologic reasons.[39] While these trends have been observed, understanding the role of patient preference or prior wishes cannot be established from large-scale, registry-based studies. To that end, the potential role of implicit sex-based 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 trials on interventions for improving outcomes after cardiac arrest. In several landmark randomized, controlled trials exploring TTM for neuroprotection, women were underrepresented in the treatment arms; in the study by Bernard et al,[40] women represented 42%; in the Hypothermia after Cardiac Arrest study,[41] 23%; and in Nielsen et al,[42] 17% of the study participants. An example of a concerning trend is the exclusion of breastfeeding women from enrollment in the HYPERION trial, a randomized, controlled trial that explored the utility of TTM in patients with cardiac arrest from initial nonshockable rhythm.[55] Ensuring adequate enrollment of female study participants is necessary to understand how sex and gender affect outcomes and therapies in cardiac arrest.

Sex Hormone Influences

Despite decades of research and revised guidelines, survival with good neurologic outcome after OHCA remains quite low, at 7.6%.[17] Outcomes may remain poor due to a paucity of mechanistic, basic scientific understanding. Sex influences how patients develop, present with CAD, and respond to treatment. Yet our understanding of the cascade of events is incomplete, with gaps in our understanding of sex-based

influences on the mechanisms of gene transcription, cell signaling, and cell death 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-based 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 peroxidation and free-radical formation.[45] In animal studies, estrogen has shown a protective effect in the brain by reducing neural injury, while testosterone increased neural injury.[46] Noppens et al[47] showed that E2 exerted neuroprotective effects mediated particularly via estrogen receptor β in specific brain regions. Estrogen has also been shown to have a protective effect in the kidney. E2 given after post–cardiac arrest resuscitation was associated with 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, which 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, an animal model (juvenile mice) of cardiac arrest indicated that although TTM conferred synaptic plasticity in both sexes, male mice required a deeper level of TTM for similar protection.[49] Such findings highlight the need for sex-specific personalized therapy.

The literature on stroke and sepsis support the concept of a dichotomous response between male and female animals that involves both sex hormone–specific processes and other, intrinsic, non–sex hormone processes.[50,51] In sepsis, female sex hormones augment immune-mediated responses, whereas male sex hormones have been shown to be immunosuppressive, thus advocating that hormonal status should be taken into account in the treatment of sepsis.[45] Similar exploration in cardiac arrest is necessary in order to improve survival and minimize the public health burden of sudden cardiac death.

Research Priorities

Despite observational data from animals and humans that demonstrate benefits of estrogen in stroke and cardiovascular disease, clinical trials such as the Women's Health Initiative have failed to show that exogenous estrogens provide protection in cardiovascular disease.[52] 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 models for a better understanding of the interaction of estrogen loss and aging on cardiomyocytes. If we are to make larger strides in neurologically intact survival after cardiac arrest, further investment in proteomics studies is needed to investigate sex- and gender-based influences on molecular processes, biomarkers, clinical outcomes, and therapeutic responses.[53]

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 to mitigate this limitation. Future animal and clinical studies on cardiac arrest need to consider treatments that modify the sex hormone profile and its effect on neurologic outcomes. Consensus statements have noted the dearth of information on sex-based differences in both acute coronary syndromes and post–cardiac arrest resuscitation, and have 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-based 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 from the data discussed here that sex and gender are 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 biological sex- and gender-based influences in the pathophysiology of disease, treatment rendered, and response to treatment. Sex-specific research has improved outcomes in women with acute coronary syndromes and acute MI and has fostered sex-specific treatment considerations. A similar research focus on

post-cardiac arrest resuscitation can do the same. Understanding and embracing sex- and gender-based differences in OHCA are key in providing appropriate and personalized resuscitative care both inside and outside the walls of the hospital, to ultimately improve survival in both men and women. As we move toward a more individualized approach to patient care, information about a patient's sex and gender should be considered as important determinants of disease, particularly with regard to the resuscitation of patients with cardiac arrest.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

REFERENCES

1. *Leading Causes of Death in Females United States, 2015 [Centers for Disease Control and Prevention website]*; 2018. Available at: https://www.cdc.gov/women/lcod/2015/index.htm. Accessed February 21, 2019.

2. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001;104:2158–2163.

3. Coute RA, Nathanson BH, Panchal AR, et al. Disability-adjusted life years following adult out-of-hospital cardiac arrest in the United States. *Circ Cardiovasc Qual Outcomes*. 2019;12, e004677.

4. Soffler M, Safdar B. It's not all chest pain: sex and gender in acute care cardiology. In: McGregor A, Becker B, eds. *Sex and Gender in Acute Care Medicine*. New York, NY: Cambridge University Press; 2016:6–23.

5. Safdar B, Nagurney JT, Anise A, et al. Gender-specific research for emergency diagnosis and management of ischemic heart disease: proceedings from the 2014 academic emergency medicine consensus conference cardiovascular research workgroup. *Acad Emerg Med*. 2014;21:1350–1360.

6. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. *N Engl J Med*. 1999;341: 217—225.

7. Vaccarino V, Krumholz HM, Yarzebski J, Gore JM, Goldberg RJ. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med*. 2001;134: 173—181.

8. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA*. 2008;300:1423 —1431.

9. Mumma BE, Umarov T. Sex differences in the prehospital management of out-of-hospital cardiac arrest. *Resuscitation*. 2016;105:161—164.

10. Casey SD, Mumma BE. Sex, race, and insurance status differences in hospital treatment and outcomes following out-of-hospital cardiac arrest. *Resuscitation*. 2018;126:125—129.

11. Bosson N, Kaji AH, Fang A, et al. Sex differences in survival from out-of-hospital cardiac arrest in the era of regionalized systems and advanced post-resuscitation care. *J Am Heart Assoc*. 2016;5, e004131.

12. Blewer AL, McGovern SK, Schmicker RH, et al. Gender disparities among adult recipients of bystander cardiopulmonary resuscitation in the public. *Circ Cardiovasc Qual Outcomes*. 2018;11, e004710.

13. Schatzkin A, Cupples LA, Heeren T, Morelock S, Kannel WB. Sudden death in the Framingham Heart Study. Differences in incidence and risk factors by sex and coronary disease status. *Am J Epidemiol*. 1984;120:888—899.

14. Nguyen HL, Gore JM, Saczynski JS, et al. Age and sex differences and 20-year trends (1986 to 2005) in prehospital delay in patients hospitalized with acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2010;3:590—598.

15. Bugiardini R, Ricci B, Cenko E, et al. Delayed care and mortality among women and men with myocardial infarction. *J Am Heart Assoc*. 2017;6, e005968.

16. Walsh MN, Joynt KE. Delays in seeking care: a women's problem? *Circ Cardiovasc Qual Outcomes*. 2016;9(suppl):S97—S99.

17. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2010;3: 63—81.

18. Perman SM, Shelton SK, Knoepke C, et al. Public perceptions on why women receive less bystander cardiopulmonary resuscitation than men in out-of-hospital cardiac arrest. *Circulation*. 2019;139:1060—1068.

19. Kirves H, Skrifvars MB, Vahakuopus M, Ekstrom K, Martikainen M, Castren M. Adherence to resuscitation guidelines during prehospital care of cardiac arrest patients. *Eur J Emerg Med*. 2007;14:75—81.

20. Lewis JF, Zeger SL, Li X, et al. Gender differences in the quality of EMS care nationwide for chest pain and out-of-hospital cardiac arrest. *Women's Health Issues*. 2018;29:116—124.

21. Malta Hansen C, Kragholm K, Dupre ME, et al. Association of bystander and first-responder efforts and outcomes according to sex: results from the North Carolina HeartRescue Statewide Quality Improvement Initiative. *J Am Heart Assoc*. 2018;7, e009873.

22. Out-of-Hospital chain of survival [American heart association website]. Available at: https://cpr.heart.org/AHAECC/CPRAndECC/AboutCPRFirstAid/CPRFactsAndStats/UCM_475731_Out-of-hospital-Chain-of-Survival.jsp. Accessed February 3, 2019.

23. Safdar B, Stolz U, Stiell IG, et al. Differential survival for men and women from out-of-hospital cardiac arrest varies by age: results from the OPALS study. *Acad Emerg Med*. 2014;21:1503—1511.

24. Morrison LJ, Schmicker RH, Weisfeldt ML, et al. Effect of gender on outcome of out of hospital cardiac arrest in the Resuscitation Outcomes Consortium. *Resuscitation*. 2016;100:76—81.

25. Ahn KO, Shin SD, Hwang SS. Sex disparity in resuscitation efforts and outcomes in out-of-hospital cardiac arrest. *Am J Emerg Med*. 2012;30: 1810—1816.

26. Akahane M, Ogawa T, Koike S, et al. The effects of sex on out-of-hospital cardiac arrest outcomes. *Am J Med*. 2011;124:325—333.

27. Bray JE, Stub D, Bernard S, Smith K. Exploring gender differences and the "oestrogen effect" in an Australian out-of-hospital cardiac arrest population. *Resuscitation*. 2013;84: 957—963.

28. Hasan OF, Al Suwaidi J, Omer AA, et al. The influence of female gender on cardiac arrest outcomes: a systematic review of the literature. *Curr Med Res Opin*. 2014;30:2169—2178.

29. Topjian AA, Localio AR, Berg RA, et al. Women of child-bearing age have better inhospital cardiac arrest survival outcomes than do equal-aged men. *Crit Care Med*. 2010;38: 1254—1260.

30. Lindgren E. Gender differences in outcome and post resuscitation care after out-of-hospital cardiac arrest. Analysis of the LINC trial. *Resuscitation*. 2015;96.

31. Kim LK, Looser P, Swaminathan RV, et al. Sex-based disparities in incidence, treatment, and outcomes of cardiac arrest in the United States, 2003-2012. *J Am Heart Assoc*. 2016;5, e003704.

32. Jeejeebhoy FM, Zelop CM, Lipman S, et al. Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. *Circulation*. 2015;132:1747—1773.

33. Stub D, Schmicker RH, Anderson ML, et al. Association

between hospital post-resuscitative performance and clinical outcomes after out-of-hospital cardiac arrest. *Resuscitation*. 2015;92:45—52.

34. Chandra NC, Ziegelstein RC, Rogers WJ, et al. Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. *Arch Intern Med*. 1998;158:981—988.

35. D'Onofrio G, Safdar B, Lichtman JH, et al. Sex differences in reperfusion in young patients with ST-segment-elevation myocardial infarction: results from the VIRGO study. *Circulation*. 2015;131:1324—1332.

36. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132(suppl):S465—S482.

37. Perman SM, Kirkpatrick JN, Reitsma AM, et al. Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia. *Crit Care Med*. 2012;40:719—724.

38. Grossestreuer AV, Gaieski DF, Abella BS, et al. Factors associated with post-arrest withdrawal of life-sustaining therapy. *Resuscitation*. 2017;110:114—119.

39. Elmer J, Torres C, Aufderheide TP, et al. Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. *Resuscitation*. 2016;102:127—135.

40. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557—563.

41. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002;346:549—556.

42. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med*. 2013;369:2197—2206.

43. Knowlton AA, Korzick DH. Estrogen and the female heart. *Mol Cel Endocrinol*. 2014;389:31—39.

44. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. *Biol Sex Differ*. 2017;8:33.

45. Pavon N, Cabrera-Orefice A, Gallardo-Perez JC, et al. In female rat heart mitochondria, oophorectomy results in loss of oxidative phosphorylation. *J Endocrinol*. 2017;232:221—235.

46. Nakano T, Hurn PD, Herson PS, Traystman RJ. Testosterone exacerbates neuronal damage following cardiac arrest and cardiopulmonary resuscitation in mouse. *Brain Res*. 2010;1357:124—130.

47. Noppens RR, Kofler J, Grafe MR, Hurn PD, Traystman RJ. Estradiol after cardiac arrest and cardiopulmonary resuscitation is neuroprotective and mediated through estrogen receptor-beta. *J Cereb Blood Flow Metab*. 2009;29:277—286.

48. Ikeda M, Swide T, Vayl A, Lahm T, Anderson S, Hutchens MP. Estrogen administered after cardiac arrest and cardiopulmonary resuscitation ameliorates acute kidney injury in a sex- and age-specific manner. *Crit Care*. 2015;19:332.

49. Dietz RM, Deng G, Orfila JE, Hui X, Traystman RJ, Herson PS. Therapeutic hypothermia protects against ischemia-induced impairment of synaptic plasticity following juvenile cardiac arrest in sex-dependent manner. *Neuroscience*. 2016;325:132—141.

50. Herson PS, Palmateer J, Hurn PD. Biological sex and mechanisms of ischemic brain injury. *Transl Stroke Res*. 2013;4:413—419.

51. Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: cardiovascular and immunological aspects. *Virulence*. 2014;5:12—19.

52. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*. 1998;280:605—613.

53. Baetta R, Pontremoli M, Martinez Fernandez A, Spickett CM, Banfi C. Proteomics in cardiovascular diseases: unveiling sex and gender differences in the era of precision medicine. *J Proteomics*. 2018;173:62—76.

54. Wigginton JG, Perman SM, Barr GC, et al. Sex- and gender-specific research priorities in cardiovascular resuscitation: proceedings from the 2014 academic emergency medicine consensus conference cardiovascular resuscitation research workgroup. *Acad Emerg Med*. 2014;21:1343—1349.

55. Lascarrou JB, Meziani F, Le Gouge A, et al. Therapeutic hypothermia after nonshockable cardiac arrest: the HYPERION multicenter, randomized, controlled, assessor-blinded, superiority trial. *Scand J Trauma Resusc Emerg Med*. 2015;23:26. https://doi.org/10.1186/s13049-015-0103-5.

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