Published in final edited form as:

Pediatr Crit Care Med. 2015 October ; 16(8): 779–780. doi:10.1097/PCC.0000000000000528.

Pediatric out-of-hospital cardiac arrest outcomes: a case of male/female inequality?

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In pediatric medicine, few conditions can compare with the high morbidity and mortality attributable to out-of-hospital cardiac arrest (OHCA). Pioneering work in cardiopulmonary resuscitation (CPR) procedures by Dr. Peter Safar and training of emergency medical services (EMS) personnel by Dr. Nancy Caroline were early contributions towards improving outcomes for these patients^{1,2}. Subsequently, development of evidenced-based basic and pediatric advanced life support guidelines, growth of EMS systems, better post-resuscitation care, and introduction of long-term rehabilitation programs for children with brain injury have led to improved outcomes in some cardiac arrest patients³. In addition, research using animal and cell culture models have broadened our understanding of the pathophysiologic mechanisms underlying brain injury and multi-organ dysfunction syndrome after cardiac arrest. Ultimately, however, the most important gauge of our collective progress is to evaluate temporal morbidity and mortality trends, to assess if the sum of these efforts is having the desired impact and inform us of opportunities to do better.

To date, epidemiologic studies of pediatric OHCA^{4–9} have been fairly consistent in terms of predictors of survival: older age, shockable initial rhythm, bystander CPR, and shorter time to EMS arrival are associated with improved outcomes. Remarkably variable, however, are the regional outcomes of OHCA, with survival ranging from < 5% in some studies to > 20% in others (although some of the differences may be due to non-uniform inclusion criteria). Studies that have investigated OHCA survival trends over time have generally been from a single center or hospital system and may have limited generalizability. As a result, comparing epidemiologic data computed from various studies over time, when taken from different countries or regions, is fraught with limitations.

Dr. Simon disclosed that he does not have any potential conflicts of interest.

In this issue of *Pediatric Critical Care Medicine*, Gelberg et al.¹⁰ report improved survival over the past two decades in pediatric and young adult patients after OHCA in Sweden. This population-based, prospective observational study utilized data from the Swedish Cardiopulmonary Resuscitation Registry between 1992 and 2012. Investigators analyzed 2,864 cases of OHCA in patients ≤ 35 years of age who had cardiac arrests that were unwitnessed by EMS crew. The primary outcomes evaluated were 30 days survival and cerebral function as measured by cerebral performance categories (CPC) score. Remarkably, they found that in subjects ≤ 21 years of age overall survival more than doubled from ~6% to 14% between 1992–2005 and 2006–2012. In young adult patients (aged 22 – 35 years), a group rarely analyzed independently from older adults, overall survival improved from 6.6% to 10.4% over the same period. In a multivariate analysis of subjects ≤ 21 years old, independent predictors of survival included: older age, male sex, bystander witnessed, shockable rhythm, and fastest arrival EMS. The authors are to be commended for the consistent reporting of neurological outcome after pediatric OHCA. Remarkably, CPC scores at 30 days, which were recorded between 2008 and 2012, was 1 (normal or mild deficit) or 2 (moderate deficit) in 91% of the survivors at 30 days.

Although we can only speculate as to the reason behind the reduction in mortality, it is likely multifactorial; a relatively high rate of bystander CPR (63–81%) and contemporary pre-hospital and post-resuscitation care all likely played a role. Sweden, generally at the forefront of OHCA resuscitation innovation, recently published their experience sending text messages to persons trained in CPR if there is a nearby cardiac arrest victim¹¹.

Aside from age, we would have liked to see how other patient- and resuscitation-related factors changed over the two decades of data collection, particularly in those found to be associated with survival such as etiology of arrest and time to EMS arrival. Additional details about public health initiatives and changes to post-resuscitation care in Sweden that have changed over time would also help to interpret the significant decrease seen in mortality. For example, public education efforts may have improved the quality of bystander CPR^{12,13}. With ~70% of cases of bystander CPR performed, this could have a significant effect on outcomes in this setting.

The second result we wish to highlight from the study by Gelberg et al. is the finding that female patients ≤ 21 years old were more likely to be dead at 30 days than male patients after OHCA (OR 0.45, 95%CI 0.24 – 0.83). To our knowledge, this is a unique finding in any age group. It would be interesting to know if the mortality difference was affected by pubertal status, dividing patients by ≤ 12 years or > 12 years of age, or if other factors affecting survival differed between male and female patients but could not be controlled for in the multivariate model. Other possibilities may have to do with individual genetic make-up, cause of the arrest, or response to injury which may affect outcome.

To recall, the 1993 NIH Revitalization Act required the inclusion of women in NIH-funded clinical research and has led to many important discoveries of gender differences across a spectrum of disease in the pathophysiology and response to therapy. More recently, Drs. Janine Clayton and Francis Collins of the NIH announced plans to support, and in cases require, sex and gender inclusion plans for preclinical research. In the same way that we find

it important to perform pediatric-specific clinical and preclinical research, so must we consider gender differences in our clinical and preclinical work, particularly in our post-pubertal patients. Investigating sex differences in cardiac arrest already has a foundation in the cell culture work by Du et al.¹⁴ who found that male and female neurons responded differently to various cytotoxic challenges to induce apoptosis.

Looking ahead, the preservation of neurologic function through the optimization of initial resuscitation, post-resuscitation care, and rehabilitation will be the greatest driver of improvements to morbidity and mortality from OHCA. Following the leadership of Dr. Peter Safar, the field of pediatric resuscitation research has focused much of the work on developing strategies for neuroprotection. Using pediatric animal models, researchers have begun to characterize the alterations in cerebral blood flow, oxidative signaling, blood brain barrier permeability, inflammation, and cell death mechanisms after asphyxia cardiac arrest.^{15–18} With the recent publication of the Therapeutic Hypothermia and Pediatric Cardiac Arrest (THAPCA) trial¹⁹, investigators have demonstrated that large, multi-center clinical trials can be successfully performed in pediatric OHCA despite a much lower incidence of this pathology in pediatrics compared with the adult population. Thus, the machinery is currently in place to translate work from preclinical studies into interventions that can be tested and used to improve outcomes for pediatric OHCA.

In summary, Gelberg et al. have demonstrated an improvement in mortality after OHCA in children and young adults in Sweden. The morbidity and mortality from pediatric OHCA remains high, but it is evident the collective effort of first responders, emergency and critical care providers, and researchers in basic and clinical resuscitation science is making important progress.

Acknowledgments

Grants/acknowledgment: T32 HD040686 (SWD), K23 NS065132 (ELF), PCORI CER-1310-08343 (ELF), R01HD075760 (MDM), R01NS084604 (MDM)

Copyright form disclosures: Dr. Manole received support for article research from the National Institutes of Health (NIH)(R01HD075760, R01 NS084604). Her institution received grant support from the NIH (NIH R01HD075760, R01NS084604). Ericka L. Fink received support for article research from the NIH and PCORI. Her institution received funding from the NIH and PCORI.

References

1. Safar P, Escarraga LA, Elam JO. A comparison of the mouth-to-mouth and mouth-to-airway methods of artificial respiration with the chest-pressure arm-lift methods. *N Engl J Med*. 1958; 258:671–7. [PubMed: 13526920]
2. Caroline NL. *Emergency Care in the Streets*: Little, Brown. 1979
3. Girotra S, Spertus JA, Li Y, et al. *Circ Cardiovasc Qual Outcomes*. 2013; 6(1):42–9. [PubMed: 23250980]
4. Young KD, Gausche-Hill M, McClung CD, Lewis RJ. A prospective, population-based study of the epidemiology and outcome of out-of-hospital pediatric cardiopulmonary arrest. *Pediatrics*. 2004; 114:157–64. [PubMed: 15231922]
5. Donoghue AJ, Nadkarni V, Berg RA, et al. Out-of-hospital pediatric cardiac arrest: an epidemiologic review and assessment of current knowledge. *Ann Emerg Med*. 2005; 46:512–22. [PubMed: 16308066]

6. Atkins DL, Everson-Stewart S, Sears GK, et al. Epidemiology and outcomes from out-of-hospital cardiac arrest in children: the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. *Circulation*. 2009; 119:1484–91. [PubMed: 19273724]
7. Deasy C, Bernard SA, Cameron P, et al. Epidemiology of paediatric out-of-hospital cardiac arrest in Melbourne, Australia. *Resuscitation*. 2010; 81:1095–100. [PubMed: 20627518]
8. Deasy C, Bray JE, Smith K, et al. Out-of-hospital cardiac arrests in young adults in Melbourne, Australia. *Resuscitation*. 2011; 82:830–4. [PubMed: 21497006]
9. Moler FW, Donaldson AE, Meert K, et al. Multicenter cohort study of out-of-hospital pediatric cardiac arrest. *Crit Care Med*. 2011; 39:141–9. [PubMed: 20935561]
10. Gelberg J, Stromsoe A, Hollenberg J, et al. Improving survival and neurologic function for younger age groups after out-of-hospital cardiac arrest in Sweden - a twenty-year comparison. *Pediatr Crit Care Med*. 2015
11. Ringh M, Rosenqvist M, Hollenberg J, et al. Mobile-Phone Dispatch of Laypersons for CPR in Out-of-Hospital Cardiac Arrest. *N Engl J Med*. 2015; 372:2316–25. [PubMed: 26061836]
12. Idris AH, Guffey D, Pepe PE, et al. Chest compression rates and survival following out-of-hospital cardiac arrest. *Crit Care Med*. 2015; 43:840–8. [PubMed: 25565457]
13. Sutton RM, Case E, Brown SP, et al. A quantitative analysis of out-of-hospital pediatric and adolescent resuscitation quality - A report from the ROC epistry-cardiac arrest. *Resuscitation*. 2015
14. Du L, Bayir H, Lai Y, et al. Innate gender-based proclivity in response to cytotoxicity and programmed cell death pathway. *J Biol Chem*. 2004; 279:38563–70. [PubMed: 15234982]
15. Drabek T, Foley LM, Janata A, et al. Global and regional differences in cerebral blood flow after asphyxial versus ventricular fibrillation cardiac arrest in rats using ASL-MRI. *Resuscitation*. 2014; 85:964–71. [PubMed: 24727136]
16. Tress EE, Clark RS, Foley LM, et al. Blood brain barrier is impermeable to solutes and permeable to water after experimental pediatric cardiac arrest. *Neurosci Lett*. 2014; 578:17–21. [PubMed: 24937271]
17. Ji J, Baart S, Vikulina AS, et al. Deciphering of mitochondrial cardiolipin oxidative signaling in cerebral ischemia-reperfusion. *J Cereb Blood Flow Metab*. 2015; 35:319–28. [PubMed: 25407268]
18. Tang M, Alexander H, Clark RS, et al. Minocycline reduces neuronal death and attenuates microglial response after pediatric asphyxial cardiac arrest. *J Cereb Blood Flow Metab*. 2010; 30:119–29. [PubMed: 19756023]
19. Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med*. 2015; 372:1898–908. [PubMed: 25913022]