The association of epinephrine with outcomes from out-of-hospital cardiac arrest (OHCA) remains poorly understood, despite epinephrine being routinely used in cardiac arrest resuscitation for more than 50 years. Randomized clinical trial evidence has shown that epinephrine increases initial survival but with an increased rate of neurologic injury, although other work has suggested that the benefit of epinephrine is dependent on the timing of administration, with earlier administration during arrest being associated with increased benefit. Whether post–cardiac arrest care using targeted temperature management (TTM), generally with a target of 33 °C or 36 °C, could lessen neurologic injury after epinephrine use in OHCA remains an important question. Although TTM is a widely used mitigation strategy for post–cardiac arrest cerebral injury, randomized clinical trials have called into question whether TTM is effective when compared with careful avoidance of fever after resuscitation. Recent work from multiple teams has suggested that TTM to 33 °C is associated with neurologic survival benefit in subgroups of patients with OHCA with more severe injury. The future development of robust methods to assign individual patients with OHCA to optimal TTM treatment plans is a critical step to improving outcomes. Epinephrine dosage could potentially serve as an early guide for subsequent decisions regarding TTM strategy.

In their cohort study, Yang et al report on a retrospective analysis of OHCA outcomes in Seattle and King County, Washington, to investigate whether post–cardiac arrest TTM was associated with survival benefit in patients who received varying doses of epinephrine during resuscitation efforts. They evaluated an adult nontraumatic cardiac arrest cohort (n = 5253) receiving resuscitation care from 2008 to 2018. Data were collected primarily through review of emergency medical services records, with TTM use and hospital outcomes reported by receiving hospitals. The study's primary outcome was neurologically favorable survival, defined as a Cerebral Performance Category of 1 or 2. The authors first demonstrated an association between larger cumulative epinephrine dose and worse neurologic outcomes, confirming findings from previous work. Neurologically favorable survival decreased with each additional milligram of epinephrine administrated: 75% at 0 mg, 38% at more than 0 to 1 mg, 24% at more than 1 to 2 mg, 17% at more than 2 to 3 mg, 16% at more than 3 to 4 mg, and 15% at more than 4 mg. The study data suggest that TTM attenuates this adverse association, particularly among patients with shockable initial rhythms. After OHCA with shockable rhythms, 31.1% of patients receiving more than 3 to 4 mg of epinephrine achieved a Cerebral Performance Category of 1 or 2 after undergoing TTM as opposed to 18.9% of a comparator group that did not receive TTM. Overall, the use of TTM was associated with improved neurologic survival.

These findings add to the increasing body of work about the potential survival benefit conferred by TTM use in subgroups of OHCA patients, in particular among those with a greater post–cardiac arrest injury severity. The work of Yang et al provides important insight into epinephrine dosage as a quantitative measure, available early during post–cardiac arrest care, that may guide subsequent decision-making regarding TTM use.

This retrospective work has some key limitations. Given that epinephrine is administered every 3 to 5 minutes during OHCA resuscitation care, it is unknown whether TTM acts to mitigate the specific neurologic impact from the drug itself or whether the epinephrine dose is simply a marker of resuscitation duration. This mechanism-related issue may not be of practical relevance during actual resuscitation care, because increased resuscitation duration is also associated with greater injury and
may similarly be useful to guide subsequent care decisions. Although the authors attempted to control for the interaction of epinephrine dose and arrest duration, finding that the epinephrine dose was independently associated with outcomes, this outcome was complicated by a high degree of missing data. A more important limitation rests in the fact that whether patients were treated with TTM was based on clinical decision-making, which could bias the results toward a higher TTM benefit. Practitioners are likely to administer TTM to patients they believe would benefit most from the intervention based on clinical factors during post-cardiac arrest care. This selection process could limit moribund patients from receiving TTM, shifting toward a higher effect size of benefit from TTM use among the patients receiving more than 3 to 4 mg and more than 4 mg of epinephrine. In addition, few data were presented by Yang et al7 regarding post-cardiac arrest care factors, such as timing of care withdrawal or time to administration of TTM therapy, both shown to have important associations with outcomes in patients who have had cardiac arrest. Patients with OHCA in the study cohort were treated at 14 receiving hospitals; it is possible that care practices varied regarding these and other important variables that have been shown to be associated with neurologic outcomes. For patients not treated with TTM, frequency of pyrexia would be a useful measure to have available, given the established evidence that fever is associated with worse neurologic outcomes.

The challenge of prospectively classifying severity of post-cardiac arrest injury remains a major unmet need in resuscitation science and care delivery. Several classification systems have been proposed that take into account clinical factors related to the findings in the current work. For example, Nishikimi et al5 have proposed a post-cardiac arrest OHCA severity score based on 5 factors: initial cardiac rhythm of arrest, witnessed arrest status, initial post-cardiac arrest pH and lactate, and Glasgow Coma Scale motor score. Evaluating how closely epinephrine dosing tracks with these variables would be a useful further analysis to determine whether adding these variables refines the association with TTM benefit or simply recapitulates the association.

It is a well-understood concept throughout medicine, and specifically in critical care, that treatment selection depends on disease severity. Just as not all patients with sepsis benefit from vasopressor therapy but some patients require it, the important work of Yang et al7 adds to the increasing recognition that patients with OHCA cannot be easily bundled under the rubric of a single therapeutic approach. The work ahead will require definition of clinically practical methods to define post-cardiac arrest injury severity to guide decisions for therapies such as TTM, regarding both target temperature and duration of therapy. Although criteria such as initial rhythm, arrest duration, and epinephrine dose are useful surrogates, it would be an important advancement to define physiologic measures that could guide initial decisions as well as ongoing monitoring during care. Whether electroencephalography, cerebral microdialysis, or serologic measures will further this goal remains an active domain of research. A future in which routine measurement of physiologic mechanisms is used to guide post-cardiac arrest care should serve as a key aspirational goal to inform the specific application of therapies such as TTM and ultimately improve brain function and survival among cardiac arrest patients.
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REFERENCES


