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Questioning the Use of Epinephrine to Treat Cardiac Arrest

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THE MOST EXCITING SCIENTIFIC PROGRESS OCCURS WHEN new research challenges conventional wisdom. Even when a medical practice is founded on less-than-perfect scientific data, testing of an established therapy is nearly impossible to justify unless compelling new data lead to questioning of standard care.[1] One example is the use of epinephrine, which has been a cornerstone of cardiac resuscitation and advanced cardiac life support since the 1960s. In this issue of *JAMA*, the report by Hagihara et al, based on one of the largest observational databases of cardiopulmonary resuscitation (CPR) ever assembled, challenges the role of epinephrine drug therapy during cardiac arrest.[2] These new data suggest that epinephrine use may be associated with lower survival and worse neurological outcomes after cardiac arrest.

The original rationale for the use of epinephrine was that this drug increases aortic blood pressure and, thus, coronary perfusion pressure during chest compressions in animals.[3,4] When CPR does not generate coronary perfusion pressure greater than 15 to 20 mm Hg, return of cardiac mechanical activity rarely or never occurs.[5] The ability of epinephrine to increase coronary perfusion pressure during CPR has been confirmed in humans.[6] Thus, administering epinephrine during CPR increases the probability of restoring cardiac activity with pulses, which is an essential intermediate step toward long-term survival. The original studies in the 1960s in dogs defined the standard 1-mg dose of epinephrine that has been used with no weight adjustment or interspecies comparison for adult patients ever since.[3,4]

Restoring pulses after cardiac arrest appears to be an immediate step toward recovery but does not guarantee good patient outcomes. During the last decade, induced hypothermia and integrated plans of care have increased the proportion of patients hospitalized after CPR who survive to hospital discharge.[7] These experiences have raised expectations that resuscitation therapies should improve not just short-term outcomes such as return of pulses but also longer-term and patient-centered outcomes such as functional status and quality of life.[8] The study by Hagihara et al surpasses many prior reports by having complete 1-month survival and functional status data, measured by Cerebral Performance Category (CPC) and Outcome Performance Category (OPC). The CPC and OPC ordinal scales describe the global functioning of patients. Patients with CPC or OPC scores of 1 or 2 can return to their lives and families, whereas patients with CPC or OPC scores of 3 or higher require long-term care and may not even be conscious.

Even the raw numbers in this report show that prehospital administration of epinephrine, despite increasing the rates of return of pulses (18% vs 5%), is associated with a more modest increase in the number of patients alive after 1 month (5.4% vs 4.7%) and lower rates of good functional status, defined as a CPC of 1 to 2 (1.4% vs 2.2%). When adjusted for important covariates or when using propensity-matched cases, the odds of both 1-month survival and better functional status were markedly lower in epinephrine-treated patients (odds ratios, 0.21-0.71). These findings were confirmed in various sensitivity analyses that accounted for in-hospital epinephrine use and CPR duration. Therefore, the association of prehospital epinephrine with worse meaningful outcomes appears to be real and robust.

If these observations are true, prehospital epinephrine use must increase morbidity and mortality after restoration of pulses to a degree that more than offsets its short-term benefits. This paradoxical effect may be related to its mechanism of action. Epinephrine increases CPR-generated aortic pressures via α-adrenergic–mediated vasoconstriction. Thus, epinephrine increases coronary perfusion pressure by decreasing blood flow to all other organs, an effect that may persist after restoration of pulses. Epinephrine impairs cerebral microcirculation during and after CPR in the laboratory.[9] Likewise, the total dose of epinephrine is associated with impaired tissue oxygen utilization and impaired lactate clearance for hours after CPR in humans.[10] These data suggest that epinephrine provides a short-term gain for the heart by incurring a metabolic debt from the body and brain. This debt may be too great for many patients.

Additional post-CPR adverse effects of epinephrine may include β-adrenergic stimulation, which promotes dys-

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rhythmias and increases myocardial oxygen demand. Also, epinephrine activates platelets and coagulation.[11] Inducing a prothrombotic state may exacerbate myocardial ischemia, which is the leading cause of cardiac arrest.[12]

Previous observational studies have found that increasing epinephrine dosage was associated with worse survival or neurological outcome after cardiac arrest.[13,14] However, these studies have had limited influence on practice because sicker patients who did not respond to therapy systematically received more epinephrine. The study by Hagihara et al spans a period during which Japan deployed epinephrine as "standard therapy." Thus, drug administration by emergency technicians was introduced into an already advanced health care system because of a policy change rather than a change in system capabilities. By virtue of having such a large database, the authors were also able to match cases and controls for duration of resuscitation, transport times, and clinical characteristics, directly addressing the limitations of prior studies. This is the best comparison of outcomes likely to be achieved in an observational study.

Randomized clinical trial data also offer no support for a beneficial effect of epinephrine on patient-oriented outcomes. Doses of epinephrine above 1 mg produced no incremental increase in survival to hospital discharge, even when these doses increased the rate of return of pulses.[15,16] Two recent randomized trials found no increase in survival from epinephrine administration during out-of-hospital cardiac arrest despite a short-term increase in return of pulses. The first trial compared survival when out-of-hospital cardiac arrest patients were allowed to have intravenous drugs from paramedics vs no intravenous drugs.[17,18] The second trial compared survival when patients received standard 1-mg boluses of epinephrine vs placebo.[19] Reflecting the reluctance to abandon traditional therapies, out-of-hospital emergency prehospital personnel in both studies were reluctant to withhold drugs or epinephrine during cardiac arrest during the trials and resumed use of epinephrine after the trials as standard treatment despite the absence of benefit during the trial.

The usual argument to give repeated doses of epinephrine during CPR has been that restoring pulses is an essential step toward long-term survival. If pulses are restored, then perhaps better intensive care can reverse the damage or restore the deficits incurred by increasing blood flow to the heart at the expense of other organs. Hagihara et al were not able to assess in-hospital intensive care, but the authors suggest that intensive care was fairly constant during the study period. In addition, the persistent use of epinephrine has been reinforced because some patients do recover after administration of this drug. Future research will need to identify whether there are subsets of patients for whom epinephrine administration is in fact beneficial.

Should clinicians stop using epinephrine during CPR based on the findings reported by Hagihara et al? There probably will never be a larger observational study of this topic. The exciting development is that these data create equipoise about the current standard of resuscitation care. The best available observational evidence indicates that epinephrine may be harmful to patients during cardiac arrest, and there are plausible biological reasons to support this observation. However, observational studies cannot establish causal relationships in the way that randomized trials can.

Thus, properly evaluating this traditional therapy now seems necessary and timely and should consist of a rigorously conducted and adequately powered clinical trial comparing epinephrine with placebo during cardiac arrest. Such a trial has previously seemed unethical, and investigators who have attempted to perform this comparison have received unwarranted criticism in their communities.[17,19] While awaiting results of such a definitive trial, physicians and other practitioners involved in cardiac resuscitation must consider carefully whether continued use of epinephrine is justified.

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Assessing the Value of "Discretionary" Clinical Care

The Case of Anesthesia Services for Endoscopy

Lee A. Fleisher, MD

As societal desire to bend the health care cost curve mounts, there is increasing attention to determining the appropriateness and value of clinical interventions. Procedures and other types of tests performed in settings not deemed appropriate by relevant professional societies raise concern about low value and unnecessary spending.[1] It is postulated that the magnitude of inappropriate use is such that reduction of low value care and elimination of no value care could lead to a marked reduction in overall health care spending. In this context, the study reported in this issue of *JAMA* by Liu and colleagues evaluating the provision of anesthesia care for low-risk patients undergoing colonoscopy and endoscopic procedures in the United States deserves careful consideration.[2]

The authors used available insurance claims and Medicare claims between 2003 and 2009 to estimate the utilization of anesthesia services (in contrast with sedation typically provided by nurses) and total costs among low-risk patients. The payment estimates for anesthesia services include both insurer payments to physicians and co-payments or deductibles from patients. As a means of highlighting the discretionary nature of the services, the investigators studied changes in utilization over time and between different geographic locations. The proportion of gastrointestinal procedures performed with anesthesia services increased from approximately 14% in 2003 to more than 30% in 2009, with wide geographic variation in the use of anesthesia services. The lowest use was in the West (Medicare fee-for-service sample, 14.0%; and commercially insured sample, 12.6% in 2009), and the highest use was in the Northeast (Medicare sample, 47.5%; commercially insured sample, 59.0% in 2009). The absolute increases were most profound in the commercial insurance group, although the percentage increase in gastrointestinal procedure use was similar between Medicare and commercial insurers. The associated spending on anesthesia services amounted to an estimated $1.1 billion in 2009.

In assessing the value of anesthesia services for colonoscopy and endoscopy, a broad set of potential outcomes and costs should be considered. Use of anesthesia services offers the opportunity for deeper sedation or general anesthesia with increased physiological monitoring compared with the lighter or more moderate sedation typically provided by nurses under the direct supervision of the endoscopist. There are several reasons endoscopists might prefer to use anesthesia services. One reason is that anesthesiologists and anesthetists provide deep sedation or general anesthesia as opposed to moderate sedation, which would potentially allow for the examination to be completed in a shorter time. There is also some suggestion that provision of deep sedation or general anesthesia allows for a more complete examination in some patients and may improve detection of disease, although a randomized trial has questioned this assumption and therefore this rationale remains speculative.[3,4]

A second reason may be related to patient acceptance. Although it is difficult to conclusively demonstrate a link between procedure volume and anesthesia services, patient acceptance of endoscopy and colonoscopy may be directly related to the assurance of deep sedation or general anesthesia for the procedure, as the authors indicated. Patients may request general anesthesia or deep sedation because they may be unwilling to undergo the procedure otherwise. Strategies that increase patient adherence with screening guidelines may be cost-effective if more patients are screened and treated with a lower total cost of treating a disease. Given recent studies, this might provide a financial justification for anesthesia for colonoscopy but not

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