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EDITORIAL COMMENT

Management of Refractory Ventricular Fibrillation

Extracorporeal Membrane Oxygenation or Epinephrine?*

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Cardiac arrest is defined as cessation of cardiac mechanical activity confirmed by the absence of signs of circulation. Often this occurs in the out-of-hospital setting, and is commonly referred to as out-of-hospital cardiac arrest (OHCA). About 20% of such patients have a first recorded rhythm that is shockable by a defibrillator (i.e., ventricular fibrillation [VF] or pulseless ventricular tachycardia). Of those who have bystander-witnessed arrest with a shockable rhythm, only 36% survive to hospital discharge (1). A subset of those who present with VF do not respond to early defibrillation. For example, about 10% of patients with OHCA may have refractory (or recurrent) VF, defined as VF still present after 5 shocks (2). Many patients with out-of-hospital VF have acute coronary occlusion that can be treated by emergency coronary angiography and percutaneous coronary intervention (PCI) (3).

Commonly used treatments for patients with OHCA combine cardiopulmonary resuscitation (CPR) and early defibrillation by bystanders, with advanced cardiac life support by emergency medical services providers that includes CPR, defibrillation, and intravenous (IV) drugs, and post-resuscitation care in hospital. Application of an automated external defibrillator by a layperson before the arrival of emergency medical services providers on scene (4), briefer time from the call for assistance to the arrival of emergency medical services providers on scene (5–10), and better quality of CPR (11–18) are associated with improved outcomes. Importantly, no hospital-based therapy other than induced hypothermia applied to achieve target temperature in <8 h has been demonstrated in trials to improve outcomes in patients with OHCA caused by VF (19,20). In a trial in which patients achieved their target temperature more slowly than those that showed induced hypothermia improved outcomes, the benefit of induced hypothermia was less clear (21). The large variation in survival after OHCA between communities (22), and recent improvement in outcomes in multiple communities (23–25), has renewed interest in improving outcomes after OHCA.

One technique that is promulgated to support patients with refractory cardiac arrest is the use of cardiopulmonary bypass during attempted resuscitation (26). This consists of emergent cannulation of a large vein and artery, then initiation of venoarterial extracorporeal circulation and oxygenation with an extracorporeal membrane oxygenator (ECMO). Multiple observational studies, primarily originating in Southeast Asia, suggest that ECMO is associated with improved outcome after refractory cardiac arrest (27–31). Because the overall survival in these locations is low compared with contemporary survival in the United States, it is unclear if one can generalize from their experience with ECMO. Observational studies in Melbourne, Australia and Paris, France suggest that early use of ECMO in combination with other interventions may be associated with good neurologic outcomes (32,33). A case-control study in Minneapolis, Minnesota of patients with refractory OHCA caused by a shockable rhythm reported that early transport to the cardiac catheterization laboratory followed by ECMO then PCI was associated with greater survival

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with good neurologic function as compared with historical control subjects (50% vs. 8.2%; $p < 0.0001$) (34). A randomized feasibility trial of ECMO in patients with refractory cardiac arrest was recently initiated in the United States (NCT03065647). In summary, there is considerable interest in the effectiveness of ECMO in humans with refractory OHCA.

Another technique that is promulgated to support patients with cardiac arrest is IV administration of medication to improve blood pressure and flow to the coronary and cerebral circulation so as to enhance the likely restoration of circulation and to reduce brain injury. Increased coronary perfusion pressure and cerebral perfusion pressure during CPR may be offset by increased myocardial work and reduced subendocardial perfusion (35). Multiple large observational studies from southeast Asia have suggested that early but not late use of epinephrine is associated with improved outcomes after OHCA (36-38). The only placebo-controlled trial of epinephrine (also called adrenalin) reported to date did not achieve its maximum expected enrollment but did observe that epinephrine significantly increased restoration of circulation and survival to admission as compared with placebo (39). Pooled analyses of prior trials confirm that vasopressin has no significant benefit over epinephrine (40). In 2 small trials in Greece, epinephrine combined with vasopressin and multiple doses of corticosteroids increased the likelihood of restoration of circulation as compared with placebo (41,42). A large pragmatic trial comparing epinephrine with placebo is currently enrolling patients with OHCA in England (ISRCTN73485024). In summary, there is considerable interest in the effectiveness of IV vasopressors in humans with refractory cardiac arrest.

Importantly, implementation of ECMO in patients with refractory cardiac arrest is likely to require specialized expertise, delay application of other potentially life-saving therapies (e.g., PCI), and incur large costs. Similarly, efforts to establish vascular access and administer a vasopressor may delay application of other potentially life-saving therapies. Clinical research resources are limited. The effectiveness of interventions must be demonstrated definitively if claims of their health benefit are to have scientific credibility (43). Thus, evidence-based practice guidelines recommend use of ECMO in patients with cardiac arrest only with a potentially reversible etiology during a limited period of mechanical cardiorespiratory support in settings where it can be rapidly implemented (26). In addition, they note that there is insufficient evidence to make a recommendation about the optimal timing and frequency of epinephrine administration in cardiac arrest (44).

In this issue of *JACC: Basic to Translational Science*, Bartos et al. (45) use a 2-by-2 factorial design to evaluate the role of ECMO and IV epinephrine in a pig model of refractory VF. This was done to simulate patients with out-of-hospital refractory VF receiving early transport to the cardiac catheterization laboratory and ECMO-facilitated coronary revascularization compared with routine CPR-based revascularization without ECMO, and to control for concurrent use of IV epinephrine. The primary outcome of 4-h survival was significantly improved with ECMO use (82% vs. 31%; $p = 0.003$). Return of spontaneous circulation following CPR was also significantly improved with ECMO use (100% vs. 44%; $p = 0.001$). A total of 9 of the 14 animals on ECMO (64%) met criteria for decannulation at 4 h. There was no significant difference in 4-h survival in pigs receiving epinephrine versus placebo (47% vs. 69%; $p = 0.47$), although the study lacked power to detect small but important differences in outcome. There was no significant interaction between use of epinephrine and ECMO.

SEE PAGE 244

This study supports the role of ECMO in refractory VF arrest, and challenges use of epinephrine in the same population. Epinephrine significantly increased aortic and coronary perfusion pressures and lactic acid levels. Although the latter decreased in all groups following reperfusion, those not receiving ECMO (i.e., CPR-only group) had substantial attrition of those with the highest lactic acid levels. Unfortunately, the study lacked power to compare post-reperfusion lactate levels.

Higher lactic acid levels are associated with worse outcomes (33) perhaps because of reduced overall perfusion, reduced local perfusion caused by vasoconstriction, increased transport out of tissues, or enhanced glycolysis. Bartos et al. (45) observed the best survival in animals in the Epi−/ECMO+ group followed by the Epi+/ECMO+ group. The Epi+/ECMO− group fared the worst. ECMO may have salvaged those with the highest lactic acid levels. It is unclear if epinephrine would have had the same effect in nonischemic refractory VF or other in cardiac arrest with a nonshockable rhythm.

A limitation of the excellent work by Bartos et al. (45) is that to simulate refractory VF, defibrillation was not administered to the animals until 45 min from arrest, which is later than is common in patients. The success of defibrillation and survival may have been different in animals receiving epinephrine versus placebo.