Commentary

Optimal vasopressor drug therapy during resuscitation

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Abstract

Optimal vasopressor support during resuscitation should theoretically enhance aortic diastolic and coronary perfusion pressure as well as coronary and cerebral blood flow/oxygen delivery without increasing cellular oxygen demand. Intravenous vasopressor support, using 1 mg doses of epinephrine every 5 minutes in adults or vasopressin 40 IU, is recommended by American Heart Association Advanced Cardiac Life Support Guidelines to maximize oxygen delivery to the heart and brain and increase cellular high energy phosphate levels. Vasopressin offers theoretical advantages over epinephrine in that it does not increase myocardial oxygen demand significantly and its receptors are relatively unaffected by acidosis. However, unlike epinephrine, it is not a myocardial stimulant. Despite these differences in physiologic actions, two large randomized clinical trials yielded virtually identical overall survival to hospital discharge when these agents were compared during in-hospital or out-of-hospital resuscitation in Canada and Europe, respectively. More recent clinical and experimental evidence suggests that a combination of vasopressin and epinephrine used during resuscitation can improve hemodynamics and perhaps survival. The verdict on a combination vasopressor strategy may soon come from a large (>2,000 patients) prospective clinical trial that is underway in France to clarify the role of combination vasopressin/epinephrine therapy in out-of-hospital resuscitation.

In this issue of *Critical Care*, Stroumpoulis and coworkers [1] reported that a combination of vasopressin and epinephrine improve hemodynamics and return of spontaneous circulation (ROSC) in an experimental cardiac arrest model. Approximately 400,000 to 460,000 cardiac arrests occur out of the hospital each year in the USA [2]. Despite major advances in resuscitation science, overall survival from out-of-hospital cardiac arrest remains poor, averaging only 5% to 8% in most communities [3]. The patient's initial cardiac rhythm is a principal determinant of resuscitation survival and neurologic outcome. A ventricular tachyarrhythmia (ventricular tachycardia or fibrillation) is the triggering event in up to 80% of cases and has the most favorable prognosis if it is treated promptly by defibrillation [4]. Approximately 25% of out-of-hospital cardiac arrest survivors require drug therapy for restoration of spontaneous circulation [5]. However, if prompt defibrillation cannot be performed and/or is unsuccessful and the resuscitation team must administer advanced life support drugs, the odds of survival to hospital discharge are under 10% [6,7].

Weisfeldt and Becker [8] proposed a three-phase model of resuscitation from cardiac arrest based on the changing physiologic needs of the patient: electrical, hemodynamic, and metabolic. For the first few minutes after the onset of ventricular fibrillation ('electrical phase'), defibrillation may be all that is needed for successful resuscitation because the myocardial cells are still relatively rich in ATP. After 3 to 4 minutes, depletion of myocardial ATP diminishes the heart's ability to resume effective contractions after defibrillation. Attempts at defibrillation during this period are often unsuccessful or result in asystole or pulseless electrical activity. A brief period of effective cardiopulmonary resuscitation before defibrillation during this second 'hemodynamic phase' can boost myocardial ATP levels, increasing the likelihood of ROSC after defibrillation. Intravenous vasopressor support, using 1 mg doses of epinephrine every 5 minutes in adults or vasopressin 40 IU, is recommended by American Heart Association Advanced Cardiac Life Support Guidelines to maximize oxygen delivery to the heart and brain and increase cellular ATP [9]. If spontaneous circulation is not restored for 8 to 9 minutes, then a cascade of cellular metabolic events usually leads to irreversible end-organ injury (including anoxic brain damage and postresuscitation myocardial dysfunction). It is believed that reperfusion protection strategies mitigate cellular damages during this third 'metabolic phase'.

Optimal vasopressor support during resuscitation should theoretically enhance aortic diastolic and coronary perfusion pressure as well as coronary and cerebral blood flow/oxygen delivery without increasing cellular oxygen demand. The principal hypothesis to explain why 'high dose epinephrine',

ROSC = return of spontaneous circulation.

which looked promising in animal models, did not improve survival in clinical resuscitation trials is that the increased coronary perfusion pressure did not increase myocardial oxygen delivery (the majority of adult cardiac arrest victims, unlike most experimental animal models, have significant coronary artery narrowing) sufficiently to offset the increased myocardial oxygen demand caused by epinephrine's β-adrenergic effects [7].

Vasopressin offers theoretical advantages over epinephrine in that it does not increase myocardial oxygen demand significantly and its receptors are relatively unaffected by acidosis. However, unlike epinephrine, it is not a myocardial stimulant. Despite these differences in physiologic action, two large randomized clinical trials yielded virtually identical overall survival to hospital discharge when these agents were compared during in-hospital [10] and out-of-hospital [6] resuscitation in Canada and Europe, respectively. In the European study, survival to discharge was better with use of vasopressin than with epinephrine for the subgroup of patients in whom asystole was the initial rhythm.

Stroumpoulis and coworkers [1] found that a combination of vasopressin and epinephrine resulted in higher aortic diastolic and coronary perfusion pressures, as well as better ROSC, compared with that achieved with epinephrine alone in an 8-minute untreated ventricular fibrillation experimental model in large piglets. This is not a new finding, but it adds further evidence alongside the results of prior animal studies that showed that this combination improves survival [11-13]. There is also clinical evidence supporting use of a vasopressin/epinephrine 'combination' (usually in the form of sequential or alternating doses of the two drugs) during resuscitation [6,14-16]. The best evidence to date comes from the out-of-hospital comparison of epinephrine versus vasopressin reported by Wenzel and coworkers [6], which showed no difference in survival between treatment groups. However, there was better survival in the group of patients who received two blinded experimental doses of vasopressin followed by unlabelled epinephrine than in patients who received just repeated doses of epinephrine.

The 2005 American Heart Association Guidelines on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care [17] recommend epinephrine (1 mg intravenously every 3 to 5 minutes) and state that 'one dose of vasopressin may replace either the first or second dose of epinephrine'. The 2005 European Resuscitation Council Guidelines for Resuscitation [18] conclude that epinephrine, '… has been the standard vasopressor in cardiac arrest. There is insufficient evidence to support or refute the use of vasopressin as an alternative to, or in combination with [epinephrine].' However, based on the mounting clinical and experimental evidence, Wenzel and Lindner [14] recently suggested that clinicians consider alternating epinephrine 1 mg intravenously with vasopressin 40 IU every 3 to 5 minutes. The verdict on a combination vasopressor strategy may come soon from a large (>2,000 patients) prospective clinical trial that is underway in France to clarify the role of combination vasopressin/epinephrine therapy in out-of-hospital resuscitation.

Competing interests

The author declares that they have no competing interests.

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