Repetitive Administration of Vasopressin but Not Epinephrine Maintains Coronary Perfusion Pressure After Early and Late Administration During Prolonged Cardiopulmonary Resuscitation in Pigs

To the Editor:

Wenzel et al provide additional evidence in favor of a change away from the use of epinephrine during cardiac arrest, which has been universally adopted due to the advanced cardiac life support guidelines. Unfortunately, the epinephrine doses of 45 and 200 µg/kg used in their study, which equate to 3.15 and 14 mg in a 70-kg patient, do not equate to those used clinically.

A side effect of epinephrine that is widely known but has not been discussed is the potent platelet aggregation that epinephrine induces. Indeed, epinephrine is so good at producing platelet aggregation that it is widely used during platelet function tests as an aggreganor (thus the importance of using equivalent doses of epinephrine to that used clinically).

We have demonstrated that an epinephrine dose of 1 mg in a 70-kg patient, which equates to 14.3 µg/kg, causes approximately 10% platelet aggregation; however, the doses used in the study by Wenzel et al, 45 and 200 µg/kg, cause 20% and 75% platelet aggregation, respectively. Thus, because they have not measured platelet aggregation, which could easily be done with the technique of microaggregation, the results of their study are confounded by a degree of platelet aggregation that is significant and that does not occur at the doses used clinically.

Cardiac arrest is mainly due to coronary thrombosis; therefore, administration of an agent that causes platelet aggregation has to be detrimental. An increased frequency of a polymorphism of the α-receptor on platelets of patients with acute coronary syndromes that causes an increased aggregation effect of epinephrine has been described.

In addition, epinephrine is a known proarrhythmic agent, being responsible for the initiation of ventricular tachycardia and ventricular fibrillation (personal experience) when administered as a bolus (50 to 100 µg) to patients after cardiac surgery who are hypotensive but in sinus rhythm.

Thus, a vasoconstrictor that has no effect on platelet aggregation and is not proarrhythmic would seem to be the ideal agent. This rules out all the other α-agonists that are available. Vasopressin is only bettered by endothelin as a vasoconstrictor, and neither has an effect on platelet aggregation or induces arrhythmias.

Perhaps the use of epinephrine should be considered more carefully, especially since its use is not associated with a lowering of the mortality rate after cardiac arrest.

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Response

Although the 45-µg/kg epinephrine dose in our experiment is greater than the recommended 15-µg/kg clinical dosage, the 45-µg/kg dose was shown to be optimal in pigs. Also, when a 15-µg/kg epinephrine dosage was used in a porcine CPR experiment, coronary perfusion pressure increased only slightly, resulting in a control group with no surviving animals. In contrast, our pigs had a significant coronary perfusion pressure increase after the first 45-µg/kg epinephrine dose to a level above 20 to 30 mm Hg, which is needed to achieve return of spontaneous circulation. Furthermore, the 200-µg/kg epinephrine dose given after 12 minutes of CPR reflects an escalating dose that is needed to restart a heart subjected to fundamental hypercarbic acidosis and hypoxia during prolonged resuscitation efforts.

A clinical study found a marked activation of blood coagulation and fibrin formation after prolonged cardiac arrest and CPR that was not balanced adequately by concomitant activation of endogenous fibrinolysis. Whether these changes may contribute to myocardial and/or cerebral reperfusion disorders, however, needs to be determined in future CPR studies. To eliminate these confounding variables in our laboratory studies, we have always injected 5000 U of heparin (about 150 U/kg) before induction of cardiac arrest. As such, we suggest that our epinephrine dose is validated and necessary to simulate a clinically realistic scenario of cardiac arrest management.

The role of epinephrine during CPR in adults is discussed controversially because of proven adverse effects such as an increase of myocardial oxygen consumption, ventricular arrhythmias, ventilation-perfusion defect, and more severe postresuscitation myocardial dysfunction in laboratory studies, as well as the lack of an improved outcome compared with saline placebo in a clinical study. Also, epinephrine given in the postresuscitation phase is a significant proarrhythmic agent. It was recently shown that an epinephrine-induced reduction of action potentials increased the probability that reentry action potentials hit excitable tissue, which may provoke or even stabilize ventricular fibrillation. Thus, if blood pressure may be endangered in the post-resuscitation phase due to, for example, vasodilatory shock, an alternative may be a continuous infusion of vasopressin, which was shown to be beneficial in patients with shock states refractory to adrenergic vasopressors. As a consequence, based on our experience with the alternative vasopressor vasopressin, we have started a multicenter clinical trial in Austria, Germany, and Switzerland under the aegis of the European Resuscitation Council to assess the effects of vasopressin versus epinephrine in cardiac arrest patients being resuscitated outside the hospital.


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