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Original Contributions

EFFECT OF THE ADDITION OF VASOPRESSIN OR VASOPRESSIN PLUS NITROGLYCERIN TO EPINEPHRINE ON ARTERIAL BLOOD PRESSURE DURING CARDIOPULMONARY RESUSCITATION IN HUMANS

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□ **Abstract—Background: Infusion of a vasopressor during cardiopulmonary resuscitation (CPR) in humans increases end decompression (diastolic) arterial blood pressure, and consequently increases vital organ perfusion pressure and survival. Several vasoactive drugs have been tested alone or in combination, but their hemodynamic effects have not been investigated clinically in humans. Study Objective: We tested the hypothesis that epinephrine (1 mg) co-administered with vasopressin (40 IU) ± nitroglycerin (300 μg) results in higher diastolic blood pressure than epinephrine alone. Study Design: A prospective, randomized, double-blinded controlled trial in the prehospital setting. The study included 48 patients with witnessed cardiac arrest. Patients received either epinephrine alone (E alone) or epinephrine plus vasopressin (E+V) or epinephrine plus vasopressin plus nitroglycerin (E+V+N). A femoral arterial catheter was inserted for arterial pressure measurement. Outcome Measures: The primary end point was diastolic blood pressure during CPR, 15 min after the first drug administration (T = 15 min). Results: After exclusions, a total of 44 patients were enrolled. Diastolic blood pressures (mm Hg) at T = 15 min were not statistically different between groups (median [interquartile range]: 20 [10], 15 [6], and 15 [13] for E alone, E+V, and E+V+N, respectively. The rate of return of spontaneous circulation was 63% (n = 10) in the epinephrine group, 43% (n = 6) in the epinephrine plus vasopressin group, and 36% (n = 5) in the triple therapy group (NS). Conclusions: Addition of vasopressin or vasopressin plus nitroglycerin to epinephrine did not increase perfusion blood pressure compared to epinephrine alone in humans in cardiac arrest, suggesting the absence of benefit in using these drug combination(s).** **© 2011 Elsevier Inc.**

□ **Keywords—epinephrine; vasopressin; nitroglycerin; out-of-hospital CPR; blood pressure; cardiac arrest**

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INTRODUCTION

Vasopressor infusion during cardiopulmonary resuscitation (CPR) in humans in cardiac arrest increases the tone of both venous and arterial vessels, venous return, arterial blood pressure, and consequently, vital organ perfusion pressure. It is recognized that during CPR, maintenance of an adequate diastolic arterial blood pressure (the pressure at the end of the chest decompression) preserves vital organ perfusion and is important for survival (1,2). Poor outcomes after cardiac arrest have raised the question of the optimal pharmacological approach to augment circulation during CPR. High-dose

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epinephrine improves return of spontaneous circulation (ROSC) and hospital admission but there is no difference in long-term survival or neurologic outcome at hospital discharge compared to low-dose epinephrine (3). The use of natural or synthesized vasopressors other than epinephrine has been the subject of many investigations. Despite encouraging results in animal studies and in human clinical trials, vasopressin alone is reported to have no benefit in improving survival to hospital discharge when compared to epinephrine in the treatment of patients with in-hospital and out-of-hospital cardiac arrest (4–10). The combination of vasopressin plus epinephrine raises arterial blood pressure in animals but is associated with a decrease in cerebral and endocardial blood flow (11,12). Based upon the hypothesis that this drug combination causes an increase in vasoconstriction in cerebral and endocardial vascular beds, animal studies have been performed with the addition of nitroglycerin as a nitric oxide releasing agent; improved vital organ blood flow was found with the combination of nitroglycerin plus vasopressin plus epinephrine, vs. epinephrine alone (13,14). However, the hemodynamic effect of the three drug combinations (epinephrine alone, epinephrine plus vasopressin, or epinephrine plus vasopressin plus nitroglycerin) remains unknown in humans in cardiac arrest. In the present study, we tested the hypothesis that the addition of vasopressin to epinephrine, with or without nitroglycerin, would result in higher diastolic arterial blood pressure than epinephrine alone during CPR for human cardiac arrest.

MATERIALS AND METHODS

This study is a prospective, randomized, double-blinded, and controlled clinical trial performed on an intention-to-treat basis. It was approved by the local Institutional Review Board (IRB; the Consultative Council for the Protection of Persons Volunteering for Biomedical Research). The IRB waived the requirement for informed consent due to clinical circumstances; signed consent was obtained from patients who eventually were discharged from the hospital. The study period was August 2001 to August 2004.

This study was performed in a single out-of-hospital setting in Paris, France. The prehospital emergency response chain of survival in Paris is two-tiered and combines basic life support (BLS) with firefighters and advanced cardiac life support (ACLS) with out-of-hospital emergency medical services, as previously described (15).

The following patients were included: adults with a witnessed out-of-hospital cardiac arrest who presented with ventricular fibrillation, pulseless electrical activity, or asystole and requiring ACLS, and for whom BLS with active compression-decompression CPR (CardioPump®, Ambu, Le Haillan, France) was already started by firefighters before the arrival of the medical team, at a compression rate of 100.min^{-1} and a compression:ventilation ratio of 15:2, according to the 2000 guidelines (16). Active compression-decompression is routinely applied by firefighters in Paris. Of note, vasopressors can be administered only by the medical team. Patients with the following criteria were excluded: unwitnessed cardiac arrest, spontaneous palpable carotid or femoral pulse restored before administration of a vasopressor, lack of intravenous access, pregnancy, traumatic injuries and anatomic abnormalities that prevented safe femoral artery cannulation. Patients with presumed irreversible death or known terminal illness at the beginning of ACLS also were not included for ethical consideration.

Figure 1 presents the timeline of the study. If all inclusion criteria were met, patients underwent randomization. Treatment assignments to the study drugs were randomly generated by a computer and placed in sealed numbered envelopes. Time intervals were noted based upon witnesses' declaration and dispatching center recordings.

Upon arrival at the scene, the prehospital medical team started ACLS that included tracheal intubation connected to an impedance threshold device (Advanced Circulatory Systems, Minneapolis, MN) and ventilation with 100% oxygen.

Immediately after the venous line was placed and after randomization, the study patients were split into three groups. Each group received a simultaneous intravenous (i.v.) administration of one of three study drugs every 5 min at T = 0, T = 5, and T = 10, except in the case of ROSC. Epinephrine (E) administration was not blinded, whereas vasopressin (V), nitroglycerin (N), or placebos were given blindly. All drugs were exclusively injected intravenously, followed by 20 mL of normal saline. The study drugs (vasopressin or nitroglycerin) were prepared every day in advance by the pharmacist of our hospital in plastic syringes according to local sterilization procedure to ensure drug stability and safety 24 h after removal from the glass ampules. The three study groups were: 1) group "E alone" received open E (1 mg) and two syringes (1 mL each) of placebo; 2) group "E+V" received open E (1 mg) + V (40 IU) + placebo; 3) group "E+V+N" received open E (1 mg) + V (40 IU) + N (300 μg). The dose of vasopressin (40 IU) was the same as that chosen in previously published human studies (6,7,9). The three successive administrations of study drugs every 5 min and the dose of nitroglycerin were adapted from two previous animal studies (pigs) in cardiac arrest (14,17). Additional interventions such as the administration of sodium bicarbonate, atropine, lidocaine, or amiodarone and fibrinolysis were used at the discretion of the physician managing the CPR. After the 15 min study period, all patients still in cardiac arrest (regardless of their study group) received 1 mg of epi-