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Short communication

Does prearrest adrenergic integrity affect pressor response? A comparison of epinephrine and vasopressin in a spontaneous ventricular fibrillation swine model☆,☆☆

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ABSTRACT

Objectives: Coronary perfusion pressure (CPP) during resuscitation from cardiac arrest has been shown to correlate with return of spontaneous circulation. Adrenergic blockade of beta-1 and alpha-1 receptors is common in the long-term management of ischemic heart disease and congestive heart failure. We sought to compare the CPP response to vasopressin vs. epinephrine in a swine model of cardiac arrest following pre-arrest adrenergic blockade.

Methods: Eight anesthetized and instrumented swine were administered 0.1 mg epinephrine and arterial pressure and heart rate response were measured. An infusion of labetalol was then initiated and animals periodically challenged with epinephrine until adrenergic blockade was confirmed. The left anterior descending coronary artery was occluded to produce ventricular fibrillation (VF). After 7 min of untreated VF, mechanical chest compressions were initiated. After 1 min of compressions, 1 mg epinephrine was given while CPP was recorded. When CPP values had returned to pre-epinephrine levels, 40 U of bolus vasopressin was given. Differences in CPP (post-vasopressor–pre-vasopressor) were compared within animals for the epinephrine and vasopressin response and with eight, non-adrenergically blocked, historical controls using Bayesian statistics with a non-informative prior.

Results: The CPP response following epinephrine was 15.1 mmHg lower in adrenergically blocked animals compared to non-adrenergically blocked animals (95% Highest Posterior Density [HPD] 2.9–27.2 mmHg lower). CPP went up 18.4 mmHg more following vasopressin when compared to epinephrine (95% HPD 8.2–29.1 mmHg). The posterior probability of a higher CPP response from vasopressin (vs. epinephrine) in these animals was 0.999.

Conclusions: Pre-arrest adrenergic blockade blunts the CPP response to epinephrine. Superior augmentation of CPP is attained with vasopressin under these conditions.

1. Introduction

Current advanced cardiac life support (ACLS) guidelines recommend the administration of a vasopressor medication, either epinephrine or vasopressin, during cardiac arrest due to PEA or asystole or if ventricular fibrillation (VF) or pulseless ventricular tachycardia persist after one or two shocks with CPR.[1] The rationale for this approach is to pharmacologically augment coronary perfusion pressure (CPP), the pressure gradient between aortic and right atrial pressures during the relaxation phase of rhythmic chest compressions. Higher CPP has been correlated with improved return of spontaneous circulation (ROSC) in animals and humans.[2–4] Despite strong rationale supported by hemodynamic

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observations in animal models, vasopressors have not been shown to improve outcome in observational reports or clinical trials.[5–7]

Medications used by patients prior to cardiopulmonary collapse may affect the response to pharmacologic therapy administered during resuscitation efforts. No consideration is currently included in ACLS guidelines regarding the use of chronic medications prior to arrest, particularly those that might affect hemodynamic variables during CPR. Approximately 80% of post-infarction patients are prescribed a beta blocker at discharge.[8] Carvedilol, classified as a non-selective beta blocker, is more commonly prescribed than selective beta-1 antagonists, including metoprolol succinate, for the management of heart failure.[9]

The purpose of this investigation was to compare the effect of epinephrine with that of vasopressin on coronary perfusion pressure in a porcine model of ischemic VF cardiac arrest when preceded by blockade of alpha-1 and beta-1 adrenergic receptors.

2. Methods

This study was approved by the Animal Care and Utilization Review Committee at our institution and conforms to the American Physiological Society's Guiding Principles in the Care and Use of Animals.

Methods for the induction of anesthesia and instrumentation have been previously described.[10] In brief, 8 male mixed breed Yorkshire swine (41 ± 3 kg) were premedicated with ketamine and xylazine and anesthesia was induced and maintained with inhaled isoflurane. End-tidal CO_2 was monitored continuously and minute ventilation was adjusted to maintain an end-tidal CO_2 between 35 and 45 mmHg. Lead II of the surface electrocardiogram was also monitored continuously throughout the protocol.

Vessels were exposed surgically and high-fidelity micromanometer tipped catheters (Millar Instruments, Houston, TX) were positioned in the ascending aorta (Ao) and the right atrium (RA) under fluoroscopic guidance. Following instrumentation, heart rate, systolic and diastolic aortic and mean RA pressures were measured and recorded (PowerLab Chart acquisition software v. 5.2, ADInstruments, Castle Hill, Australia). Arterial blood gas was analyzed (I-Stat EG7+, I-Stat Corp, Princeton, NJ) at baseline following instrumentation and at intervals throughout the investigation.

After control measurements were made, a 0.1 mg bolus of epinephrine was administered via the RA catheter and the heart rate and arterial pressure response recorded. After heart rate and arterial pressure returned to baseline values, an intravenous infusion of labetalol was begun and continued until an additional epinephrine challenge produced a <10 beat/min change in heart rate and systolic arterial pressure increased by <25%, a definition based on the consensus agreement of the investigators. (Carvedilol is currently unavailable in a titratible intravenous formulation, which is why labetalol was chosen as comparable mixed agonist.)

After adrenergic blockade, the left anterior descending (LAD) coronary artery distal to the first septal perforator was occluded with a standard angioplasty catheter and balloon (Voyager 4.0 mm × 20 mm PTCA balloon, Abbott Vascular, Temecula CA). The site of coronary occlusion and confirmation of complete cessation of coronary flow distal to the balloon were confirmed with manual contrast injections. Animals were observed until spontaneous VF occurred.

Following 7 min of untreated VF, closed mechanical chest compressions with the Thumper® (Michigan Instruments, Grand Rapids, MI) were initiated with force sufficient to depress the sternum 1.5–2.0 in. Following 1 min of closed chest compressions, epinephrine 1 mg was administered via the RA during continuous recording of CPP. When the CPP had returned to pre-epinephrine baseline, vasopressin, 40 U, was delivered via the RA catheter. The order of administration was chosen due to the relatively short half-life of epinephrine (approximately 5 min) and the relatively long half-life (approximately 20 min) of vasopressin in an attempt to minimize carryover effects and temporal declines in vascular responsiveness. Each animal served as their own control to reduce the potential effect of genetic and physiologic variability on the differential response.

An identical protocol, omitting pre-arrest adrenergic blockade or epinephrine challenge, was performed in eight additional swine who served as non-adrenergically blocked controls.

2.1. Data analysis

Data were entered into an Excel Spreadsheet (v. 12.0, Microsoft Corp, Redmond, WA) and imported into SAS statistical software (v. 9.2, SAS Institute, Cary, NC) for analysis. CPR coronary perfusion pressure (diastolic or relaxation phase Ao-RA pressure difference) was determined by measuring the mean peak CPP over the 30 s period (approximately 50 compression cycles) preceding medication administration (epinephrine or vasopressin) and the 30 s period following medication administration.

Differences in CPP response to epinephrine (post-epinephrine CPP–pre-epinephrine CPP) between adrenergically blocked and non-adrenergically blocked animals and the differences in CPP response to vasopressin vs. epinephrine within blocked animals were modeled using Bayesian statistics. Utilizing Markov-Chain Monte Carlo random sampling methods, the Bayesian model allows for the assignment of exact probability values to specific hypotheses, rather than simply the null hypothesis. Specifically, the Bayes option of the SAS procedure, PROC GENMOD, was invoked for this purpose. We used non-informative, uniform prior distributions (assigning equal probability to all values), to model uncertainty regarding the location of the parameter μ, the difference in mean CPP response. A default, non-informative gamma prior probability distribution was used to model uncertainty in the scale parameter (σ) of the target distribution. Markov chain convergence was assessed using visual inspection of trace plots and three standard diagnostics: Lag autocorrelations, Geweke diagnostic statistics, and effective sample sizes. We report median values and 95% highest posterior density (HPD) intervals for the posterior probability distributions. These intervals reflect the parameter values which are assigned 95% of the posterior probability.

3. Results

An average of 7 ± 2 mg/kg of labetalol was required to produce blockade of alpha 1 and beta-1 receptors. Fig. 1 demonstrates the change in CPP following administration of either epinephrine or vasopressin to adrenergically blocked animals when compared to pharmacologically naïve (non-adrenergically blocked) animals.

Markov chain convergence was satisfactory for all posterior sampling densities. Table 1 provides results of posterior

Table 1
Posterior probability estimates for the coronary perfusion pressure response following vasopressor administration in a swine model of cardiac arrest.

Vasopressor	Mean ΔCPP (mmHg)	95% HPD[a] (mmHg)
Non-blocked ($n = 8$)		
Epinephrine	24.6	15.9–32.8
Non-selective blockade ($n = 8$)		
Epinephrine	9.5	5.6–12.9
Vasopressin	27.9	16.8–39.6

[a] Highest posterior density: the range of parameter values assigned the 95% highest posterior probability.