The Physiologic Response to Rescue Therapy with Vasopressin versus Epinephrine during Experimental Pediatric Cardiac Arrest

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Research

Keywords: Cardiac arrest, cardiopulmonary resuscitation, pediatrics, coronary perfusion pressure, cerebral blood flow, vasopressin, epinephrine

DOI: https://doi.org/10.21203/rs.3.rs-50678/v1

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Abstract

Background: While epinephrine is the mainstay of therapy during cardiopulmonary resuscitation, it is potentially detrimental to the cerebral vasculature and ineffective in certain populations. This study compares a rescue dose of vasopressin to a rescue dose of epinephrine after ineffective initial doses of epinephrine in diverse models of pediatric in-hospital cardiac arrest. 67 one- to three-month old female swine (10-30kg) in six experimental cohorts from one laboratory received hemodynamic-directed CPR, a resuscitation method where high quality chest compressions are provided and vasopressor administration is titrated to coronary perfusion pressure (CoPP) ≥20 mmHg. Vasopressors are given when CoPP is <20 mmHg, in sequences of two doses of 0.02 mg/kg epinephrine separated by minimum one-minute, then a rescue dose of 0.4 U/kg vasopressin followed by minimum two-minutes. Invasive measurements were used to evaluate and compare the hemodynamic and neurologic effects of each vasopressor dose.

Results: Increases in CoPP and cerebral blood flow (CBF) were greater with vasopressin rescue than epinephrine rescue (CoPP: +8.16 [4.35, 12.06] mmHg vs. +5.43 [1.56, 9.82] mmHg, p=0.022; CBF: +14.58 [-0.05, 38.12] vs. +0.00 [-0.77, 18.24] perfusion units (PFU), p=0.005). Twenty animals (30%) failed to achieve CoPP ≥20 mmHg after two doses of epinephrine; 9/20 (45%) non-responders achieved CoPP ≥20 mmHg after vasopressin. Among all animals, the increase in CBF was greater with vasopressin (+14.58 [-0.58, 38.12] vs. 0.00 [-0.77, 18.24] PFU, p=0.005).

Conclusions: CoPP and CBF rose significantly more after rescue vasopressin than after rescue epinephrine. Importantly, CBF increased after vasopressin rescue, but not after epinephrine rescue. In the 30% that failed to meet CoPP of 20mmHg after two doses of epinephrine, 45% achieved target CoPP with a single rescue vasopressin dose.

Background

Pediatric in-hospital cardiac arrest (IHCA) occurs in 1.4-6% of children admitted to pediatric intensive care units (Berg et al. 2016). Less than half of these children survive to hospital discharge and many have new functional morbidities post-arrest(Wolfe et al. 2019). During cardiopulmonary resuscitation (CPR), coronary perfusion pressure (CoPP), the difference between the aortic pressure and the right atrial (RA) pressure during the relaxation phase of chest compressions (“diastole”), is a major determinant of achieving return of spontaneous circulation (ROSC)(Paradis et al. 1990) and surviving to hospital discharge (Berg et al. 2018). Vasopressors are therefore given during CPR to increase systemic vascular resistance and thereby increase diastolic blood pressure (DBP) and CoPP(Berg et al. 2001). However, vasopressors may have adverse neurologic effects during CPR, with particular concern that epinephrine decreases cerebral blood flow(Gedeborg et al. 2000; Ristagno et al. 2007; Ristagno et al. 2008).

Our group developed and investigated the use of hemodynamic-directed CPR (HD-CPR), using systolic blood pressure-guided chest compression force and CoPP-guided vasopressor administration to improve
outcomes (Chopra et al. 2016). In numerous pre-clinical studies, this HD-CPR strategy led to higher coronary and cerebral perfusion pressures, higher rates of survival, superior neurologic outcomes, and improved mitochondrial respiration in the heart and brain as compared to standard, guideline-based CPR (Friess et al. 2013; Lautz et al. 2019; Morgan et al. 2017; Naim et al. 2016; Sutton et al. 2013; Sutton et al. 2014). The vasopressor strategy employed in HD-CPR requires vasopressors to be administered in a protocolized manner if the CoPP is <20 mmHg. An initial dose of 0.02 mg/kg epinephrine is given as dictated by CoPP, followed by a minimum duration of one minute, and a second dose of 0.02mg/kg epinephrine if CoPP is <20 mmHg. After an additional one-minute minimum duration, 0.4 Units/kg of vasopressin is administered if CoPP remains <20 mmHg. Despite the efficacy of HD-CPR, the specific physiologic effects of vasopressin rescue have not been explicitly studied.

Therefore, the primary objective of this study was to compare the physiologic responses to a rescue dose (second dose) of epinephrine with a rescue dose of vasopressin. We hypothesized that CoPP and CBF would increase more following vasopressin than epinephrine(Ristagno et al. 2007). Additionally, we sought to characterize the physiologic response to vasopressin in a group of animals that failed to achieve CoPP ≥20 mmHg after either of two doses of epinephrine (i.e., epinephrine non-responders). We hypothesized that many of these epinephrine “non-responders” would have increases in CoPP and CBF following a single dose of vasopressin.

**Materials And Methods**

**Study Design and Data Sources:**

This was a retrospective analytic study of data from laboratory experiments utilizing HD-CPR in porcine models of pediatric IHCA. Inclusion criteria were having HD-CPR as the resuscitation method and ≥2 doses of epinephrine and ≥1 dose of vasopressin administered. Animals did not require CBF data for inclusion, but were excluded if hemodynamic data were non-evaluable.

**Data Collection:**

The Children's Hospital of Philadelphia Institutional Animal Care and Use Committee approved all experimental protocols, which were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Comprehensive descriptions of animal preparation, anesthetic, and surgical methods are available in previous publications(Friess et al. 2013; Lautz et al. 2019; Morgan et al. 2016; Morgan et al. 2017; Morgan et al. 2018; Naim et al. 2016; Sutton et al. 2013; Sutton et al. 2014). Briefly, female Yorkshire swine were anesthetized and mechanically ventilated. To broadly study the pediatric age range, 1-month-old (~10 kg) and 3-month-old (~30 kg) swine were utilized. Vascular catheters were placed and high-fidelity pressure transducers were advanced to the RA, pulmonary artery (PA), and aorta for continuous hemodynamic measurements. Before and during the experimental protocol, the electrocardiogram (ECG), aortic pressure, RA pressure, PA pressure, pulse
oximetry, and end-tidal carbon dioxide (ETCO2) values and waveforms were displayed and recorded. Coronary perfusion pressure was automatically calculated and displayed in real time by subtracting the RA pressure from the aortic pressure (Morgan et al. 2017). A CPR quality-recording defibrillator (Zoll R Series Plus; Zoll Medical Corporation) was used during CPR and recorded chest compression rate (per minute) and depth (centimeters). A subset of animals underwent invasive neuromonitoring with a PeriFlux laser Doppler (Perimed, Inc.) monitor to measure CBF, located in the superficial cerebral cortex.

**Experimental Protocol:**

**Injury Period:** Animals underwent one of the following injuries:

1) Primary ventricular fibrillation (VF) cardiac arrest (3-month-old swine): VF was electrically induced and left untreated for seven minutes, followed by a minimum of 10 minutes of HD-CPR and defibrillation (Friess et al. 2013; Naim et al. 2016).

2) Asphyxia-associated cardiac arrest (1- and 3-month-old swine): Asphyxia was induced by clamping the endotracheal tube for 7 minutes, following which VF was induced and HD-CPR commenced (Lautz et al. 2019; Morgan et al. 2017; Sutton et al. 2013; Sutton et al. 2014). The induction of VF ensured a consistent 10-minute CPR period as effective CPR after asphyxia-induced cardiac arrest alone typically results in ROSC within 2-4 minutes (Berg et al. 1999; Berg et al. 2000).

3) Lipopolysaccharide (LPS)-induced shock-associated IHCA (3-month-old swine): Animals received 45 minutes of an intravenous LPS infusion to induce shock, followed by induction of VF to ensure an adequate cardiac arrest period in which to study HD-CPR (Morgan et al. 2018). A subset of these animals received nitric oxide (iNO) therapy.

**Resuscitation Period:** In all subjects, chest compressions were provided with a target rate of 100 per minute guided by metronome. Per our established HD-CPR algorithm (Figure 1), chest compression depth was titrated to maintain a systolic blood pressure (SBP) of 90 mmHg for 10 kg swine and 100 mmHg for 30 kg swine. Vasopressors were given by protocol, as needed, to maintain a goal CoPP of ≥20 mmHg. Beginning two minutes into CPR, epinephrine was administered (0.02 mg/kg as recommended for swine models (Berg et al. 1994; Brown et al. 1987; Gonzalez et al. 2014)) if CoPP <20 mmHg during mid-diastole for at least three consecutive chest compressions. If CoPP was <20 mmHg one minute after first epinephrine dose or at any subsequent time, an additional dose of epinephrine was administered. If CoPP was <20 mmHg one minute after second epinephrine dose or any subsequent time, vasopressin (0.4
U/kg) was administered. The cycle restarted two minutes following vasopressin, with these minimum intervals based on the peak effect of each vasopressor.

**Data Collection and Processing:**

All physiologic measurements were recorded at 1000 Hz (PowerLab, ADInstruments, Inc.). Vasopressor administration was recorded in real-time. The one minute preceding each vasopressor dose, the one minute following each epinephrine dose, and the two minutes following each vasopressin dose were divided into 15-second data epochs. Mean values for each physiologic parameter were calculated for each epoch. Data were analyzed from only the first cycle of vasopressors (i.e., epinephrine, epinephrine, vasopressin) for each experiment to minimize confounding. For comparison of physiologic response between rescue vasopressors after initial epinephrine dose failed to sustain the target CoPP, the second dose of epinephrine was compared to the rescue vasopressin dose.

**Statistical Analyses:**

The primary analysis compared the physiologic change following vasopressin to that observed following the second dose of epinephrine. The primary outcomes were changes in CoPP and CBF. All measurements were treated as non-normally distributed after a Shapiro-Wilk analysis was performed and were reported as medians with interquartile ranges and compared using non-parametric analyses. The change in each physiologic variable from mean of the four pre-vasopressor epochs to highest post-vasopressor epoch (four epochs following epinephrine and eight epochs following vasopressin) was calculated and these values were compared between vasopressin and epinephrine with Wilcoxon signed-rank tests.

For the secondary analyses, an epinephrine CoPP threshold non-responder cohort was defined *a priori* as animals that failed to have any 15-second mean CoPP ≥20 mmHg after either dose of epinephrine. These subjects were characterized as vasopressin responders if their CoPP was ≥20 mmHg in any 15-second epoch during the two minutes after vasopressin administration. The above analyses were repeated in subgroups of epinephrine responders, epinephrine non-responders, and in epinephrine non-responders that responded to vasopressin.

In prospectively planned supplemental analyses, the change in CoPP following the second dose of epinephrine to *a priori* response targets (³3 mmHg; ³5 mmHg; ³7 mmHg; ³10 mmHg) were utilized as alternative definitions of epinephrine responsiveness. The number of responders and non-responders in each of these categories was summarized, as were the number of vasopressin responders (according to the same definition) among each epinephrine non-responder population.
Results

Physiologic Responses in the Overall Population

Data from 98 experiments were compiled and evaluated for study inclusion. After exclusion of 31 subjects that were epinephrine responders and did not require three vasopressor doses, 67 remained for analysis (Figure 2). In the overall cohort (n = 67), the mean baseline CBF prior to cardiac arrest was 348.16 ± 38 PFU (SEM), which dropped to 0 PFU in all animals at the start of CPR. There was a significant increase in CoPP and CBF after both doses of epinephrine and after vasopressin (Supplemental Table 1; Figures 3 and 4). Vasopressin generated a greater rise in CoPP (+8.16 [4.35, 12.06] mmHg vs. +5.43 [1.56, 9.82] mmHg; p=0.22), mean PA pressure (+4.05 [0.42, 7.80] mmHg vs. +5.90 [1.98, 13.82] mmHg, p <0.001) and CBF (+14.58 [-0.05, 38.12] PFU vs. +0.00 [-0.77, 18.24] PFU, p=0.005) relative to the second dose of epinephrine (Table 1).

Physiologic Responses among Epinephrine Non-Responders

In 20/67 (29.9%) experiments, neither dose of epinephrine resulted in any epoch with CoPP ≥20 mmHg. Nine of these 20 (45%) achieved a CoPP of ≥20 mmHg within 2 minutes after a single dose of rescue vasopressin. Among these 20 epinephrine non-responders, the change in CBF of -0.28 [-2.33, 6.91] PFU after the epinephrine rescue was significantly less than after vasopressin rescue +14.58 [3.55 – 34.90] PFU (p=0.045) (Table 1; Figure 4). The change in CoPP with was +2.76 [1.28, 6.58] mmHg with epinephrine rescue and +7.64 [4.86, 11.02] mmHg with vasopressin rescue (Table 1; Figure 3c).

Alternative characterization of epinephrine responsiveness

Alternative definitions of vasopressin responsiveness according to change in CoPP attributable to the second dose of epinephrine are depicted in Supplemental Table 2. Thirty-one of 67 (46%) animals showed a rise of ≥ 3 mmHg after the second dose of epinephrine while 36/67 (54%) did not. Of the 36 who did not meet the goal rise of ≥ 3 mmHg, 20 (56%) rose ≥ 3 mmHg after vasopressin. In this population of epinephrine non-responders (n = 36), CBF fell -0.003 [-0.9, 14.60] PFU after the second dose of epinephrine compared to rising +10.6 [0.08, 37.4] PFU after rescue vasopressin (p = 0.01). 21/67 (31%) saw an increase in CoPP ≥ 5 mmHg after the second dose of epinephrine, whereas 46/67 (69%) did not meet this goal. In this population (n = 46), CBF rose +0.07 [-0.7, 16.3] PFU after the second dose of epinephrine compared to +21.2 [0.04, 39.20] PFU after vasopressin (p = 0.002).

Discussion

In this large analytic study of swine treated with HD-CPR across several diverse pathophysiologic models of IHCA (i.e., asphyxia, ventricular fibrillation, endotoxemia), the increases in coronary perfusion pressure
and importantly, cerebral blood flow were consistently greater after vasopressin rescue than after rescue with a second dose of epinephrine. In the 30% of animals who failed to achieve the *a priori* hemodynamic goal CoPP of 20 mmHg after two doses of epinephrine (i.e. epinephrine non-responders), CBF increased more and nearly half attained the CoPP goal of 20 mmHg after a single “rescue” dose of vasopressin (Table 1). While prior published data do not support the routine use of vasopressin as a substitute for epinephrine or combined with epinephrine (Panchal et al. 2019) our data support the consideration of vasopressin as a potential rescue therapy when epinephrine does not achieve adequate CoPP response. The use of rescue vasopressin in this manner may raise CBF more than providing another dose of epinephrine.

In the overall cohort, vasopressin had significantly greater effect on CoPP, a value that directly correlates with ROSC (Paradis et al. 1990), than the preceding rescue dose of epinephrine. The magnitude of the difference in CoPP response between vasopressin and epinephrine was greatest in epinephrine non-responders (+7.64 [4.86, 11.02] mmHg vs. +2.76 [1.28, 6.58] mmHg), though this difference did not reach statistical significance. This improvement in CoPP is consistent with prior work showing significantly higher CoPP after a combination of vasopressin and epinephrine than after either medication alone (Mayr et al. 2001).

To ensure these findings were robust and potentially translatable to a practical clinical setting, we sought to further characterize the response to the second dose of epinephrine and offer alternative definitions of epinephrine responsiveness based upon thresholds of CoPP rising ≥ 3 mmHg, ≥5 mmHg, ≥7 mmHg, or ≥10 mmHg after the second dose of epinephrine (Supplemental Table 2). Since less than half of animals (31/67, 46%) achieved an increase in CoPP of ≥ 3 mmHg, it is clear that a population of epinephrine non-responders exists even with alternative definitions. Cumulatively, these data demonstrate heterogeneity in the hemodynamic response to epinephrine and that some animals with a poor response to epinephrine do, in fact, respond to vasopressin (Figure 3c).

Vasopressin also increased CBF more than the rescue dose of epinephrine in all responder groups (Table 1). The second “rescue” dose of epinephrine did not increase median CBF (Figure 4). Vasopressor effects on the cerebral vasculature are complex and highly variable, with high doses of vasopressors at risk to decrease rather than increase perfusion to critical areas of brain (Thorup et al. 2019). Epinephrine, a potent mixed alpha- and beta-adrenergic agonist and the mainstay of vasopressor therapy during CPR (de Caen et al. 2015), has potential detrimental cerebral effects, and higher rescue doses of epinephrine have been shown to induce cerebral vasoconstriction in animal studies (Gedeborg et al. 2000). These effects can include decreased cerebral oxygenation (Ristagno et al. 2007; Ristagno et al. 2009) and impaired cerebral microvascular blood flow (Ristagno et al. 2009). In addition, the large, randomized clinical trial PARAMEDIC II suggested that cardiac arrest survivors treated with epinephrine had more severe neurologic impairment than those without epinephrine (Perkins et al. 2018).

Vasopressin may have less adverse effects on the cerebral microvasculature than epinephrine. Previous porcine translational models of cardiac arrest have demonstrated greater CBF, higher cerebral pH, lower
PCO2, and lower cerebral oxygen extraction after vasopressin vs. epinephrine (Prengel et al. 1996), and improved rates of survival with good neurologic outcomes (Wenzel et al. 2000b). Other porcine studies have shown vasopressin to be more effective in raising cerebral blood flow either alone (Wenzel et al. 2000a) or in combination with epinephrine (Voelckel et al. 2000; Voelckel et al. 2002). A large, randomized clinical trial showed that vasopressin combined with epinephrine and steroids, compared to epinephrine alone, may increase survival to hospital discharge with favorable neurological status (Mentzelopoulos et al. 2013). However, vasopressin remains a Class IIb recommendation in adults and Class Indeterminate recommendation in children by current resuscitation guidelines (Panchal et al. 2019).

Through activation of V1a receptors on smooth muscle cells, vasopressin may facilitate a more pronounced blood flow shift from peripheral to vital organs. These mechanistic differences, coupled with superior systemic hemodynamics, may explain the greater CBF changes following vasopressin relative to epinephrine, and these may be more pronounced in combination with epinephrine, specifically as a rescue therapy. Cumulatively, these existing studies and the present data support the conduct of head-to-head prospective studies comparing CBF and neurologic outcome with rescue vasopressin compared to rescue standard dose epinephrine (e.g. usual care).

Most pediatric cardiac arrests occur in ICUs and many of these patients have arterial catheters in place at the time of arrest (Berg et al. 2013), thus one could determine which patients fail physiologic response to initial epinephrine boluses. Prior negative adult human randomized controlled trials have randomized initial vasopressin therapy vs epinephrine therapy (Wenzel et al. 2004) or combined initial vasopressin-epinephrine vs epinephrine therapy (Gueugniaud et al. 2008), but meta-analyses of combined routine vasopressin-epinephrine therapies have only shown promise for out of hospital adult asystolic arrest (Mentzelopoulos et al. 2012). Vasopressin in these trials was administered in a standardized manner without regard to hemodynamic responses, so it is possible that there would be increased efficacy when administered to achieve diastolic blood pressure goals that are associated with improved outcomes (Berg et al. 2018). Future work should compare rescue epinephrine and vasopressin head-to-head in a physiology-directed fashion, stratified by initial host response to epinephrine.

This study has limitations. First, its pre-clinical nature could limit translatability to the bedside. However, experiments were conducted in established translational porcine models of cardiac arrest, subjects underwent consistent and standardized injuries, received consistent and highly protocolized resuscitations to minimize variability, and had closed systems of invasive monitoring for hemodynamic and neurologic data collection, with paired analyses allowing effect comparisons within a single subject. In addition, these laboratory models are relevant to patients in the ICU setting with arterial catheters in place at the time of cardiac arrest. Second, as this was an observational analysis of animals receiving HD-CPR, we did not compare vasopressin “rescue” to “rescue” with a third dose of epinephrine. Because these animals had less response to the second dose of epinephrine than to the first dose (Figure 3a, Figure 4), and subsequent boluses of epinephrine have diminishing effects (Nosrati et al. 2019; Wenzel et al. 1999), it is likely that the differences would have been more marked if we compared a third dose of epinephrine to vasopressin as the third vasopressor dose.
Conclusions

In translational models of CPR, rescue doses of vasopressin increased coronary perfusion pressure and cerebral blood flow greater than rescue doses of epinephrine. Among the 30% of animals who failed to meet a CoPP threshold of 20mmHg after two standard epinephrine doses (epinephrine non-responders), CBF increased more with vasopressin than epinephrine and 45% attained the CoPP goal of 20 mmHg after a single “rescue” dose of vasopressin. These findings suggest that rescue doses of vasopressin may potentially be beneficial for selected patients who did not respond adequately to epinephrine during CPR.

Declarations

Ethics approval and consent to participate:

The Children’s Hospital of Philadelphia Institutional Animal Care and Use Committee approved all experimental protocols, which were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Institutional Animal Care and Use Committee (IACUC) Protocol #’s:

IAC 16-001023

IAC 14-00112

Consent for publication: Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

Morgan receives grant funding from the NIH and serves on the American Heart Association (AHA) Emergency Cardiovascular Care Committee. Dr. Berg receives grant funding from the NIH. Dr. Sutton receives grant funding from the NIH, serves on the AHA Emergency Cardiovascular Care Committee, and is Vice Chair of the AHA Get with the Guidelines-Resuscitation Pediatric Task Force. Dr. Kilbaugh receives grant funding from the National Institutes of Health (NIH) and the Department of Defense. Dr Nadkarni receives unrestricted grant funding from the NIH, AHRQ, Zoll Medical, American Heart Association, Laerdal Medical, Nihon Kohden, Inc and serves as a volunteer committee member for the American Heart Association, International Liaison Committee on Resuscitation, Citizen CPR Foundation, and Society for Critical Care Medicine.

Funding
Financial support was provided through Russell Raphaely Endowed Chair funds at the Children’s Hospital of Philadelphia and grant funding through the NIH National Heart, Lung, and Blood Institute (R01HL141386 & K23HL148541) and Eunice Kennedy Shriver National Institute for Child Health and Human Development (R21HD089132).

**Authors' contributions.** *All authors read and approved the final manuscript.*

JS analyzed and interpreted the data, performed statistical analyses, and wrote the manuscript.

RWM analyzed and interpreted the data, performed statistical analyses, and contributed major changes and revisions to the manuscript.

WPL collected and analyzed all data, along with data interpretation and manuscript revision.

ALR collected and analyzed data and revised the manuscript.

AMM collected and analyzed data and revised the manuscript.

CDM collected and analyzed data and revised the manuscript.

YL collected and analyzed data.

TK collected and analyzed data and revised the manuscript.

VMN collected and analyzed data and provided multiple rounds of insights to edit the concept and content of the manuscript.

RAB analyzed data and provided multiple rounds of insights to edit the concept and content of the manuscript.

RMS analyzed data and provided multiple rounds of insights to edit the concept and content of the manuscript.

TJK analyzed and interpreted the data, performed statistical analyses, and contributed major changes and revisions to the manuscript.

**Acknowledgements:** Not applicable.

**Authors' information** (optional)

Robert A Berg is the co-founding director of the Center for Pediatric Resuscitation and a Russell Raphaely Endowed Chair as the division chief of Critical Care Medicine within the Department of Anesthesiology and Critical Care Medicine.

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Table 1: Comparison of the effects of the second dose of epinephrine in a.) the total cohort (n = 67), b.) epinephrine responders (n = 47), and c.) epinephrine non-responders (n = 20).

Vasopressor effects were defined as the difference between pre-vasopressor mean and post-vasopressor maximum. Medians are reported with interquartile ranges. These differences were compared using Wilcoxon rank sum statistical tests.

IQR = interquartile range; CoPP = coronary perfusion pressure; MAP = mean arterial pressure; Mean PA = mean pulmonary artery pressure; RAP = right atrial pressure; EtCO2 = end tidal carbon dioxide; CBF = cerebral blood flow; PbtO2 = brain tissue oxygenation.

A. The total cohort (n = 67)
|                          | Epinephrine #2 D  | Vasopressin D  | p   |
|--------------------------|-------------------|----------------|-----|
| **Total Cohort (n=67)**  |                   |                |     |
| CoPP                     | 5.43 (1.56 – 9.82)| 8.16 (4.35 – 12.06)| 0.022 |
| CBF                      | 0.00 (-0.77 – 18.24) | 14.58 (-0.05 – 38.12) | 0.005 |
| MAP                      | 5.90 (1.98 – 13.82) | 8.62 (3.90 – 13.16) | 0.21 |
| Mean PA                  | 0.04 (-0.80 – 2.98) | 4.05 (0.42 – 7.80) | <0.001 |
| RAP                      | 0.94 (0.43 – 1.61) | 0.70 (0.19 – 1.39) | 0.25 |
| ETCO2                    | -0.18 (-2.37 – 2.83) | -0.19 (-1.5 – 0.98) | 0.74 |
| **Epinephrine Responders (n=47)** |                 |                |     |
| CoPP                     | 6.89 (2.46 – 10.65) | 8.24 (4.18 – 13.99) | 0.21 |
| CBF                      | 0.065 (-0.51 – 22.67) | 16.03 (-0.15 – 44.8) | 0.04 |
| MAP                      | 9.00 (3.32 – 14.62) | 9.02 (4.40 – 13.99) | 0.60 |
| Mean PA                  | 0.23 (-0.65 – 2.98) | 4.26 (0.66 – 8.39) | 0.001 |
| RAP                      | 0.91 (0.43 – 1.38) | 0.81 (0.91 – 1.44) | 0.64 |
| ETCO2                    | -0.02 (-2.11 – 2.93) | -0.18 (-1.31 – 0.98) | 0.63 |
| **Epinephrine Non-responders (n=20)** |             |                |     |
| CoPP                     | 2.76 (1.28 – 6.58) | 7.64 (4.86 – 11.02) | 0.22 |
| CBF                      | -0.28 (-2.33 – 6.91) | 14.58 (3.55 – 34.90) | 0.045 |
| MAP                      | 2.53 (0.91 – 7.29) | 6.84 (3.68 – 10.34) | 0.16 |
| Mean PA                  | -0.13 (-1.71 – 2.37) | 2.45 (0.44 – 6.59) | 0.01 |
| RAP                      | 1.19 (0.49 – 2.05) | 0.70 (0.22 – 1.29) | 0.23 |
| ETCO2                    | -0.82 (-2.86 – 1.29) | -0.47 (-1.87 – 0.90) | 0.95 |

**Figures**
Figure 1

Hemodynamic-directed CPR protocol Footnote: CPR = cardiopulmonary resuscitation; ETT = endotracheal tube; VF = ventricular fibrillation; HD = hemodynamic-directed; SBP = systolic blood pressure; CoPP = coronary perfusion pressure; ROSC = return of spontaneous circulation
Figure 2

Study population enrollment and characteristics.
**Figure 3**

a: Coronary perfusion pressure during cardiac arrest in the total cohort (n = 67) b: Coronary perfusion pressure during cardiac arrest in a population of epinephrine non-responders (n = 20), defined by coronary perfusion pressure < 20mmHg after both doses of epinephrine. c: Coronary perfusion pressure during cardiac arrest in the population of epinephrine non-responders with subsequent response to vasopressin (n = 9), defined by coronary perfusion pressure ≥ 20mmHg after vasopressin. *The time course of CPR is depicted non-linearly due to the fact that vasopressors are delivered when needed as based on CoPP <20mmHg. The first two vertical lines represent the first and second epinephrine doses and the third vertical line represents the vasopressin dose. The two minutes before the first dose of epinephrine, then the one minute of data between vasopressors, and lastly the two minutes post-vasopressin are depicted. The dashed, horizontal line depicts the a priori CoPP goal of 20mmHg.

**Figure 4**

Cerebral blood flow during cardiac arrest in the total cohort of subjects with neuromonitoring devices in place (n = 62). *The time course of CPR is depicted non-linearly due to the fact that vasopressors are delivered when needed as based on CoPP <20mmHg. The first two vertical lines represent the first and second epinephrine doses and the third vertical line represents the vasopressin dose. The two minutes before the first dose of epinephrine, then the one minute of data between vasopressors, and lastly the two minutes post-vasopressin are depicted.

**Supplementary Files**
This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTable1.docx