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Experimental paper

Hemodynamic directed CPR improves short-term survival from asphyxia-associated cardiac arrest☆

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ABSTRACT

Aim: Adequate coronary perfusion pressure (CPP) during cardiopulmonary resuscitation (CPR) is essential for establishing return of spontaneous circulation. The objective of this study was to compare short-term survival using a hemodynamic directed resuscitation strategy versus an absolute depth-guided approach in a porcine model of asphyxia-associated cardiac arrest. We hypothesized that a hemodynamic directed approach would improve short-term survival compared to depth-guided care.
Methods: After 7 min of asphyxia, followed by induction of ventricular fibrillation, 19 female 3-month old swine (31 ± 0.4 kg) were randomized to receive one of three resuscitation strategies: (1) hemodynamic directed care (CPP-20): chest compressions (CCs) with depth titrated to a target systolic blood pressure of 100 mmHg and titration of vasopressors to maintain CPP > 20 mmHg; (2) depth 33 mm (D33): target CC depth of 33 mm with standard American Heart Association (AHA) epinephrine dosing; or (3) depth 51 mm (D51): target CC depth of 51 mm with standard AHA epinephrine dosing. All animals received manual CPR guided by audiovisual feedback for 10 min before first shock.
Results: 45-Min survival was higher in the CPP-20 group (6/6) compared to D33 (1/7) or D51 (1/6) groups; $p = 0.002$. Coronary perfusion pressures were higher in the CPP-20 group compared to D33 ($p = 0.011$) and D51 ($p = 0.04$), and in survivors compared to non-survivors ($p < 0.01$). Total number of vasopressor doses administered and defibrillation attempts were not different.
Conclusions: Hemodynamic directed care targeting CPPs > 20 mmHg improves short-term survival in an intensive care unit porcine model of asphyxia-associated cardiac arrest.

1. Introduction

The success of cardiopulmonary resuscitation (CPR) depends on adequate myocardial blood flow.[1–4] Nevertheless, current guidelines for the treatment of cardiac arrest assume that all patients can be treated with a uniform chest compression (CC) depth despite a paucity of data indicating that a specific depth consistently provides adequate myocardial blood flow.[5,6] A treatment strategy to titrate compression depth and vasopressor dosing to physiological parameters that are more closely related to myocardial blood flow would presumably be a more successful approach, and would be a major paradigm shift in the field of resuscitation.

During CPR, coronary perfusion pressure (CPP), the aortic pressure minus the right atrial pressure during the relaxation ("diastolic") phase of CPR, is the primary determinant of myocardial blood flow.[2,7,8] Therefore, it is not surprising that in both human and animal studies, CPP is also associated with resuscitation outcome.[3,4,9–11] Failure to generate a CPP of at least 15–20 mmHg during CPR is rarely associated with a successful resuscitation.[2,3,11] Importantly, many patients with in-hospital cardiac arrests are in intensive care units and have invasive hemodynamic monitoring,[12,13] so a hemodynamic directed CPR strategy targeted to attain an adequate CPP could be implemented.

This randomized investigation compared short-term survival with a hemodynamic directed resuscitation strategy intended to attain CPPs > 20 mmHg (CPP-20) versus absolute depth-guided CPR in a porcine model of asphyxia-associated cardiac arrest. We

Abbreviations: AHA, American Heart Association; CC, chest compression; CPP, coronary perfusion pressure; $ETCO_2$, end tidal carbon dioxide.

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further subdivided the depth-guided CPR into two groups: one with CC depth targeted to previously documented "usual care" of 33 mm (D33) and one with CCs targeted to the American Heart Association (AHA) 2010 guideline recommended depth of 51 mm (D51). We hypothesized that the CPP-20 resuscitation strategy would improve short-term survival compared to either D33 or D51.

2. Methods

2.1. Animal preparation

The experimental protocol was approved by The University of Pennsylvania Institutional Animal Care and Use Committee. Nineteen healthy 3-month old female domestic swine were anesthetized and mechanically ventilated using a Datex Ohmeda anesthesia machine (Modulus SE) on a mixture of room air and titrated isoflurane (~1.0–2.5%) with a tidal volume of 12 mL/kg, PEEP 6 cm H_2O, rate of 12 breaths/min, and titration of rate to maintain end-tidal carbon dioxide ($ETCO_2$) at 38–42 mmHg (NICO, Novametrix Medical Systems Inc.).

High fidelity, solid-state, micromanometer-tipped catheters (MPC-500, Millar Instruments) were advanced through the right femoral artery and external jugular vein into thoracic locations to measure continuous aortic and right atrial pressures respectively. A Swan-Ganz Thermodilution catheter (Edwards Lifesciences) was advanced into the pulmonary artery, and a bipolar pacing catheter (Edwards Lifesciences) was advanced into the right ventricle. All catheter placements were confirmed with fluoroscopy. Unfractionated heparin 200 U/kg was provided to prevent catheter clotting. Prior to obtaining any baseline measurements, all animals received 20 mL/kg of 0.9% normal saline intravenously to replace overnight fasting fluid deficits.

2.2. Measurements

Thermodilution cardiac outputs (ICU monitor: model HP66, Hewlett Packard) were obtained at baseline. Arterial blood gas specimens were obtained from the thoracic aorta at baseline (before asphyxia), at 2 min, 4 min, and 6 1/2 min of asphyxia, and then 2 1/2 min and 6 min after the induction of ventricular fibrillation (VF) during CPR in the protocol resuscitation period. Coronary perfusion pressure (CPP) was calculated by subtracting the mid-diastolic right atrial pressure from the mid-diastolic aortic pressure.

To guide and record manual CPR quality, the Philips Heart Start MRx defibrillator with Q-CPR option was deployed during the experimental protocol. Using force transducer/accelerometer technology, the defibrillator records CPR quality and provides audiovisual feedback to the chest compression (CC) provider for rate (CC/min), depth (mm), and incomplete chest wall recoil (residual leaning force (g)).[14–17]

2.3. Experimental protocol

2.3.1. Overview (Fig. 1)

The novel protocol utilized in this experiment was designed to address asphyxia-associated cardiac arrest occurring in an intensive care unit. Asphyxia was induced by endotracheal clamping and confirmed by absence of exhaled CO_2. After 7 min of asphyxia with severe arterial hypoxemia, VF was induced by electrical pacing to assure that the animal would not have return of spontaneous circulation from CPR alone in less than 10 min. This model therefore allowed us to compare outcomes following 10 min of three different CPR and advanced life support strategies, because the duration of most in-hospital CPR is at least 10 min for both survivors and non-survivors.[12]

In all treatment arms, CCs were provided with a target rate of 100 CC/min and ventilations at 6 breaths/min with 100% oxygen. Brief interruptions in CPR every 2 min mimicked pulse checks/rhythm analysis. Animals randomly received one of three resuscitation strategies: (1) hemodynamic directed care (CPP-20): CCs with depth titrated to a target systolic blood pressure of 100 mmHg and titration of vasopressors to maintain CPP > 20 mmHg; (2) depth 33 mm (D33): target CC depth of 33 mm[14–19] with standard AHA epinephrine dosing interval; or (3) depth 51 mm (D51): target CC depth of 51 mm with standard AHA epinephrine dosing interval. Animals in the D33 *and* D51 groups received intravenous epinephrine (0.02 mg/kg) every 4 min starting at minute 9 of the protocol (2 min after CPR was started). Animals in the CPP-20 group only received intravenous vasopressor if the CPP was <20 mmHg, starting at minute 8 of the protocol. The order of drug administration in CPP-20 was epinephrine (0.02 mg/kg) – epinephrine (0.02 mg/kg) – vasopressin (0.4 U/kg). The dosing interval was 1 min between epinephrine doses, and if vasopressin was given, 2 min elapsed before the cycle was restarted with another epinephrine dose. After 10 min of CPR (minute 17 of the protocol), the initial 200 J biphasic waveform defibrillation attempt was provided. Resuscitation according to treatment strategy continued until sustained ROSC was attained or at minute 27 of the protocol (after an additional 10 min of resuscitation post-initial defibrillation attempt). If ROSC was attained, the animals were supported for 45 min in a simulated intensive care setting. After ROSC, mechanical ventilation was provided with 100% oxygen and adjusted to obtain an $ETCO_2$ of 38–42 mmHg. Isoflurane was administered as necessary. At 45 min, the animals were euthanized with pentobarbital and potassium chloride. All animals received a post-mortem examination for detection of visceral injuries.

2.4. Data analysis/outcomes

The primary outcome of the study was 45-min ICU survival. Secondary outcomes included: (1) return of spontaneous circulation (ROSC); (2) hemodynamic measures (specifically CPP); and (3) CPR quality variables. Statistical analysis was completed using the Stata-IC statistical package (Version 12.0, StataCorp, College Station, TX). Normality of continuous variables was assessed using the Skewness–Kurtosis test. Normally distributed continuous variables were described as mean ± SEM and compared by ANOVA. Continuous variables that were not normally distributed were described as median (25%, 75%) and evaluated by the Kruskal–Wallis test. Comparisons of dichotomous variables, such as 45-min ICU survival and rate of return of spontaneous circulation were evaluated by Fisher's exact test. To control for correlation of CPR epochs within animals, differences in CPPs over time and between treatment groups and between survivors/non-survivors were assessed using generalized estimating equations.[20]

3. Results

The primary outcome variable of 45-min ICU survival and the secondary outcome variable of any ROSC were both significantly different across treatments (Table 1) with superior survival rates in the CPP-20 group. In a model using generalized estimating equations (GEE), coronary perfusion pressure (Fig. 2) was significantly higher in the CPP-20 group compared to both D33 ($p = 0.011$) and D51 ($p = 0.04$), and higher in survivors compared to non-survivors irrespective of treatment group ($p < 0.01$).

3.1. Resuscitation variables

Chest compression depth was significantly different among groups: D33 = 30 ± 0.2 mm; D51 = 48 ± 0.3 mm;

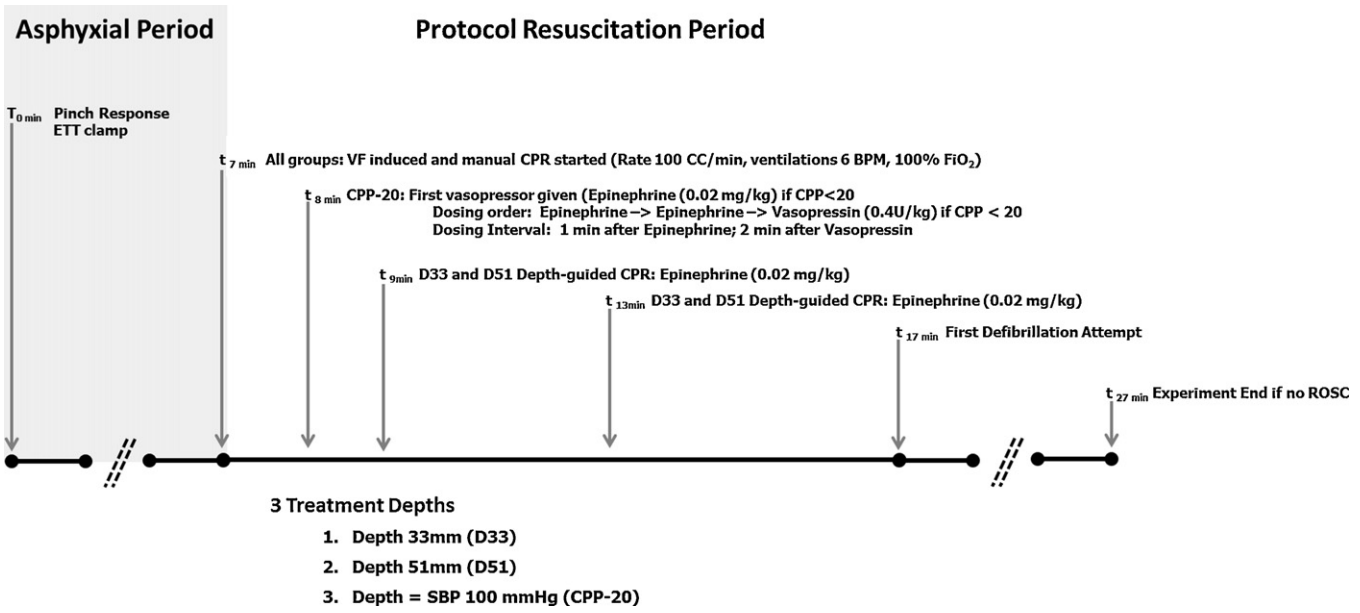

Fig. 1. Protocol design. During protocol resuscitation period, animals were randomized to receive one of three resuscitation strategies. SBP indicates systolic blood pressure. D33 and D51 refer to depth-directed CPR at 33 mm and 51 mm, respectively. CPP-20 refers to CPR directed to attain coronary perfusion pressure >20 mmHg.

Table 1
Rates of survival across treatment groups. Depth 33 and depth 51 refer to depth-guided CPR at 33 mm and 51 mm, respectively. CPP-20 refers to CPR directed to attain coronary perfusion pressure >20 mmHg.

	Depth 33 (n = 7)	Depth 51 (n = 6)	CPP-20 (n = 6)	p
Survival [n (%)]				
Any ROSC	1 (14)	2 (33)	6 (100)	0.006
45 min ICU survival	1 (14)	1 (17)	6 (100)	0.002

CPP-20 = 38 ± 0.8 mm (p < 0.01). Other CPR quality variables were not different (rate = 100 ± 0.1 CC/min; no flow fraction = 3.2 ± 0.2%; less than 0.01% of compressions had measurable residual leaning). Total number of vasopressors doses administered was not different (D33 = 4 (4, 5); D51 = 4.5 (4, 5); CPP-20 = 6 (3, 8), p = 0.14), although more doses were provided before the initial defibrillation attempt in the CPP-20 group (D33 = 2 (2, 2); D51 = 2 (2, 2); CPP-20 = 4.5 (3, 6), p < 0.01). Overall number of defibrillation attempts was not different among groups (D33 = 4 (3, 5); D51 = 4.5 (3, 6); CPP-20 = 2 (1, 4), p = 0.3). Only 1 surviving animal in the study required vasopressor support during the intensive care unit period after ROSC; that animal was in the D51 group.

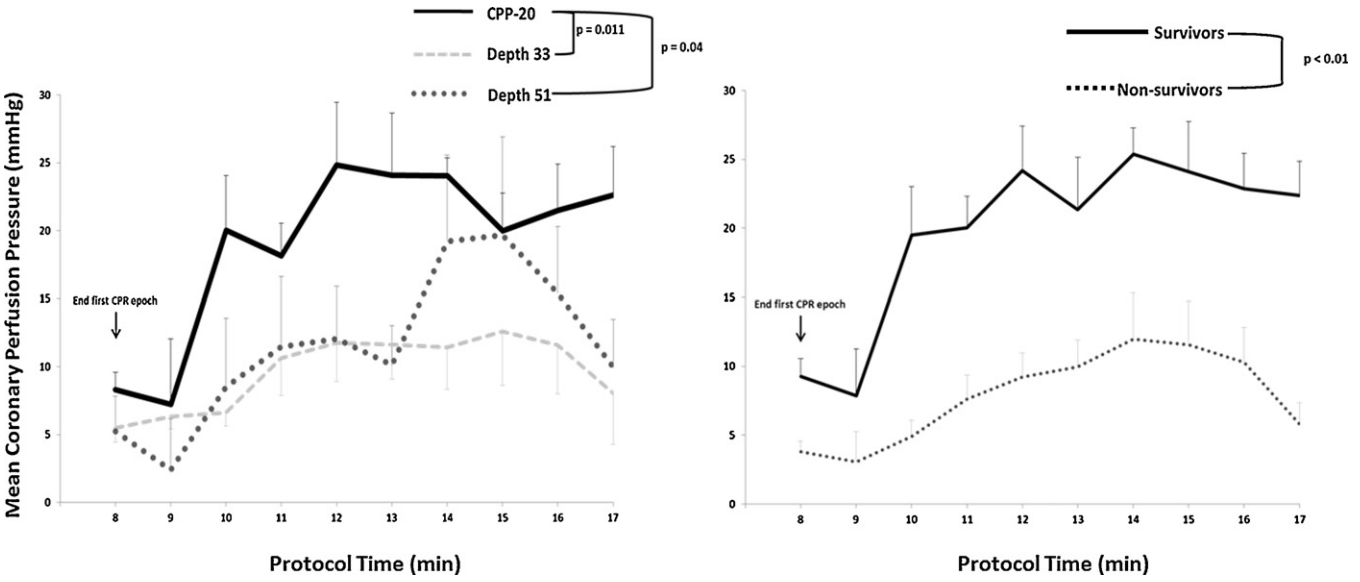

Fig. 2. Mean coronary perfusion pressure during each minute of CPR across treatment groups (left) and between survivors and non-survivors (right). Error bars represent SEM. D33 and D51 refer to depth-directed CPR at 33 mm and 51 mm, respectively. CPP-20 refers to CPR directed to attain coronary perfusion pressure >20 mmHg.

Table 2
Hemodynamic variables.

	Depth 33 ($n=5$)	Depth 51 ($n=5$)	CPP-20 ($n=5$)	p
Baseline				
CO (L/min)	2.8 (0.2)	2.9 (0.3)	2.9 (0.3)	0.89
Aos	87 (5)	108 (6)	105 (11)	0.17
AoD	64 (4)	85 (3)	81 (10)	0.09
RAD	6 (3)	10 (3)	6 (4)	0.65
CPP	58 (6)	76 (2)	75 (9)	0.13
End of asphyxial period[a]				
AoS	48 (13)	42 (10)	77 (21)	0.26
AoD	27 (4)	26 (4)	41 (8)	0.15
RAD	13 (1)	16 (2)	16 (3)	0.53
CPP	14 (4)	10 (5)	25 (5)	0.11
End of resuscitation period[b]				
AoS	45 (15)	111 (27)	120 (11)	0.03[‡,§]
AoD	18 (4)	29 (4)	38 (4)	0.02[‖]
RAD	10 (1)	20 (1)	16 (3)	0.03[¶]
CPP	8 (4)	10 (3)	23 (4)	0.03[**,††]
ET CO_2	20 (6)	30 (3)	21 (3)	0.18

Pressures in mmHg. AoS, aortic systolic pressure; AoD, aortic diastolic pressure; RAD, right atrial diastolic pressure; CPP, coronary perfusion pressure; ET CO_2, end tidal carbon dioxide. Depth 33 (D33) and depth 51 (D51) refer to depth-guided CPR at 33 mm and 51 mm, respectively. CPP-20 refers to CPR directed to attain coronary perfusion pressure >20 mmHg. Data presented as mean (SEM).

[a] Last epoch during asphyxial period (minutes 6–7).
[b] Last epoch during protocol resuscitation period CPR (minutes 16–17).
[‡] CPP-20 versus D33: $p=0.004$.
[‖] CPP-20 versus D33: $p=0.007$.
[**] CPP-20 versus D33: $p=0.024$.
[§] D51 versus D33: $p=0.06$.
[¶] D51 versus D33: $p=0.0005$.
[††] CPP-20 versus D51: $p=0.036$.

3.2. Hemodynamics and arterial blood gases

There were no differences among groups for weight (31 ± 0.4 kg, $p=0.14$). Hemodynamic variables were not different at pre-asphyxia baseline or at the end of the asphyxial period (Table 2). During the last minute of the resuscitation period (minutes 16–17), there were significant differences across treatment groups for all hemodynamic variables measured (Table 2). There was a trend toward higher end tidal CO_2 in the D51 group that did not reach statistical significance. There were no differences in arterial blood gases obtained at baseline, at the end of the asphyxial period, or after 6 min of CPR (Table 3).

4. Discussion

This study establishes that short-term survival from asphyxia-associated cardiac arrest can be superior after hemodynamic directed CPR to maintain coronary perfusion pressure >20 mmHg (CPP-20) compared to resuscitation with depth of compressions guided to either 33 mm or 51 mm and standard AHA vasopressor dosing. Congruent with previous investigations,[2,3,11] coronary perfusion pressures were higher in survivors compared to non-survivors irrespective of treatment group, providing mechanistic validity for this model and for the differential outcomes in the experimental groups.

This animal model was intended to address CPR of 10 min duration for an asphyxia-associated cardiac arrest because most in-hospital cardiac arrests are associated with an acute asphyxial event and at least 10 min of CPR.[12,13] In previous studies of CPR for asphyxial cardiac arrests without the induction of VF, the animals that were successfully resuscitated almost always attained restoration of circulation during the first several minutes of CPR.[21,22] Because those models would have precluded the opportunity to evaluate the three different resuscitation strategies for more than a few minutes of CPR, we chose a model that combined a severe asphyxial insult with induction of VF so that we could study these three resuscitation strategies during an entire 10-min epoch of CPR.

In-hospital cardiac arrests are occurring more often in intensive care units, thought to be in part due to the emergence of medical emergency teams.[12,13,23–25] Invasive hemodynamic monitoring is available for many patients in these settings, yet AHA recommendations for CPR focus on depth and rate of compressions and fixed vasopressor dosing rather than titrating compression depth and vasopressor dosing to hemodynamics. Coronary perfusion pressure (CPP) during CPR refers to aortic pressure minus right atrial pressure in the relaxation phase (aortic "diastolic" pressure minus right atrial "diastolic" pressure).[4] The relationship between CPP and myocardial blood flow, and in turn, resuscitation outcome is well established.[1–4,9–11] However, to our knowledge, this is the first investigation to evaluate a treatment algorithm with manually provided CCs titrated to a hemodynamic goal (systolic blood pressure) and vasopressor administration targeted to CPPs. In short, our findings highlight a new therapeutic strategy that could be applied during actual resuscitation attempts. In addition, this strategy focuses on individualizing resuscitation to the appropriate hemodynamic goal rather than a standard "one-size-fits-all" strategy.

All three groups in this investigation received high quality quantitatively evaluated manual CPR (CC rate 100/min, full chest wall recoil, and a ventilation rate of 6/min). As planned, there were differences in CC depth across treatment groups. Previous investigations have shown that deeper compressions are associated with superior outcomes,[18,26,27] because deeper compressions are often associated with higher CPPs. In apparent contrast to those investigations, deeper compressions in the D51 group did not translate into improved survival even with excellent systolic blood pressures, because these D51 animals did not attain adequate coronary perfusion after this severe asphyxial insult. Compared with the D51 group, the CPP-20 animals had higher CPPs and were therefore more likely to survive. As in previous studies, the surviving animals from all three groups had substantially higher CPPs than the non-surviving animals.

In numerous experimental models, noninvasive end-tidal carbon dioxide correlates well with cardiac output and resuscitation success.[28–36] However, $ETCO_2$ correlates better with cardiac output and pulmonary blood flow than with coronary perfusion pressure, because the CO_2 from the tissues is delivered to the lungs via pulmonary blood flow in relation to the cardiac output. During actual resuscitation attempts, achieving $ETCO_2$ levels >10–15 mmHg has been associated with survival,[30,32] and similarly, low $ETCO_2$ (<10 mmHg) is a strong predictor of unsuccessful CPR (death).[32] In addition, an abrupt increase in exhaled CO_2 is an indicator of restoration of a spontaneous circulation because of the attendant increased cardiac output and pulmonary blood flow.[34] For all of these reasons, continuous $ETCO_2$ monitoring is now recommended during cardiac arrest resuscitation when available.[5,6] In this investigation, the $ETCO_2$ levels were as high or higher in the AHA-51 group with deeper compressions compared with the other two groups with less deep compressions. Among the physiological measurements during CPR, the CPP measurements were better predictors of outcomes than the $ETCO_2$ measurements. These data support the concept that invasive hemodynamic monitoring during CPR is superior to $ETCO_2$ monitoring.

This laboratory study has notable limitations. First, we evaluated 45-min ICU survival, a short-term outcome. The effect of targeting hemodynamic goals during resuscitation on long-term survival and neurological outcome remains unknown. Nevertheless, inability to achieve short-term survival in the depth-guided groups precludes the potential for long-term survival. In the CPP-20 group, vasopressors were often provided earlier per the CPP titration and the median number of vasopressor doses during CPR were greater than

Table 3
Arterial blood gases.

	Depth 33 ($n=7$)	Depth 51 ($n=6$)	CPP-20 ($n=5$)	p
Baseline				
pH	7.53 (0.02)	7.53 (0.01)	7.54 (0.01)	0.96
pCO_2 (mmHg)	46 (1)	44 (2)	45 (1)	0.42
pO_2 (mmHg)	127 (8)	120 (10)	136 (9)	0.49
End of asphyxial period[a]				
pH	7.28 (0.02)	7.25 (0.02)	7.31 (0.02)	0.23
pCO_2 (mmHg)	82 (5)	84 (4)	75 (7)	0.51
pO_2 (mmHg)	10 (1)	12 (1)	14 (2)	0.25
After 6 min of CPR[b]				
pH	7.44 (0.05)	7.32 (0.04)	7.40 (0.02)	0.13
pCO_2 (mmHg)	35 (5)	49 (7)	35 (7)	0.23
pO_2 (mmHg)	312 (88)	220 (67)	211 (67)	0.58

Depth 33 and depth 51 refer to depth-guided CPR at 33 mm and 51 mm, respectively. CPP-20 refers to CPR directed to attain coronary perfusion pressure >20 mmHg.
[a] Sample drawn at 6 min 30 s during asphyxial period.
[b] Sample drawn at 6 min during protocol resuscitation period.

in the other two groups. However, some of these CPP-20 animals survived with no more vasopressors than the median number of doses in the other two groups. The determinant of outcome was adequacy of CPP rather than number of vasopressor doses per se. There were also differences between groups in the type of vasopressor administered. As the primary objective was to evaluate a resuscitation approach targeting hemodynamic goals, the CPP-20 animals received vasopressin when 2 doses of epinephrine could not maintain CPP >20 mmHg. Rather than continuing to administer a therapy that was not achieving treatment goals, we chose to alter our vasopressor choice so as to evaluate a dynamic treatment algorithm that was targeted to subject physiology (CPP-20 goal-directed) rather than an approach that was uniform across subjects (D33 or 51). Although clinical studies have not shown better outcomes with vasopressin,[37–40] such studies have not used vasopressin to actively titrate CPP, which may explain the superior survival outcomes in the CPP-20 group. Another important limitation is lack of blinding. By its very nature, this study could not be blinded. Those participating in the resuscitation attempts needed to be aware of the resuscitation strategy. However, strict adherence to resuscitation regimens was intended, and the statistical differences in chest compression depths – while other CPR quality variables were similar among the groups – provides evidence that this bias was minimized. Finally, while we evaluated one valid model of in-hospital cardiac arrest, future studies should investigate whether a coronary perfusion directed resuscitation strategy would also improve outcomes when other common etiologies of in-hospital arrests (e.g., sepsis/hypotension) are evaluated.

5. Conclusions

In this novel intensive care unit model of asphyxia-associated cardiac arrest, short-term survival was improved when resuscitation therapy was titrated to CPR-generated physiology with specific hemodynamic goals as compared to currently recommended uniform guidelines even with excellent 51 mm compression depth. This treatment protocol individualizes therapy to the patient's hemodynamic status in contrast to the usual "one-size-fits-all" strategy. As more in-hospital cardiac arrests are occurring after transfer to intensive care units, these findings highlight a promising new therapeutic strategy that could be applied during actual resuscitation attempts in highly monitored patients.

Conflict of interest statement

This study was funded by the Laerdal Foundation for Acute Care Medicine, the National Institute of Child Health and Human Development (RMS K23), the National Institute of Neurological Disorders and Stroke (SHF K08), and CHOP CCM Endowed Chair Funds.

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