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Experimental paper

Association of diastolic blood pressure with survival during paediatric cardiopulmonary resuscitation



Caitlin E. O'Brien^a, Polan T. Santos^a, Michael Reyes^a, Shawn Adams^a,
C. Danielle Hopkins^a, Ewa Kulikowicz^a, Jennifer L. Hamrick^b, Justin T. Hamrick^b,
Jennifer K. Lee^a, Sapna R. Kudchadkar^{a,c,d}, Elizabeth A. Hunt^{a,c,e},
Raymond C. Koehler^a, Donald H. Shaffner^{a,*}

^a Department of Anesthesiology/Critical Care Medicine, Johns Hopkins University School of Medicine, 1800 Orleans Street, Bloomberg Children's Center Suite 6302, Baltimore, MD 21287 United States

^b Department of Anesthesiology, Rady Children's Hospital, 3020 Children's Way, San Diego, CA 92123 United States

^c Department of Pediatrics, Johns Hopkins University School of Medicine, 1800 Orleans Street, Bloomberg Children's Center Suite 6302, Baltimore, MD 21287 United States

^d Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, 600 N Wolfe St, Baltimore, MD 21287 United States

^e Division of Health Sciences Informatics, Johns Hopkins University School of Medicine, 2024 East Monument St. S 1-200, Baltimore, MD 21205 United States

Abstract

Aim: To examine the relationship between survival and diastolic blood pressure (DBP) throughout resuscitation from paediatric asphyxial cardiac arrest.

Methods: Retrospective, secondary analysis of 200 swine resuscitations. Swine underwent asphyxial cardiac arrest and were resuscitated with predefined periods of basic and advanced life support (BLS and ALS, respectively). DBP was recorded every 30 s. Survival was defined as 20-min sustained return of spontaneous circulation (ROSC).

Results: During BLS, DBP peaked between 1–3 min and was greater in survivors (20.0 [11.3, 33.3] mmHg) than in non-survivors (5.0 [1.0, 10.0] mmHg; $p < 0.001$). After this transient increase, the DBP in survivors progressively decreased but remained greater than that of non-survivors after 10 min of resuscitation (9.0 [6.0, 13.8] versus 3.0 [1.0, 6.8] mmHg; $p < 0.001$). During ALS, the magnitude of DBP change after the first adrenaline (epinephrine) administration was greater in survivors (22.0 [16.5, 36.5] mmHg) than in non-survivors (6.0 [2.0, 11.0] mmHg; $p < 0.001$). Survival rate was greater when DBP improved by ≥ 26 mmHg after the first dose of adrenaline (20/21; 95%) than when DBP improved by ≤ 10 mmHg (1/99; 1%). The magnitude of DBP change after the first adrenaline administration correlated with the time to ROSC ($r = -0.54$; $p < 0.001$).

Conclusions: Survival after asphyxial cardiac arrest is associated with a higher DBP throughout resuscitation, but the difference between survivors and non-survivors was reduced after prolonged BLS. During ALS, response to adrenaline administration correlates with survival and time to ROSC. If confirmed clinically, these findings may be useful for titrating adrenaline during resuscitation and prognosticating likelihood of ROSC.

Institutional Protocol Numbers: SW14M223 and SW17M101

Keywords: Cardiopulmonary resuscitation, Cardiac arrest, Pediatrics, Diastolic blood pressure, Survival, Swine

* Corresponding author at: 1800 Orleans Street, Bloomberg Suite 6322 Baltimore, MD 21287 United States.

E-mail address: dshaffn1@jhmi.edu (D.H. Shaffner).

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Introduction

Cardiac arrest occurs in 2–3% of children admitted to the paediatric intensive care unit.^{1,2} Although outcomes have improved over the last decade, less than half of these children survive to hospital discharge.^{3–5} Sufficient myocardial perfusion pressure is an important determinant of return of spontaneous circulation (ROSC) after cardiac arrest.^{6–8} When invasive hemodynamic monitoring is present, the diastolic blood pressure (DBP) can be used as a surrogate marker of myocardial perfusion during cardiopulmonary resuscitation (CPR).⁹ Mean,⁶ pre-shock,¹⁰ and maximal¹¹ DBP during CPR have been reported to be greater in survivors than in non-survivors. Several preclinical studies demonstrated improved survival using haemodynamic thresholds to titrate chest compression delivery and vasoactive medication administration.^{12–17} Further, the use of physiologic parameters to guide CPR quality is associated with both improved haemodynamics and likelihood of ROSC in adults.^{18,19}

In a consensus statement and in the most recent paediatric guidelines, the American Heart Association (AHA) recommends that DBP be used, when available, to guide chest compression delivery during CPR.^{20,21} However, evidence is insufficient to ascertain whether mean or improving values are more prognostic; the relative importance of initial, mean, and pre-defibrillation values; and how vasoactive medications affect their interpretation. Target values for mean DBP during resuscitation of infants (≥ 25 mmHg) and children (≥ 30 mmHg) have recently been described based on analysis of mean values early in cardiac arrest and in a majority of patients already receiving vasoactive infusions.²² An enhanced understanding of the prognostic value of DBP associated with the phases of resuscitation and with the administration of vasoactive medications could be useful.

In this study, we retrospectively reviewed 200 swine resuscitations and examined the association between survival and DBP throughout the course of resuscitation from asphyxial cardiac arrest. Based on our preliminary observations, we hypothesized that survivors would have higher DBP early in the resuscitation and a greater improvement in DBP after the initial administration of adrenaline (epinephrine) than would non-survivors.

Methods

Overall study design

We performed a retrospective, secondary analysis of several preclinical swine asphyxial cardiac arrest experiments that were originally performed to compare survival among various resuscitation strategies.^{23,24}

Animal preparation

All studies were approved by the Animal Care and Use Committee at the Johns Hopkins University and complied with the United States Public Health Service Policy on the Humane Care and Use of Laboratory Animals. The protocols have been described previously.^{23,24} Briefly, 7–14-day-old Yorkshire swine (3–4 kg) were housed in cages in groups of three and fasted overnight with provision of water. The next morning, they were anesthetized with 2% isoflurane, 70% nitrous oxide, and 30% oxygen. A 4.0 cuffed tracheal tube was

secured via tracheostomy. The femoral artery was cannulated and a catheter was advanced to the mid-thoracic aorta for continuous haemodynamic monitoring and arterial blood gas measurements. A femoral venous catheter was advanced to the mid-thoracic vena cava for administration of sedation prior to asphyxia and adrenaline during resuscitation. In some experiments, a pacing wire was placed through the contralateral femoral vein and advanced until ventricular irritation confirmed right ventricular placement. Pressure-controlled mechanical ventilation was adjusted to maintain a PaCO₂ of 35–45 torr at a rate of 20 breaths per minute during surgery and stabilization. The FiO₂ was decreased from 0.30 to 0.21 for at least 10 min to ensure normoxia prior to protocol initiation. After the surgeries were completed, isoflurane and nitrous oxide were discontinued and fentanyl (10 mcg/kg) and vecuronium (0.3 mg/kg) were administered for animal comfort. Once the asphyxia began, no further anaesthetics were administered.

Experimental protocols

Asphyxial arrest was induced by clamping the endotracheal tube for 11–23 min depending on the assigned protocol. Some piglets were assigned to an asphyxial-fibrillatory arrest and 50 mA of alternating current was applied via the femoral pacing wire for the final 6 min of arrest.^{23,24} At the end of asphyxia, paediatric basic life support (BLS) with chest compressions and mechanical ventilation was initiated. Pressure-controlled mechanical ventilation was resumed with an FiO₂ of 1.0 at the pre-arrest rate (20 breaths/minute), inspiratory pressure, and expiratory pressure settings. The ventilation rate of 20 breaths per minute is higher than that recommended by the AHA, but was intended to offset the reduced tidal volumes achieved when using pressure-limited ventilation during chest compression delivery. Chest compressions were performed with a two-thumb-encircling hands technique, and compressors switched every 2 min per AHA guidelines. Most groups received BLS for 10 min, but some pigs received BLS for 6 min according to their assigned protocols. After completion of BLS, resuscitators initiated advanced life support (ALS), which included administration of adrenaline (300 mcg) and defibrillation attempts (30 joules), if indicated. No additional medications nor fluid resuscitation was provided during BLS or ALS. Physiologic data were recorded at baseline and every 30 s during asphyxia and resuscitation.

Pigs were randomized to one of three resuscitation strategies: (1) standard, (2) end-tidal carbon dioxide (ETCO₂)-guided, and (3) algorithm. In the standard group, chest compressions were delivered at a rate of 100 compressions per minute and a depth of 1/3 the anteroposterior diameter (achieved via a visual marker) per the AHA guidelines.²⁰ Full release between compressions was ensured in real time by a coach. In the ETCO₂-guided group, resuscitators adjusted the rate, depth, force, and thumb position to maximize the ETCO₂ level. The ETCO₂ level was the only physiologic data available to the resuscitator and there was no specific goal. In both the standard and ETCO₂ groups, pigs received adrenaline every 4 min during ALS. In the algorithm group, the chest compression rate was titrated to a target ETCO₂ >30 torr by sequentially increasing the chest compression rate by 10 per minute for each minute that the ETCO₂ was <30 torr. In this group, adrenaline was administered every 2 min if the ETCO₂ was <30 torr during ALS. None of the groups used DBP as a metric for compression quality. Resuscitation in all groups was continued until either ROSC or 20 min of CPR, at which point the experiment was terminated. Survival was defined as sustained ROSC with only fluid administration for 20 min.

Statistical analysis

Normality of continuous variables was assessed with the D'Agostino-Pearson test. Physiologic data are presented as mean \pm standard error of the mean (SEM) for normally distributed data and median with interquartile ranges for non-normally distributed data. Baseline characteristics of survivors and non-survivors were compared by unpaired t-test or Mann-Whitney test as appropriate. Differences in DBP values between survivors and non-survivors at specific time points during resuscitation were compared with the Mann-Whitney test, and two sided p values ≤ 0.05 were considered significant. Only DBP values during active resuscitation were analysed. DBP values during the 30-s interval in which ROSC occurred and thereafter were excluded from the analyses. The DBP response to adrenaline was measured at 90 s after administration based on prior work identifying this time point as the maximal DBP response to adrenaline in this model. Correlation between variables was calculated with Spearman's rank correlation coefficient. All data were analysed in GraphPad Prism 8.0.0 (GraphPad Software, La Jolla, CA, USA) or SPSS 25.0 (Statistics for Windows, Armonk, NY, USA).

Results

Two hundred pigs underwent asphyxial cardiac arrest. Seventy pigs were included in protocols with 6 min of BLS, whereas 130 received 10 min of BLS. The overall rate of ROSC with 20-min survival was 33% (65/200). Some animals had ROSC before administration of adrenaline ($n=20$) and were therefore excluded from analyses to evaluate the effect of adrenaline. Table 1 shows baseline characteristics of survivors and non-survivors. All parameters were within normal limits for paediatric swine.

Table 1 – Baseline characteristics of survivors and non-survivors.

Parameter	Survivors ($n=65$)	Non-survivors ($n=135$)	p
Weight (kg)	3.6 (0.1)	3.6 (0.1)	0.83
HR (beats/min)	252 (202, 273)	226 (198, 265)	0.20
MAP (mmHg)	87 (2)	85 (1)	0.45
DBP (mmHg)	71 (62, 84)	70 (61, 82)	0.58
ETCO ₂ (torr) ^a	47.1 (0.5)	48.0 (0.3)	0.73
ICP (mmHg)	11 (9, 12)	12 (9, 14)	0.08
Temperature (°C)	38.7 (38.5, 38.9)	38.7 (38.4, 39.0)	0.40
pH ^a	7.39 (0.01)	7.39 (0.01)	0.73
PaO ₂ (torr)	84 (75, 107)	87 (69, 114)	0.82
PaCO ₂ (torr) ^a	40 (38, 43)	41 (39, 43)	0.10
Hb (g/dL)	10.1 (0.2)	9.9 (0.1)	0.33

Data were collected prior to asphyxia and are presented as mean (SEM) or median (interquartile range).

DBP, diastolic blood pressure; ETCO₂, end-tidal carbon dioxide; Hb, hemoglobin; HR, heart rate; ICP, intracranial pressure; MAP, mean arterial blood pressure; PaCO₂, arterial carbon dioxide partial pressure; PaO₂, arterial oxygen partial pressure; pH, arterial pH.

^a $n=154$ because animals subjected to pre-arrest hypercarbia as part of an experimental protocol were excluded.

Diastolic blood pressure during BLS and ALS

Fig. 1 shows the changes in DBP in survivors ($n=65$) and non-survivors ($n=135$) over the 20-min resuscitation period. A transient increase in the DBP was observed in survivors over the first 3 min of BLS. Thirty seconds after the initiation of chest compressions, survivors had higher DBP than did non-survivors (10.1 [5.0, 18.1] versus 4.0 [0.0, 8.0] mmHg, $p < 0.001$; Fig. 1). After 90 s of BLS, the DBP was significantly higher in survivors than in non-survivors (20.0 [11.3, 33.3] versus 5.0 [1.0, 10.0] mmHg, $p < 0.001$; Fig. 2A). The transient increase in the DBP at the beginning of BLS in survivors appeared to occur earlier and to be increased in protocols with shorter asphyxial durations (Fig. 3). After the transient increase, the DBP progressively decreased in survivors and approached levels near that of non-survivors by 7 min of chest compressions (approximately 10 mmHg, Fig. 1). In the animals that received 6 min of BLS ($n=65$), the mean DBP at the end of BLS in survivors was 12.0 (7.0, 17.0) mmHg versus 3.5 (−2.0, 6.0) mmHg in non-survivors ($p < 0.001$; Fig. 2B). In the animals that received 10 min of BLS ($n=128$), the DBP at the end of BLS was 9.0 (6.0, 13.8) mmHg in survivors versus 3.0 (1.0, 6.8) mmHg in non-survivors ($p < 0.001$; Fig. 2C).

During ALS, the DBP peaked 90 s after the administration of adrenaline (Fig. 1) and was significantly greater in survivors than in non-survivors (34.0 [24.0, 46.5] versus 11.0 [5.0, 16.0] mmHg, $p < 0.001$; Fig. 2D). The increase in DBP produced by the adrenaline was sustained, and the DBP gradually increased with subsequent administrations in the survivors (Fig. 1).

Magnitude of DBP response to adrenaline

The magnitude of increase in DBP after adrenaline administration was greater in survivors than in non-survivors (22.0 [16.5, 36.5] versus 6.0 [2.0, 11.0] mmHg, $p < 0.001$). The change in DBP after adrenaline was more predictive of survival than the DBP prior to adrenaline administration (Fig. 4A). When the improvement in DBP after the first dose of adrenaline was ≤ 10 mmHg, survival was only 1% (1 out of 99, Fig. 4B). Conversely, when the improvement in DBP after the first dose of adrenaline was ≥ 26 mmHg, 95% of pigs survived (20 out of 21, Fig. 4B). Finally, there was a significant linear correlation between the magnitude of DBP change after the first dose of adrenaline and the time to ROSC ($r = -0.54$, $p < 0.001$; Fig. 5).

Discussion

In this neonatal swine model, we show a consistent pattern in which the DBP is associated with survival during the phases of CPR. First, survivors had higher DBP than non-survivors during BLS. Survivors exhibited a transient rise in the DBP to >20 mmHg during the first 3 min of chest compressions that was not observed in non-survivors. This increase in DBP during BLS may be associated with the response of the vasculature to the circulation of endogenous adrenaline released by the adrenal glands and sympathetic nerve terminals during cardiac arrest. The levels of plasma catecholamines increase 50–100 fold during early resuscitation from cardiac arrest in both animal models^{25–27} and in humans.²⁸ In swine, a previous study showed the peak in endogenous adrenaline levels occurred one minute after the initiation of chest compressions following a five minute ventricular fibrillation arrest, and correlated with a peak in DBP early in BLS.²⁵ Therefore, we hypothesize the early peak in DBP observed in survivors in this study may be due to

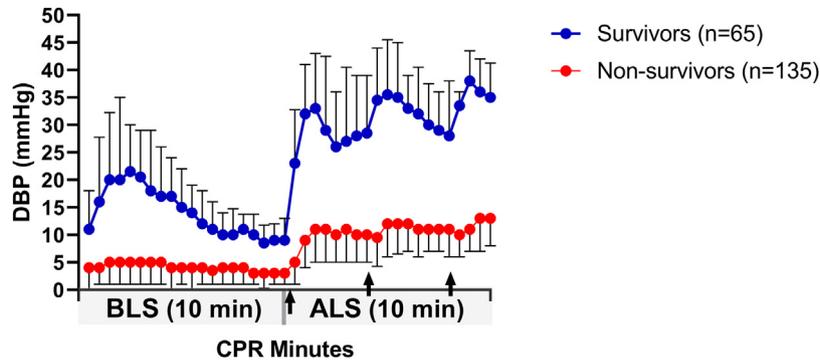


Fig. 1 – Diastolic blood pressure (DBP) in survivors (n = 65) and non-survivors (n = 135) over 20 min of cardiopulmonary resuscitation (CPR). Each point is a 30-s interval during 10 min of basic life support (BLS) followed by 10 min of advanced life support (ALS). Arrows indicate administration of adrenaline at 0, 4, and 8 min of ALS. Data are shown as medians with interquartile ranges.

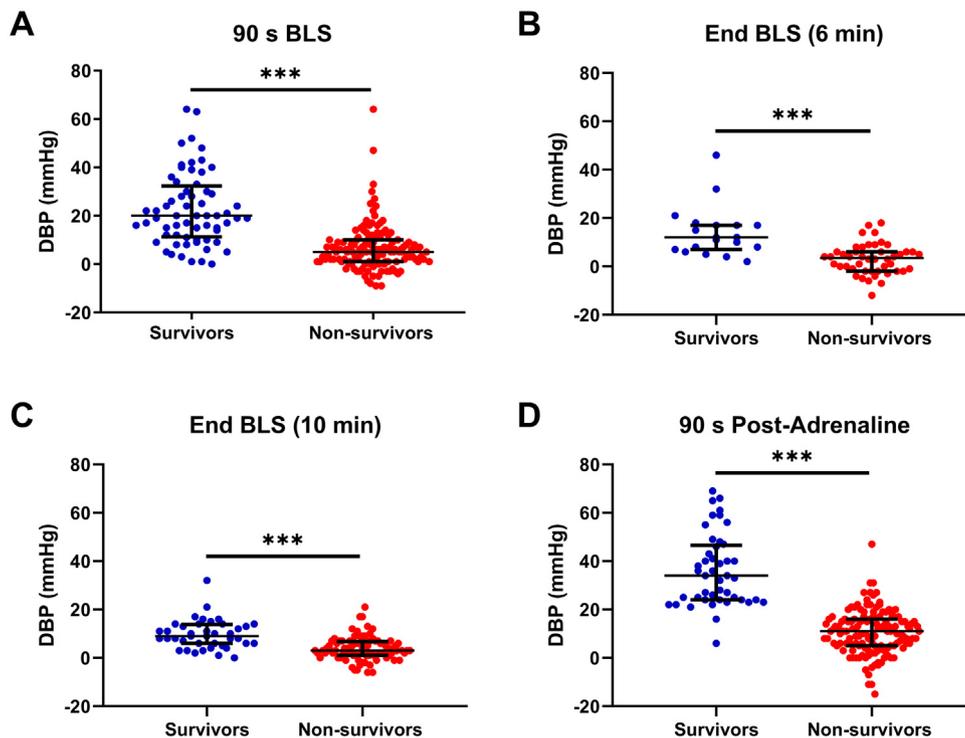


Fig. 2 – Diastolic blood pressure (DBP) at 4 time points during resuscitation in survivors and non-survivors. (A) DBP at 90 s of basic life support (BLS; n = 199). (B and C) DBP at the end of BLS in the animals that received 6 min of BLS (n = 65) and those that received 10 min of BLS (n = 128), respectively. (D) DBP at 90 s after the administration of adrenaline (n = 180). Medians and interquartile ranges for each group are presented. Each circle represents one piglet. * $p < 0.001$.**

either increased levels of endogenous catecholamines or a more robust vascular response. We believe that our study is the first to indicate that the height and timing of this peak in blood pressure related to endogenous adrenaline circulation is affected by the duration of cardiac arrest (Fig. 3). The intensity and the acuity of the peak in DBP appear to be inversely related to the duration of asphyxia. This may indicate that a maximal endogenous adrenaline response occurred in all five asphyxial durations, but that the distribution of the endogenous adrenaline or the response to the distribution were less robust in the more severely asphyxiated animals. Interestingly, survivors maintain a higher DBP

than non-survivors even as the endogenous adrenaline levels fall later in BLS. However, the use of DBP thresholds to predict survival at this stage of the resuscitation may be less helpful because both survivors and non-survivors had $DBP < 10$ mmHg, and the difference in DBP between the groups was only 6 mmHg.

The second phase of CPR in which DBP is highly associated with survival is with the first dose of adrenaline at the beginning of ALS. The DBP increased to 34 mmHg in survivors with the initial adrenaline administration, and the magnitude of change was significantly greater than that of non-survivors. Also noted was that throughout ALS,

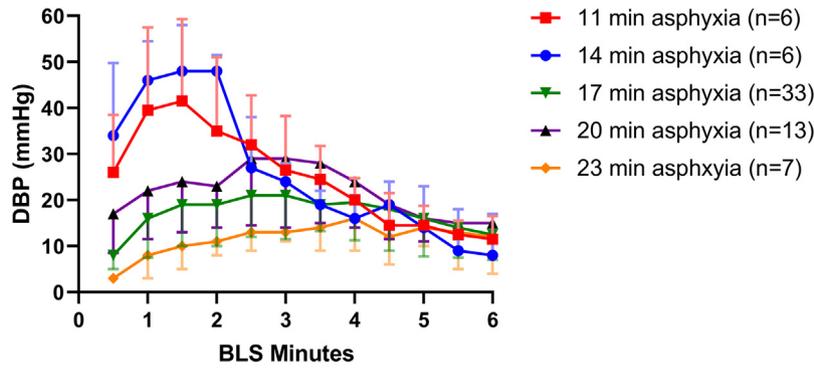


Fig. 3 – Diastolic blood pressure (DBP) during the first 6 min of basic life support (BLS) in survivors. Groups that underwent five different pre-determined durations of asphyxia (ranging from 11-23 min) are graphed separately. Medians with interquartile ranges are presented.

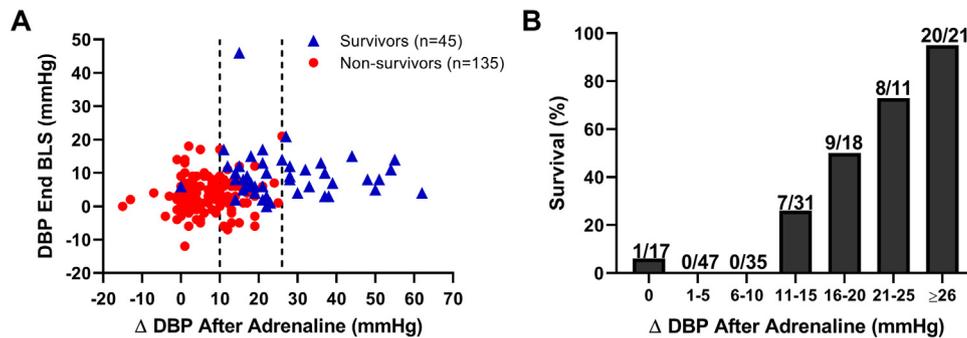


Fig. 4 – Relationships among diastolic blood pressure (DBP) at the end of basic life support (BLS), the magnitude of change in DBP after the first dose of adrenaline, and survival. (A) Survival was more closely associated with the magnitude of DBP change after adrenaline than with the DBP at the end of BLS. Each point in the scatter plot represents one individual animal (n = 180). Survival was 1% when the change in DBP was ≤ 10 mmHg after the first dose of adrenaline (left vertical dashed line) and 95% when the change in DBP was ≥ 26 mmHg (right vertical dashed line). (B) Bar graph showing survival with each 5 mmHg increase in the magnitude of DBP change after the first dose of adrenaline. The number of survivors and the total number of animals in each bin are shown.

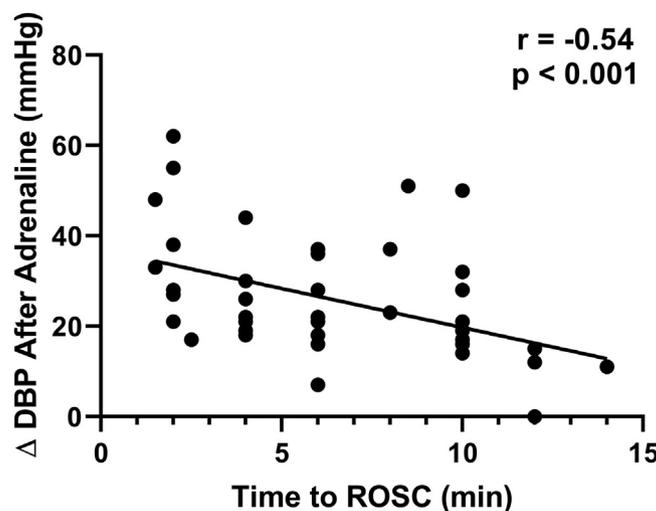


Fig. 5 – Time to return of spontaneous circulation (ROSC) and the magnitude of change in diastolic blood pressure (DBP) after the first dose of adrenaline in survivors (n = 43). A larger improvement in the DBP was associated with a shorter time-to-ROSC ($r = -0.54$, $p < 0.001$).

survivors maintained a mean DBP greater than that of non-survivors. Additionally, in survivors the size of the response in the DBP to the first dose of adrenaline correlated with the time-to-ROSC. This finding supports assumptions that the vascular response to adrenaline is a key determinate of ROSC and it will be interesting to see if other studies confirm that the degree of improvement in DBP after the initial adrenaline dose correlates with both percent ROSC and the time-to-ROSC.

These observations support previous findings that the DBP is an important surrogate for coronary perfusion pressure and is associated with ROSC.^{6,7,9} Similar findings in an adult swine model of ventricular fibrillation showed that the magnitude of improvement in coronary perfusion pressure after vasopressor administration was significantly greater in survivors than in non-survivors.²⁹ Our study was not intended to identify numeric targets for DBP during paediatric CPR. However, our observation that survivors maintained a DBP > 30 mmHg during ALS is congruent with previous studies. In a paediatric swine model of haemodynamically guided resuscitation, mean DBP prior to the first defibrillation attempt was 36 mmHg in survivors and was significantly greater than that of non-survivors.¹⁵ Additionally, maintenance of mean DBP \geq 25 mmHg in infants and \geq 30 mmHg in children was associated with both survival and survival with favourable neurologic outcome after cardiac arrest in the paediatric intensive care unit.²²

The arterial vascular response to asphyxia appears to differ in survivors and non-survivors. Despite the acidosis, hypoxia, and hypercarbia produced by prolonged asphyxia (11–23 min), survivors showed a greater degree of systemic vascular resistance and responsiveness to both endogenous adrenaline at the initiation of chest compressions and exogenous adrenaline administered during ALS. The explanation for this is unknown, but may include innate differences in the response of vascular smooth muscle cells or in cellular anaerobic metabolism. Additional investigation into the mechanisms of vascular responsiveness in these animals is warranted.

The applicability of these findings to clinical practice remains to be determined. A robust improvement in the DBP after adrenaline administration during resuscitation might portend ROSC and support more frequent dosing of adrenaline, or other vasopressors, to maintain DBP above goal. Alternatively, if there is minimal change in the DBP after adrenaline administration, the clinician might focus on improving the quality of chest compression delivery, ruling out reversible causes, and activating extracorporeal life support earlier.

Limitations to our study include that it was retrospective in nature and involved a variety of CPR delivery methods and arrest conditions. However, none of the CPR methods involved targeted feedback from DBP. Experiments had variable asphyxial times, but the association of higher DBP with survival over variable and prolonged asphyxial periods may improve the generalizability. Evaluation of DBP during CPR requires vascular access and may only be relevant to patients with pre-existing arterial catheters who suffer a cardiac arrest in the intensive care unit or operating room. However, over 90% of paediatric in-hospital cardiac arrests occur in the intensive care unit³⁰ and approximately 50% of infants and children who suffer cardiac arrest have an arterial catheter at the time of the event.³¹ The finding that the DBP was < 10 mmHg in both survivors and non-survivors (and of less prognostic value) when BLS went beyond 7 min may have limited clinical relevance as it would be unusual for a child to have arterial monitoring during CPR but not have access to early adrenaline administration. Ours is a preclinical model, though the pig's chest has

a shape, size, and compliance similar to that of a human.³² The age range of this model favours a cardiac pump mechanism for blood flow during CPR, and our findings may be relevant only to neonates and infants who are most likely to have equally compliant chests. Despite these limitations, our study provokes interest in clinical comparisons of the DBP trends and the response to the initial adrenaline administration in paediatric survivors and non-survivors of cardiac arrest.

Conclusions

In this neonatal model of asphyxial cardiac arrest, we found variations in the association between DBP and survival during prolonged resuscitation. The strongest associations between DBP and survival in this model were early in BLS and after the first dose of adrenaline. If confirmed clinically, these findings may be helpful to bedside providers regarding estimation of the severity of no-flow injury, titration of adrenaline administration during resuscitation, prognostication of the likelihood of ROSC, and activation of extracorporeal life support.

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Conflict of interest statement

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest. Dr. Hunt has served as a consultant for Zoll Medical Corporation, which has supplied honoraria and travel expenses for speaking engagements. Dr. Hunt and colleagues have been awarded patents for developing several educational simulation technologies for which Zoll Medical Corporation has a non-exclusive license with the potential for royalties. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.resuscitation.2019.07.030>.

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