Published in final edited form as:

Resuscitation. 2018 May ; 126: 137–142. doi:10.1016/j.resuscitation.2018.03.011.

Physiologic response to pre-arrest bolus dilute epinephrine in the pediatric intensive care unit★

Catherine E. Ross^{a,*}, Lisa A. Asaro^b, David Wypij^{b,c}, Conor C. Holland^d, Michael W. Donnino^{e,f}, and Monica E. Kleinman^g

^a Division of Medicine Critical Care, Department of Medicine, Boston Children's Hospital and Harvard Medical School, 333 Longwood Avenue, Boston, MA, 02115, USA

^b Department of Cardiology, Boston Children's Hospital and Harvard Medical School, 333 Longwood Avenue, Boston, MA, 02115, USA

^c Department of Biostatistics, Harvard T.H. Chan School of Public Health, 655 Huntington Avenue, Boston, MA, 02115, USA

^d Etiometry Platform™, Etiometry Inc, 119 Braintree Street, Suite 210, Allston, MA, 02134, USA

^e Department of Emergency Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, 359 Brookline Avenue, Boston, MA, 02115, USA

^f Division of Pulmonary and Critical Care Medicine, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, 359 Brookline Avenue, Boston, MA, 02115, USA

^g Division of Critical Care Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital and Harvard Medical School, 300 Longwood Avenue, Boston, MA, 02115, USA

Abstract

Aim: To quantify the physiologic effects of pre-arrest bolus dilute epinephrine in the pediatric intensive care unit.

Methods: Patients <18 years old and ≥37 weeks gestation who received an intravenous bolus of dilute epinephrine (10 mcg/mL) in the pediatric intensive care units at our institution from January 2011 to March 2017 were retrospectively identified. Patients were excluded if doses exceeded 20 mcg/kg, or under the following circumstances: orders limiting resuscitation, extracorporeal membrane oxygenation, active chest compressions, simultaneous administration of other blood

★A Spanish translated version of the abstract of this article appears as Appendix in the final online version at <https://doi.org/10.1016/j.resuscitation.2018.03.011>.

* Corresponding author at: 333 Longwood Avenue, Division of Medicine Critical Care, Boston, MA, 02115, USA. Catherine.Ross@childrens.harvard.edu (C.E. Ross).

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.resuscitation.2018.03.011>.

pressure-altering interventions or documented normotension prior to epinephrine. The primary outcome was change in systolic blood pressure within 5 min of epinephrine. Patients were categorized as non-responders if the change in systolic blood pressure was ≤ 10 mmHg.

Results: One hundred forty-four patients were analyzed. The median index dose was 0.7 mcg/kg (IQR, 0.3–2.0), and the mean increase in systolic blood pressure was 31 mmHg (95% CI, 25–36; $P < 0.001$). Thirty-nine (27%) patients were classified as non-responders. Compared to responders, non-responders had higher rates of cardiac arrest or extracorporeal membrane oxygenation within 6 h (26% vs 10%; relative risk, 2.69; 95% CI, 1.21–5.97; $P = 0.03$), and had higher in-hospital mortality (51% vs 21%; relative risk, 2.45; 95% CI, 1.51–3.96; $P < 0.001$).

Conclusions: In the majority of pre-arrest pediatric patients, bolus dilute epinephrine resulted in an increase in systolic blood pressure, and lack of blood pressure response was associated with poor outcomes. Optimal dosing of dilute epinephrine remains unclear.

Keywords

Pediatric cardiac arrest; Acute hypotension; Epinephrine; Bolus-dose pressors

Introduction

Although significant improvements in outcomes following pediatric in-hospital cardiac arrest (IHCA) have been achieved over the last two decades, morbidity and mortality remain high [1]. The American Heart Association emphasizes early recognition and reversal of shock and respiratory failure to prevent cardiac arrest in children. To this end, medical emergency teams and pediatric early warning systems have been developed, mainly targeting decompensation on the general care wards [2]. However, up to 96% of pediatric IHCA in the United States occur in an intensive care unit (ICU) in the setting of continuous monitoring and advanced therapies [3], highlighting the need for more strategies to prevent progression from the pre-arrest state to cardiac arrest.

Given that hypotension is the physiologic derangement most commonly identified prior to pediatric IHCA [4], its prevention and timely reversal is of high yield. The clinical practice of administering low-dose vasopressor boluses (commonly known as “push-dose”, “bolus-dose”, “dwindle-dose” or “spritzer” vasopressors) for acute hypotension has emerged, despite little published evidence describing its physiologic effects or impact on outcomes [5–8]. This practice likely originated from common obstetrical anesthesia practices for hypotension [9–11], but few studies have looked at the use of bolus-dose vasopressors in other settings [12–14]. As etiologies of hypotension in the pediatric ICU may differ from other practice locations, the efficacy of bolus-dose vasopressors outside the operating room warrants investigation. To date, the only study to examine pre-arrest bolus dilute epinephrine (BDE) in the pediatric ICU is one by Reiter et al. consisting of 19 patients which found that most BDE administrations resulted in significant increases in mean arterial pressure (MAP) [15]. They also described a subset of patients who had little to no response and went on to require extracorporeal membrane oxygenation (ECMO). There are currently no guidelines for use of epinephrine or other vasopressors in the pre-arrest state. Therefore, we aimed to

quantify the physiologic response to BDE and assess differences in outcomes between responders and non-responders.

Methods

Setting

We performed a retrospective review of BDE in the medical, medical/surgical and cardiac intensive care units at Boston Children's Hospital (BCH). BCH is a 404-bed quaternary-care academic children's hospital that offers a full complement of medical and surgical subspecialties and robust transplant programs. During the study period, BCH used the Cerner electronic medical record system (Millennium, Cerner, Kansas City, MO, USA). This study was approved by the BCH Institutional Review Board.

In our institution, dilute epinephrine (10 mcg/mL, formerly 1:100,000) is compounded at an outside licensed facility and stocked in the intensive care units, readily accessible for emergency situations. Given the paucity of data, no hospital-wide policies currently exist regarding indications for use or standardized dosing. Practice details are at the discretion of the clinician.

Study population

Patients were identified by a query of pharmacy records of every bolus dose of the dilute solution of epinephrine recorded from January 1st, 2011 to March 31st, 2017. This form of dilute epinephrine is generally limited to pre-arrest use at our institution and can be distinguished from intra-arrest epinephrine in most cases for which the 100 mcg/mL (formerly 1:10,000) solution is used. Inclusion criteria were index BDE doses in hospitalized patients less than 18 years of age. Exclusion criteria were gestational age less than 37 weeks; BDE administered outside of the cardiac, medical and medical/surgical ICUs; BDE doses greater than 20 mcg/kg, as these appeared to be documentation errors; active do not resuscitate orders or ECMO in place prior to BDE; active chest compressions at the time of BDE; BDE doses that were simultaneously given with other blood pressure-altering interventions (fluid bolus, blood transfusion, calcium or other vasopressor bolus) such that the documentation of the physiologic effects could not be distinguished from one another; or missing systolic blood pressure (SBP) recorded within 5 min prior to or 5 min following, index BDE. Additionally, patients who did not have any hypotension documented within the study window were excluded. Hypotension was defined as per the Pediatric Advanced Life Support guidelines [16] based on SBP as follows: less than 28 days of age, SBP < 60 mmHg; 1 month to 12 months, SBP < 70 mmHg; 1 year to 10 years, SBP < 70 + 2 × (age in years) mmHg; and over 10 years, SBP < 90 mmHg.

Data collection

Baseline characteristics were collected from the BCH data warehouse and intervention details surrounding the index dose per patient were abstracted from the medical record. Because charting during these emergent situations was often done retrospectively and vital sign changes were rapid and dynamic, manual chart review was performed to clarify exact timing and dose of the index BDE per the nursing documentation. The lowest SBP within 5

min before or 1 min after BDE was selected as the “pre-BDE” minute from which the corresponding MAP, diastolic blood pressure (DBP) and heart rate (HR) were also collected. The “post-BDE” minute was defined as the time after the pre-BDE minute with the highest SBP up to 5 min after BDE, and the corresponding vital signs in the same minute were extracted. If a cardiac arrest occurred immediately after the pre-BDE minute, HR and all blood pressure parameters were considered to be zero.

Additionally, we screened for reactive hypertension and relative tachycardia and bradycardia related to BDE. Reactive hypertension was defined as post-BDE SBP >99th percentile by age group [17]. Relative tachycardia and bradycardia were defined as an increase or decrease in HR by 30 bpm from pre- to post-BDE measurements, respectively. We did not include patients who had immediate cardiac arrest in this analysis as the relative drop in HR to zero was viewed as failure to rescue as opposed to an effect of BDE. As there are no descriptions of these parameters in children receiving pre-arrest bolus-dose vasopressors, these cutoffs were chosen by the author team as a conservative measure of unintended effects of BDE. Event outcomes included cardiac arrest (defined as receiving chest compressions) or initiation of ECMO within 6 h after index BDE and mortality at hospital discharge.

Statistical analysis

The primary outcome was change in SBP within 5 min of the index dose of BDE. A paired *t*-test was performed to compare the mean change of blood pressure and HR measurements pre- and post-BDE administration. Subgroup analyses for the primary outcome were performed by age group (analysis of variance), invasive versus non-invasive measurement and presence versus absence of vasopressor infusion prior to BDE (*t*-tests). Dose-response effect was analyzed using a Pearson correlation.

“Non-responders” were defined *a priori* as those patients who experienced 10 mmHg increase in SBP following BDE. Although this criterion has not been previously defined, we chose this cutoff as a conservative measure of a clinically meaningful response to BDE. Responders and non-responders were compared using Wilcoxon ranksum tests for continuous variables and Fisher’s exact tests for categorical variables. All statistical analysis was performed in STATA, version 15 (College Station, TX, StataCorp LP, USA).

T3 data collection

As an illustrative adjunct to the primary study, we examined stored data from T3 (Etiometry, Boston, MA), a FDA-cleared software application to collect, store and visualize ICU monitor data that has been implemented at BCH since September 2010. Data for this research was collected using the Etiometry Platform™, a clinical data aggregation and visualization software suite. For this analysis, we examined all patients from the original cohort who had sufficient data stored in T3 for SBP (arterial line measurements only) and HR (continuous electrocardiogram). Values for each parameter were collected every five seconds for the 30 min before and after BDE. Means $\pm$ SD of SBP and HR measurements were calculated at key time points. The baseline was determined by the mean of the population over the first 10 min of the tracing, ending 20 min prior to BDE. The plateau was the mean of the population over the last 10 min of the tracing, starting 20 min after BDE.

Results

During the study period, 1848 doses of BDE given to 554 patients were identified. After exclusions, the final cohort consisted of 144 patients, including 105 responders (73%) and 39 non-responders (27%, Supplementary Fig. 1). Responders and non-responders had similar baseline characteristics and received similar doses per kilogram and total number of doses (Table 1). Overall, the median index dose of BDE was 0.7 mcg/kg (IQR, 0.3–2.0) and patients received a median of 2 doses (IQR, 1–4).

Physiologic effects

For the overall cohort, SBP significantly increased following the index BDE dose (mean +31 mmHg; 95% CI, 25–36; $P < 0.001$; Fig. 1, Table 2). Within the responder group, the mean change in SBP was +42 mmHg (95% CI, 36–47; $P < 0.001$). The remaining blood pressure parameters showed similar patterns. HR did not change significantly in the overall cohort, but a mean increase of nine beats per minute reached statistical significance in the responder group (95% CI, 4–15; $P < 0.001$). The recorded time of pre-BDE vital signs was equal to the time of BDE administration in all but 13 patients, whose measurements ranged from 3 min prior to 1 min after BDE was documented. The median time to peak recorded SBP within the study window was 2 min after BDE (IQR, 1–4).

Subgroup analyses did not reveal any differences in change in SBP with respect to measurement by arterial line or presence of pre-existing vasopressor infusions; however, older children experienced a greater increase in SBP ($P = 0.002$, Supplementary Table 1). Higher doses of BDE were not associated with larger increases in SBP ($r = -0.02$, $P = 0.81$). In the overall cohort, 13 patients (9%) experienced reactive hypertension. Relative tachycardia and bradycardia were observed in 19 (14%) and 6 (4%) of 134 patients who had pre- and post-BDE HR measurements, respectively. Two patients (1%) transiently experienced HR below 60 bpm which did not require intervention.

T3 monitor data

Sixty-two patients (45 responders and 17 non-responders) had sufficient arterial line SBP data and 80 patients (61 responders and 19 non-responders) had sufficient HR data in T3. The total T3 data set included 43,020 invasive SBP measurements and 55,849 HR measurements. Nadir and peak values within 5 min before and after BDE were similar to the charted values for the original cohort (Figs. 2 and 3).

Patient outcomes

Two patients (1%) had cardiac arrest immediately after index BDE. Compared to responders, non-responders were more likely to have subsequent cardiac arrest or require ECMO within 6 h of the index BDE (26% vs 10%; relative risk, 2.69; 95% CI, 1.21–5.97; $P = 0.03$) and had a higher rate of mortality at hospital discharge (51% vs 21%; relative risk, 2.45; 95% CI, 1.51–3.96; $P < 0.001$) (Table 3).

Discussion

In this single-center study, the majority of patients had a robust increase in all blood pressure parameters following BDE, supporting its potential use for rapid reversal of hypotension in the pediatric ICU; however, we did not evaluate outcomes of this approach compared to other management strategies. Our overall cohort had a high frequency of critical care interventions in place prior to BDE, reflecting the high acuity of this patient population, and this likely explains the high mortality rate observed. A minority of patients had little to no response to BDE and experienced worse outcomes.

There was wide variability in dosing of BDE, as evidenced by a near 7-fold difference in index dose per kilogram within the interquartile range. In the adult literature, concerns for dosing errors have been raised surrounding the process of bedside dilution of the 100 mcg/mL epinephrine solution by clinicians who generally have less experience with drug dilution [7,8,18]. However, our institution stocks pre-mixed dilute epinephrine (10 mcg/mL), and therefore this issue would not have contributed to dosing variability. It is more likely that clinicians chose different starting doses based on their personal experience or training with BDE. There was also wide variability in the change in SBP, even when analyzing the responder group alone. However, this variability did not reflect a dose-response effect, as increases in dose per kilogram did not correlate with greater change in SBP in our study. Given Reiter et al. showed less effect with BDE doses <1 mcg/kg [15], the optimal dosing of BDE for this population is unclear, and further research is warranted to better delineate the appropriate dosing range.

Reactive hypertension and relative tachycardia and bradycardia were observed but were rare and transient. Our rates of reactive hypertension were similar to adult patients treated in the emergency room with bolus-dose phenylephrine [13]; however, given the pediatric population in our study, our definition differed significantly from that used in the adult study, making this a difficult comparison. As these transient effects can be observed with titration of epinephrine infusion and do not appear to cause harm, we do not consider them adverse events, but rather a normal variant of the physiologic response to BDE. However, in select patient populations these effects may pose risk and must be considered carefully when using BDE.

Another common concern regarding bolus-dose vasopressors is that clinicians may circumvent more appropriate interventions such as fluid boluses [13,18]. However, 88 of the 421 charts reviewed (21%) were excluded because other interventions were simultaneously administered with BDE, and many more patients received multiple interventions during the event outside of the pre- and post-BDE timeframe. Additionally, 81% of our final cohort were already receiving vasoactive infusions prior to BDE, indicating that clinicians were generally not using BDE as a first line or isolated treatment of hypotension. Given the paucity of data at present, it is unclear if BDE is superior to traditional treatments for hypotension in the pediatric ICU. Therefore, BDE may be considered for patients who have failed traditional measures or who experience rapid and profound hypotension, such as that which may occur in the peri-intubation period or with impending cardiac arrest. Additional

candidate patients may be those for whom additional fluid load is thought to be detrimental (i.e., certain patients with heart, renal or respiratory failure).

Finally, we showed significant differences in outcomes between responders and non-responders. Given that the two groups were similar with regard to baseline characteristics, critical care interventions in place and dose per kilogram, the inability to mount a response to the index dose of BDE may indicate higher risk for ECMO, cardiac arrest and death upon hospital discharge. The non-responders' inability to raise their blood pressure following BDE likely reflects differences in underlying physiology compared to responders, including severity of acidosis, degree of cardiovascular depression and/or etiology of hypotension. These inherent differences likely predisposed non-responders to poor outcomes rather than the direct lack of effect of BDE.

Several limitations were associated with this retrospective study design. First, charting during these emergent situations was often done retrospectively by the bedside nurse and inconsistencies and missing data were common. In some instances, this may have led to exclusion of patients who lacked documented hypotension prior to BDE, underestimation of change in SBP or miscategorizing of responder status. Additionally, charting was limited to one-minute increments and may have led to slight overestimation of time to peak effect. Second, although we excluded patients who received other simultaneous interventions, we could not determine exact timing of changes in vasopressor infusion rates, which may have inflated the apparent effect of BDE. However, we believe this effect was minimal, as the patients who were not on vasopressor infusions had similar increases in SBP to the ones who were. Third, the defining cutoff of SBP change ≥ 10 mmHg for non-responders was selected by the author team to represent a clinically non-significant change in blood pressure, however this may not be the optimal cutoff point most associated with poor outcomes. Similarly, the author team selected cutoffs for relative tachycardia and bradycardia in terms of absolute change to represent a significant clinical event, recognizing that the percent change may vary widely depending on the initial heart rate. Finally, we were unable to compare BDE with other bolus vasopressors such as phenylephrine or traditional measures and cannot comment on the optimal treatment for acute hypotension in the pediatric ICU.

Conclusion

Bolus dilute epinephrine may be useful in treating acute hypotension in certain patients in the pediatric ICU, and lack of response to BDE may indicate poor outcomes. The optimal dose in this setting remains unclear and requires prospective study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Dr. Donnino's work is supported by 1R01HL136705-1.

We would like to thank Garima Kumari, MS; Varun Konanki, BS; Eric Mubang; Deanna Lee; Jane Romano, RN, MS and Shannon Manzi, PharmD for their assistance in the retrieval and formatting of data. We would also like to

thank Parth Patel, RN for his assistance with data and graph formatting and Francesca Montillo, MM for her assistance with manuscript preparation.

Abbreviations:

IHCA	in-hospital cardiac arrest
ICU	intensive care unit
BDE	bolus dilute epinephrine
ECMO	extracorporeal membrane oxygenation
BCH	Boston Children's Hospital
SBP	systolic blood pressure
MAP	mean arterial pressure
DBP	diastolic blood pressure
HR	heart rate

References

- [1]. Girotra S, Spertus JA, Li Y, Berg RA, Nadkarni VM, Chan PS. Survival trends in pediatric in-hospital cardiac arrests: an analysis from get with the guidelines-resuscitation. *Circ Cardiovasc Qual Outcomes* 2013;6:42–9. [PubMed: 23250980]
- [2]. de Caen AR, Berg MD, Chameides L, Gooden CK, Hickey RW, Scott HF, et al. Part 12: Pediatric advanced life support: 2015 american heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;132:S526–42. [PubMed: 26473000]
- [3]. Berg RA, Sutton RM, Holubkov R, Nicholson CE, Dean JM, Harrison R, et al. Ratio of picu versus ward cardiopulmonary resuscitation events is increasing. *Crit Care Med* 2013;41:2292–7. [PubMed: 23921270]
- [4]. Nadkarni VM, Larkin GL, Peberdy MA, Carey SM, Kaye W, Mancini ME, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA* 2006;295:50–7. [PubMed: 16391216]
- [5]. Selde W Push dose epinephrine: a temporizing measure for drugs that have the side-effect of hypotension. *Jems* 2014;39:62–3.
- [6]. Weingart S Push-dose pressors for immediate blood pressure control. *Clin Exp Emerg Med* 2015;2:131–2. [PubMed: 27752585]
- [7]. Cole JB. Bolus-dose vasopressors in the emergency department: first, do no harm; second, more evidence is needed. *Ann Emerg Med* 2018;71:93–5. [PubMed: 28754354]
- [8]. Holden D, Ramich J, Timm E, Pauze D, Lesar T. Safety considerations and guidelinebased safe use recommendations for bolus-dose vasopressors in the emergency department. *Ann Emerg Med* 2018;71:83–92. [PubMed: 28601272]
- [9]. Doherty A, Ohashi Y, Downey K, Carvalho JC. Phenylephrine infusion versus bolus regimens during cesarean delivery under spinal anesthesia: a double-blind randomized clinical trial to assess hemodynamic changes. *Anesth Analg* 2012;115:1343–50. [PubMed: 23011562]
- [10]. Siddik-Sayyid SM, Taha SK, Kanazi GE, Aouad MT. A randomized controlled trial of variable rate phenylephrine infusion with rescue phenylephrine boluses versus rescue boluses alone on physician interventions during spinal anesthesia for elective cesarean delivery. *Anesth Analg* 2014;118:611–8. [PubMed: 24299932]

- [11]. Mohta M, Harisinghani P, Sethi AK, Agarwal D. Effect of different phenylephrine bolus doses for treatment of hypotension during spinal anaesthesia in patients undergoing elective caesarean section. *Anaesth Intensive Care* 2015;43:74–80. [PubMed: 25579292]
- [12]. Panchal AR, Satyanarayan A, Bahadir JD, Hays D, Mosier J. Efficacy of bolus-dose phenylephrine for peri-intubation hypotension. *J Emerg Med* 2015;49:488–94. [PubMed: 26104846]
- [13]. Schwartz MB, Ferreira JA, Aaronson PM. The impact of push-dose phenylephrine use on subsequent preload expansion in the ed setting. *Am J Emerg Med* 2016;34:2419–22. [PubMed: 27720568]
- [14]. Gottlieb M Bolus dose of epinephrine for refractory post-arrest hypotension. *Cjem* 2017;1–5.
- [15]. Reiter PD, Roth J, Wathen B, LaVelle J, Ridall LA. Low-dose epinephrine boluses for acute hypotension in the picu. *Pediatr Crit Care Med* 2018.
- [16]. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 10: Pediatric advanced life support. The american heart association in collaboration with the international liaison committee on resuscitation. *Circulation* 2000;102:I291–342. [PubMed: 10966679]
- [17]. Report of the second task force on blood pressure control in children—1987. *Pediatrics* 1987;79:1–25. [PubMed: 3797155]
- [18]. Acquisto NM, Bodkin RP, Johnstone C. Medication errors with push dose pressors in the emergency department and intensive care units. *Am J Emerg Med* 2017;35:1964–5.

Fig. 1.

Charted vital sign data before and after index administration of BDE by responder status. Each point represents the mean with the SD represented by the bars.

Fig. 2.

Overlay graph of T3 invasive SBP data with respect to BDE administration. The hashed vertical line represents the recorded administration of the index BDE, set to time = 0. The bolded line represents the mean of all patients, and the shaded area represents ± 1 SD. Callout values were calculated from the population mean for the baseline, nadir, peak and plateau.

Fig. 3. Overlay graph of T3 continuous electrocardiogram HR data with respect to BDE administration. The hashed vertical line represents the recorded administration of the index BDE, set to time = 0. The bolded line represents the mean of all patients, and the shaded area represents ± 1 SD. Callout values were calculated from the population mean for the baseline, nadir, peak and plateau.

Table 1

Baseline characteristics and intervention details, according to responder status.

Characteristic	All (n =144)	Responders (n = 105)	Non-Responders (n = 39)	P Value*
Baseline Characteristics				
Age group, No. (%)				0.59
< 1year	68 (47)	46 (44)	22 (56)	
1year to< 5 years	24 (17)	18 (17)	6 (15)	
5 years to< 12 years	21 (15)	16 (15)	5 (13)	
12 years to <18 years	31 (22)	25 (24)	6 (15)	
Female sex, No. (%)	55 (38)	42 (40)	13 (33)	0.56
Hospital location, No. (%)				0.47
Cardiac ICU	77 (53)	59 (56)	18 (46)	
Medical ICU	16 (11)	12 (11)	4 (10)	
Medical/Surgical ICU	51 (35)	34 (32)	17 (44)	
Admitting team, No. (%)				0.18
Cardiac ICU	56 (39)	42 (40)	14 (36)	
Cardiology	20 (14)	16 (15)	4 (10)	
General pediatric critical or intermediate care	39 (27)	25 (24)	14 (36)	
General pediatrics	12 (8)	9 (9)	3 (8)	
Hematology/oncology/stem cell transplant	4 (3)	1 (< 1)	3 (8)	
Neurology/pulmonology/renal	7 (5)	6 (6)	1 (3)	
Surgical	6 (4)	6 (6)	0	
Critical care interventions prior to BDE, No. (%)				
Arterial catheter	92 (64)	67 (64)	25 (64)	> 0.99
Vasoactive infusion	116 (81)	84 (80)	32 (82)	> 0.99
Invasive mechanical ventilation	111 (77)	83 (79)	28 (72)	0.38
Pert-intubation**	28 (19)	20 (19)	8 (21)	0.82
Intervention Details				
Index BDE dose in mcg/kg, median (IQR)	0.7 (0.3–2.0)	0.8 (0.4–1.9)	0.5 (0.3–2.6)	0.59
Number of BDE doses, median (IQR)	2 (1–4)	2 (1–4)	2 (1–3)	0.43

* PValues for the comparison between responders and non-responders were calculated using Fisher's exact tests or Wilcoxon rank-sum tests.

Peri-intubation BDE use was defined as intubation one hour before or after index BDE dose.
**

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Vital sign data before and after index administration of dilute epinephrine.

Vital Sign	Number of Measurement Pairs	Pre-BDE	Post-BDE	Change	P Value*
All (n = 144)					
SBP (mmHg)	144	55 ± 13	86 ± 33	+31 (25–36)	<0.001
MAP (mmHg)	142	40 ± 9	62 ± 24	+22 (19–26)	<0.001
DBP (mmHg)	144	33 ± 9	51 ± 21	+18 (16–21)	<0.001
HR (bpm)	136	133 ± 28	138 ± 36	+5 (0–10)	0.06
Responders (n = 105)					
SBP (mmHg)	105	55 ± 12	96 ± 31	+42 (36–47)	<0.001
MAP (mmHg)	103	40 ± 9	70 ± 22	+30 (27–34)	<0.001
DBP (mmHg)	105	33 ± 8	58 ± 19	+25 (22–28)	<0.001
HR (bpm)	99	132 ± 29	142 ± 34	+9 (4–15)	<0.001
Non-Responders (n = 39)					
SBP (mmHg)	39	57 ± 14	58 ± 21	+1 (–3 to 5)	0.76
MAP (mmHg)	39	40 ± 10	41 ± 15	+1 (–2 to 4)	0.56
DBP (mmHg)	39	33 ± 10	34 ± 14	+1 (–2 to 5)	0.42
HR (bpm)	37	136 ± 23	128 ± 38	–8 (–20 to 5)	0.21

Pre- and post-BDE values are mean ± SD. Change is the mean difference (95% CI).

* P Values were calculated using paired *t*-tests.

Table 3

Outcomes, according to responder status.

Outcome	All (n = 144)	Responders (n = 105)	Non-Responders (n = 39)	P Value*
Cardiac arrest or ECMO within 6 h of index BDE, No. (%)	20 (14)	10 (10)	10 (26)	0.03
Mortality at discharge, No. (%)	42 (29)	22 (21)	20 (51)	<0.001

* P-values for the comparison between groups were calculated using Fisher's exact tests.