UCSF

Title

Outcomes and characteristics of cardiac arrest in children with pulmonary hypertension: A secondary analysis of the ICU-RESUS clinical trial.

Permalink

https://escholarship.org/uc/item/83m0k8p5

Authors

Morgan, Ryan
Reeder, Ron
Ahmed, Tageldin
et al.

Publication Date

2023-09-01

DOI

10.1016/j.resuscitation.2023.109897

Peer reviewed

Outcomes and Characteristics of Cardiac Arrest in Children with Pulmonary Hypertension: A Secondary Analysis of the ICU-RESUS Clinical Trial

Ryan W Morgan, MD, MTR[1], Ron W Reeder, PhD[2], Tageldin Ahmed, MD[3], Michael J Bell, MD[4], John T Berger, MD[4], Robert Bishop, MD[5], Matthew Bochkoris, MD[6], Candice Burns, MD[7], Joseph A Carcillo, MD[6], Todd C Carpenter, MD[5], J Michael Dean, MD[2], J Wesley Diddle, MD[4], Myke Federman, MD[8], Richard Fernandez, MD[9], Ericka L Fink, MD, MS[6], Deborah Franzon, MD[10], Aisha H Frazier, MD, MPH[11,12], Stuart H Friess, MD[13], Kathryn Graham, MLAS[1], Mark Hall, MD[9], David A Hehir, MD[1], Adam S Himebauch, MD, MSCE[1], Christopher M Horvat, MD[6], Leanna L Huard, MD[8], Tensing Maa, MD[9], Arushi Manga, MD[13], Patrick S McQuillen, MD[10], Kathleen L Meert, MD[3], Peter M Mourani, MD[5,14], Vinay M Nadkarni, MD, MS[1], Maryam Y Naim, MD, MSCE[1], Daniel Notterman, MD[15], Kent Page, MStat[2], Murray M Pollack, MD[4], Anil Sapru, MD[8], Carleen Schneiter, MD[5], Matthew P Sharron, MD[4], Neeraj Srivastava, MD[8], Sarah Tabbutt, MD, PhD[10], Bradley Tilford, MD[3], Shirley Viteri, MD[12], David Wessel, MD[4], Heather A Wolfe, MD, MSHP[1], Andrew R Yates, MD[9], Athena F Zuppa, MD[1], Robert A Berg, MD[1], Robert M Sutton, MD, MSCE[1]

[1]Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA

[2]Department of Pediatrics, University of Utah, Salt Lake City, UT, USA

[3]Department of Pediatrics, Children's Hospital of Michigan, Central Michigan University, Detroit, MI, USA

[4]Department of Pediatrics, Children's National Hospital, George Washington University School of Medicine, Washington, DC, USA

[5]Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO, USA

[6]Department of Critical Care Medicine, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, PA, USA

[7]Department of Pediatrics and Human Development, Michigan State University, Grand Rapids, MI, USA

Address for Corresponding Author / Reprints: Ryan W. Morgan, MD, MTR, Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Division of Critical Care Medicine – 9NW70, Philadelphia, PA 19104, MorganR1@chop.edu.

DECLARATIONS OF INTEREST:
None.

[8]Department of Pediatrics, Mattel Children's Hospital, University of California Los Angeles, Los Angeles, CA, USA

[9]Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University, Columbus, OH, USA

[10]Department of Pediatrics, Benioff Children's Hospital, University of California, San Francisco, San Francisco, CA, USA

[11]Nemours Cardiac Center, Nemours Children's Health, Delaware and Thomas Jefferson University, Wilmington, DE, USA

[12]Department of Pediatrics, Nemours Children's Health, Delaware and Thomas Jefferson University, Wilmington, DE, USA

[13]Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA

[14]Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, AR, USA

[15]Department of Molecular Biology, Princeton University, Princeton, NJ, USA

Abstract

Background: Previous studies have identified pulmonary hypertension (PH) as a relatively common diagnosis in children with in-hospital cardiac arrest (IHCA), and preclinical laboratory studies have found poor outcomes and low systemic blood pressures during CPR for PH-associated cardiac arrest. The objective of this study was to determine the prevalence of PH among children with IHCA and the association between PH diagnosis and intra-arrest physiology and survival outcomes.

Methods: This was a prospectively designed secondary analysis of patients enrolled in the ICU-RESUS clinical trial (NCT02837497). The primary exposure was a pre-arrest diagnosis of PH. The primary survival outcome was survival to hospital discharge with favorable neurologic outcome (Pediatric Cerebral Performance Category score 1-3 or unchanged from baseline). The primary physiologic outcome was event-level average diastolic blood pressure (DBP) during CPR.

Results: Of 1276 patients with IHCAs during the study period, 1129 index IHCAs were enrolled; 184 (16.3%) had PH and 101/184 (54.9%) were receiving inhaled nitric oxide at the time of IHCA. Survival with favorable neurologic outcome was similar between patients with and without PH on univariate (48.9% vs. 54.4%; p=0.17) and multivariate analyses (aOR 0.82 [95%CI: 0.56, 1.20]; p=0.32). There were no significant differences in CPR event outcome or survival to hospital discharge. Average DBP, systolic BP, and end-tidal carbon dioxide during CPR were similar between groups.

Conclusions: In this prospective study of pediatric IHCA, pre-existing PH was present in 16% of children. Pre-arrest PH diagnosis was not associated with statistically significant differences in survival outcomes or intra-arrest physiologic measures.

Keywords

Cardiac arrest; cardiopulmonary resuscitation; pulmonary hypertension; blood pressure; pediatrics

---

INTRODUCTION:

Annually, more than 15,000 children in the United States have cardiac arrests while hospitalized.[1] As most of these occur in critically ill children in intensive care units (ICUs), their cardiac arrests are generally the result of diverse disease processes and associated organ dysfunction and failure.[2] Understanding the clinical characteristics of these patients can facilitate the development of patient-specific and pathophysiology-targeted therapies during and around the time of cardiac arrest.

Recent clinical studies demonstrate that pulmonary hypertension is a relatively common pre-existing condition in children with in-hospital cardiac arrest (IHCA). A single-center observational study identified echocardiographic evidence of pulmonary hypertension in 35% of children with IHCAs,[3] and a retrospective large multicenter database study identified an association between pulmonary hypertension diagnosis codes and lower IHCA survival rates.[4] Translational laboratory data demonstrate that pulmonary hypertension is associated with deleterious physiology during cardiopulmonary resuscitation (CPR). Specifically, diastolic blood pressure (DBP), which is associated with pediatric CPR outcomes,[5,6] is low in animals with pulmonary hypertension-associated cardiac arrest. Provision of inhaled nitric oxide (iNO) can increase DBP during CPR and improve survival outcomes for animals with pulmonary hypertension-associated cardiac arrest.[7-10] The physiology of IHCA in patients diagnosed with PH and of iNO therapy during and around the time of IHCA have not been well described clinically.

The objectives of this study were to: 1) determine the prevalence of pre-arrest pulmonary hypertension among children receiving CPR in ICUs and the association of pulmonary hypertension with outcomes and 2) describe the association of pulmonary hypertension and of iNO therapy with intra-arrest physiology. To mitigate limitations of previous clinical observational studies of pediatric cardiac arrest in patients with a diagnosis of pulmonary hypertension, we leveraged the prospectively collected data from the ICU Resuscitation Project clinical trial (NCT02837497),[11,12] which included clinical hemodynamic waveform data.

METHODS:

Study Setting and Patient Population

The ICU-RESUS study was a multicenter, hybrid stepped-wedge cluster-randomized trial of a physiology-directed bedside CPR training and post-cardiac arrest debriefing in 18 pediatric intensive care units (PICUs) and pediatric cardiac intensive care units (CICUs) in the United States.[11,12] The central institutional review board (IRB) at the University of Utah and the IRB at each clinical site approved the study with waiver of informed consent. This secondary study was designed during the course of the ICU-RESUS trial without prior examination of the data. Only prospectively collected ICU-RESUS data were included.

The ICU-RESUS study enrolled patients who received CPR of any duration in any of the participating ICUs and were 18 years of age and 37 weeks post-gestational age.

Exclusion criteria are detailed in previous publications.[6,11,12] Only the index IHCA event for a particular hospital admission was included.

Data Collection and Physiologic Waveform Evaluation

Trained research coordinators at each study site collected standardized cardiac arrest data elements.[13,14] Pre-arrest pulmonary hypertension diagnosis as an active hospital problem (Y/N) was recorded based on medical record review. Pulmonary hypertension crisis as a the cause of IHCA was not specifically captured. Among patients with pulmonary hypertension, whether they were receiving iNO or other pulmonary hypertension medications (treprostinil, epoprostenol, iloprost, selexipag, ambristentan, sitaxsentan, bosentan, macisentan, sildenafil, tadalafil, vardenafil, riociguat) at the time of IHCA onset was recorded. The primary indication for receiving iNO (e.g., pulmonary hypertension, acute respiratory distress syndrome) was recorded. The timing of initiaiton or escalation of PH therapies immediately prior to or during the arrest were not captured. Study staff downloaded bedside monitor waveform data for up to the first ten minutes of CPR using clinical waveform acquisition systems, which underwent processing and clinical review by investigators who were blinded to pulmonary hypertension status and outcomes. The waveform acquisition, processing, and analysis methods are described in full detail in previous publications.[6,12,15] In short, the clinical review processes identified starts and stops in CPR and all periods of non-evaluable arterial BP data or non-sustaned spontaneous circulation in order to only include periods of CPR in the hemodynamic analyses. Custom-designed code (MATLAB, The MathWorks, Inc., Natick, MA, USA) measured systolic blood pressure (SBP) and DBP for each individual evaluable chest compression, values of which were then summarized as averages over 30-second data epochs. End-tidal carbon dioxide (ETCO2) values during CPR were also determined in patients for whom these data were evaluable.

Exposures, outcomes, and statistical analysis

The primary exposure was whether the patient had pulmonary hypertension. A secondary exposure of "treated pulmonary hypertension" included only patients with pulmonary hypertension who were receiving any non-iNO pulmonary vasodilator or were receiving iNO with the specific indication of treatment for pulmonary hypertension. The primary outcome was survival to hospital discharge with favorable neurologic outcome (Pediatric Cerebral Performance Category [PCPC] score of 1-3 or no worse from baseline).[14,16,17] Secondary survival outcomes were survival to hospital discharge and sustained return of spontaneous circulation (ROSC) 20 minutes.[14,17] The primary physiologic outcome was event-level average DBP. Secondary physiologic outcomes were event-level average SBP and ETCO2 and binary measures of event-level "adequate" DBP and SBP according to predetermined thresholds (DBP: 25 mmHg for infants and 30 mmHg for children 1 year; SBP: 60 mmHg for infants and 80 mmHg for children 1 year).[6]

Categorical variables were presented using counts and percentages and continuous variables were summarized with median [first quartile, third quartile]. Differences in subject and event characteristics between subjects with and without pulmonary hypertension were evaluated using Fisher's exact test for nominal variables and the Wilcoxon rank-sum test for continuous variables. The associations of pulmonary hypertension with survival and

physiologic outcomes were assessed using logistic regression for binary outcomes and linear regression for continuous measures. Multivariable models controlled for unit as a random effect and the following *a priori* fixed covariates: illness category (medical cardiac, surgical cardiac, medical non-cardiac, surgical non-cardiac, trauma),[18,19] age category (<1 month, 1 month - <1 year, 1 year - <8 years, 8 years to <19 years),[20] first documented CPR rhythm (asystole or pulseless electrical activity, bradycardia with poor perfusion, ventricular fibrillation or ventricular tachycardia),[21,22] and CPR time category (weekday vs. weeknight/ weekend).[23] Among subjects with pulmonary hypertension, the association of iNO use at the time of CPR with survival outcomes and event hemodynamic measures was modeled analogously. The temporal trajectory of DBP and SBP was graphically depicted according to pulmonary hypertension status. For each timepoint, the Wilcoxon rank-sum test was used to determine whether there is a statistically significant difference in mean DBP or SBP for those with versus without pulmonary hypertension. Analyses were performed with SAS 9.4 (SAS Institute; Cary, NC). All p-values were based on testing with a two-sided alternative, and p-values less than 0.05 were considered statistically significant.

A *post hoc* exploratory analysis compared patients with "treated pulmonary hypertension," as defined above, with all other patients. This aimed to specifically investigate pulmonary hypertension that was clinically significant enough to prompt pre-arrest treatment. An additional *post hoc* analysis excluded all patients with a primary illness category of "surgical cardiac" as the pulmonary hypertension in these patients is often fundamentally different (i.e., related to post-operative / post-cardiopulmonary bypass pulmonary vascular reactivity). Both of these additional analyses were conducted in the same manner described for the primary analysis.

RESULTS:

During the ICU-RESUS study, 1276 patients in participating ICUs experienced 1389 cardiac arrests, of which 1129 index CPR events were included in the study. Of these 1129 patients, 184 (16.3%) had a pre-arrest diagnosis of pulmonary hypertension. Patient demographics and characteristics are described in Table 1. Children with pulmonary hypertension were more frequently infants (1 month-1 year old) and 1 to 8 years of age, and were less frequently neonates (1 month old) and older children (8 years). Children with pulmonary hypertension were more frequently Black/African American; they more frequently had pre-existing respiratory insufficiency, heart failure, congenital heart disease (CHD), and cardiac illness categories and less frequently had a history of trauma. Patients with pulmonary hypertension had more neurologic and functional morbidity at baseline, as evidenced by higher PCPC scores and functional status scores (FSS). Other characteristics, including pre-arrest severity of illness as determined by the Pediatric RISk of Mortality (PRISM) IV score, were similar between patients with and without pulmonary hypertension.

Table 2 describes pulmonary hypertension-directed medications. At the time of IHCA and the start of CPR, 101/184 (54.9%) of children with pulmonary hypertension were receiving iNO; in 77/101 (76.2%) patients, iNO was initiated for a cardiac indication (including specifically for pulmonary hypertension in 32 patients) and in 24/101 (23.8%), it was provided for a primary respiratory indication. Among the 184 patients with pulmonary

hypertension, 97 (52.7%) were receiving at least one pulmonary hypertension medication other than iNO prior to arrest; the most frequent were sildenafil (91/184; 49.5%), bosentan (27/184; 14.7%), and treprostinil (14/184; 7.6%).

Cardiac arrest characteristics are described in Table 3. Patients with pulmonary hypertension more frequently received CPR in a CICU and less frequently in a PICU. They more frequently had cyanosis without respiratory decompensation and less frequently had hypotension as the immediate cause of the arrest. They had similar durations of CPR, but received fewer doses of epinephrine during CPR and less frequently received calcium or a fluid bolus during CPR.

Outcomes are described in Table 4. There was no difference in survival with favorable neurologic outcome between patients with and without pulmonary hypertension on univariate (48.9% vs. 54.4%; OR 0.80 [95% CI: 0.58, 1.10]; p=0.173]) or multivariate analysis (aOR 0.82 [95% CI: 0.56, 1.20]; p=0.318). Mean DBP, the primary physiologic outcome, did not differ between patients with and without pulmonary hypertension (37.9 [30.1, 51.8] mmHg versus 38.9 [30.6, 49.0] mmHg; adjusted point estimate −2.94 [95% CI: −6.05, 0.16] mmHg, p=0.116). There were no differences between groups in secondary survival outcomes or any other physiologic outcomes.

Supplemental Table 1 contains the secondary analysis comparing outcomes between pulmonary hypertension patients according to whether they were receiving iNO at the time of IHCA. Survival with favorable neurologic outcome occurred in 44.6% of pulmonary hypertension patients receiving iNO versus 54.2% not receiving iNO (unadjusted OR 0.68 [95% CI: 0.38, 1.21]; p=0.193; aOR 0.67 [95% CI: 0.36, 1.25]; p=0.209). Patients receiving iNO had lower unadjusted odds of ROSC (OR 0.50 [95% CI: 0.25, 0.96]; =0.040), which did not reach significance after adjusting for confounders (aOR 0.49 [95% CI: 0.24, 1.00]; p=0.051). The unadjusted point estimate for average ETCO2 for patients receiving iNO was −8.73 [95% CI: −15.89, −1.57] mmHg; p=0.015. After adjusting for confounders, this difference did not reach statistical significance, nor did any other survival or physiologic comparisons related to iNO.

Figure 1 depicts SBP (Figure 1A) and DBP (Figure 1B) over the first ten minutes of CPR in patients with and without pulmonary hypertension. There were no significant differences in BPs between these groups at any specific time point.

Supplemental Table 2 contains the exploratory analysis comparing 110 patients with "treated pulmonary hypertension" to all others (n=1019). There were no significant differences in survival outcomes or intra-arrest physiology between groups. Supplemental Table 3 contains the exploratory analysis excluding patients with a surgical cardiac illness category (n=383). There were no significant differences in survival outcomes or intra-arrest physiology between patients with and without pulmonary hypertension in this analysis.

DISCUSSION:

In this secondary observational study of prospectively collected data from a pediatric IHCA trial, 16% of children who received CPR in intensive care units had a pre-existing

diagnosis of pulmonary hypertension at the time of IHCA. We did not observe difference in neurologically favorable discharge status or other survival outcomes between patients with and without pulmonary hypertension, nor did we observe differences in invasively measured blood pressures or ETCO2 during CPR. These findings build upon those of other recent studies[3,4] describing the epidemiology of cardiac arrest in children with pulmonary hypertension and to our knowledge, this study represents the first dedicated clinical description of physiology during CPR in children with pulmonary hypertension.

The observed prevalence of pulmonary hypertension in children with IHCA is substantial and is relatively consistent with other recent studies focusing on this topic. A multicenter administrative database study revealed an 8.3% pulmonary hypertension prevalence among children with IHCA, but depended entirely on abstracted diagnosis codes,[4] whereas the current study utilized prospectively designed data elements and trained research coordinators and likely represents a more accurate account of the epidemiologic burden of pulmonary hypertension in this population. Conversely, we observed lower prevalence than the 35% from a single center study that defined pulmonary hypertension according to pre-arrest echocardiography.[3] Regardless, this prevalence highlights the clinical and scientific importance of elucidating the physiology and outcomes of children with pulmonary hypertension during and around the time of cardiac arrest.

We failed to detect statistically significant survival differences in children with pulmonary hypertension in this study. However, the non-significant 3.3% difference in survival (54.9% verus 58.2%) was of similar magnitude to the survival difference observed in the aforementioned database study.[4] With substantially more patients, survival differences in that study reached statistical significance after propensity matching and conditional logistic regression despite the predicted survival difference of only 2.5% (59.1% in the pulmonary hypertension group versus 61.6% in the non-pulmonary hypertension group).[4] Thus, statistical power may have limited our ability to detect a statistically significant difference. However, the lack of a survival difference may be due to the severity of pulmonary hypertension in this cohort. Quantifiable echocardiographic or cardiac catheterization data were not collected, but information regarding pulmonary hypertension medications prescribed prior to IHCA offers a clue regarding disease severity. Though more than half of patients with pulmonary hypertension (101/184; 54.9%) were receiving iNO at the onset of arrest, a minority (32/101; 31.7%) were receiving iNO specifically for pulmonary hypertension. Additionally, more than 20% were not receiving any pulmonary vasodilator therapies. We attempted to address this through an exploratory analysis explicitly comparing patients receiving pulmonary hypertension-directed therapies to all other patients and similarly did not identify survival or physiologic differences. Regardless, it is likely that many of the patients with pulmonary hypertension in our study likely did not have progressive, severe pulmonary hypertension leading up to their cardiac arrest.

In the sub-analysis examining pulmonary hypertension patients according to whether they were receiving iNO, we also did not detect differences in hospital discharge survival rates. Although we expected that iNO would be of therapeutic benefit in many of these patients, patients treated with iNO actually had lower unadjusted odds of ROSC (OR: 0.50 [95% CI: 0.25, 0.96]; p=0.04). As the exact timing and dose of this intervention was not captured

prospectively, we anticipate that it may have been an indirect marker of disease severity in many patients (i.e., bias by indication).[24]

Patients with pulmonary hypertension differed from other patients in a number of respects. This included a higher proportion of Black or African American children in the pulmonary hypertension group. As previous work has established increased mortality risk among Black children with pulmonary hypertension,[25] this deserves evaluation in broader cohorts of pulmonary hypertension patients. Other differences between groups, such as in baseline PCPC score could have been confounders in our analyses. Though we controlled for *a priori* selected covariates, it is possible that outcomes were biased by known patient characteristics or unmeasured confounders. Pulmonary hypertension is heterogenous in terms of its causes and manifestations[26-28] and may be a particularly problematic characteristic in some but may actually be associated with favorable or protective conditions or etiologies in others. Some patients have a reactive pulmonary vasoconstriction component that might respond to oxygen or pulmonary vasodilator therapy. Others have IHCAs secondary to a pulmonary hypertensive crisis with a reversible trigger such as tracheal suctioning or agitation that may have been quickly addressed in the ICUs included in this study. Conversely, patients with severe, progressive pulmonary hypertension leading to right ventricular failure and IHCA may present a physiologic circumstance that is difficult to reverse. Importantly, we studied pulmonary hypertension as a pre-arrest diagnosis, rather than focusing on pulmonary hypertensive crisis as a cardiac arrest etiology, which merits independent evaluation.

This study included analyses of intra-arrest blood pressures and ETCO2 to draw corrolaries with preclinical animal studies and to discern potential physiologic targets during IHCA in patients with a diagnosis of pulmonary hypertension. We did not detect statistically significant differences in event-level averages for DBP or SBP or for the percentage of events meeting predetermined thresholds for these during the first 10 minutes of CPR. Visual inspection of the temporal trends in DBP and SBP (Figure 1) suggest a divergence in these values between patients with and without pulmonary hypertension after 7 to 8 minutes of CPR, as BP appears lower in pulmonary hypertension patients. This did not reach statistical significance, but theoretically could reflect worsening acidemia and hypoxemia in children over the course of IHCA causing increased pulmonary vascular resistance, compromised pulmonary blood flow and left ventricular filling, and thereby diminished systemic pressures during CPR. The possibility that BP differences during CPR increased further later in CPR could not be addressed, as our hemodynamic data only included the first 10 minutes of CPR. We did not observe BP differences according to iNO status, but in our unadjusted analysis, ETCO2 was significantly lower in patients recieiving iNO. This finding conflicts with the expected physiology of iNO increasing pulmonary blood flow and thus leading to higher ETCO2 during CPR. However, as previously noted, this secondary analysis was significantly confounded by indication and other factors.

This study has important limitations to consider. The definition of pulmonary hypertension was not specified by echocardiographic or cardiac catheterization data, limiting our ability to comment on pulmonary hypertension severity or consistency in diagnostic criteria between sites. Additionally, our goal was to describe IHCA in patients with pulmonary hypertension rather than specifically evaluating pulmonary hypertension crisis as a cause of arrest – thus,

we could not specifically comment on this group of children. This study cohort represented a convenience sample of children enrolled in a clinical trial that was not prospectively powered to address these specific objectives. Thus, inadequate statistical power may have limited our ability to detect differences between groups. Lastly, this observational study was confounded by patients receiving pulmonary hypertension-directed therapies and by the heterogenous characteristics of children with IHCA. Though our statistical methods attempted to address this, the confounding and bias inherent to observational studies cannot be entirely mitigated. Nonetheless, the prospective design of this study and clinical trial-quality data collection enhances the validity of our findings.

CONCLUSIONS:

In this prospective study of children who received CPR in intensive care units, a pre-existing diagnosis pulmonary hypertension was present in 16% of children but was not associated with statistically significant differences in survival outcomes or intra-arrest physiologic measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

CONFLICTS OF INTEREST:

REFERENCES:

1. Holmberg MJ, Ross CE, Fitzmaurice GM, et al. Annual Incidence of Adult and Pediatric In-Hospital Cardiac Arrest in the United States. Circ Cardiovasc Qual Outcomes. Jul 9 2019;12(7):e005580. doi:10.1161/CIRCOUTCOMES.119.005580 [PubMed: 31545574]

2. Berg RA, Sutton RM, Holubkov R, et al. Ratio of PICU versus ward cardiopulmonary resuscitation events is increasing. Crit Care Med. Oct 2013;41(10):2292–7. doi:10.1097/CCM.0b013e31828cf0c0 [PubMed: 23921270]

3. Morgan RW, Topjian AA, Wang Y, et al. Prevalence and Outcomes of Pediatric In-Hospital Cardiac Arrest Associated With Pulmonary Hypertension. Pediatr Crit Care Med. Apr 2020;21(4):305–313. doi:10.1097/PCC.0000000000002187 [PubMed: 31688674]

4. Morgan RW, Himebauch AS, Griffis H, et al. Pulmonary hypertension among children with in-hospital cardiac arrest: A multicenter study. Resuscitation. Nov 2021;168:52–57. doi:10.1016/j.resuscitation.2021.09.009 [PubMed: 34536558]

5. Berg RA, Sutton RM, Reeder RW, et al. Association Between Diastolic Blood Pressure During Pediatric In-Hospital Cardiopulmonary Resuscitation and Survival. Circulation. Apr 24 2018;137(17):1784–1795. doi:10.1161/CIRCULATIONAHA.117.032270 [PubMed: 29279413]

6. Berg RA, Morgan RW, Reeder RW, et al. Diastolic Blood Pressure Threshold During Pediatric Cardiopulmonary Resuscitation and Survival Outcomes: A Multicenter Validation Study. Crit Care Med. Jan 1 2023;51(1):91–102. doi:10.1097/CCM.0000000000005715 [PubMed: 36519983]

7. Morgan RW, Sutton RM, Karlsson M, et al. Pulmonary Vasodilator Therapy in Shock-associated Cardiac Arrest. Am J Respir Crit Care Med. Apr 1 2018;197(7):905–912. doi:10.1164/rccm.201709-1818OC [PubMed: 29244522]

8. Morgan RW, Sutton RM, Himebauch AS, et al. A randomized and blinded trial of inhaled nitric oxide in a piglet model of pediatric cardiopulmonary resuscitation. Resuscitation. Mar 22 2021;162:274–283. doi:10.1016/j.resuscitation.2021.03.004 [PubMed: 33766668]

9. Brucken A, Derwall M, Bleilevens C, et al. Brief inhalation of nitric oxide increases resuscitation success and improves 7-day-survival after cardiac arrest in rats: a randomized controlled animal study. Crit Care. Nov 17 2015;19:408. doi:10.1186/s13054-015-1128-x [PubMed: 26577797]

10. Derwall M, Ebeling A, Nolte KW, et al. Inhaled nitric oxide improves transpulmonary blood flow and clinical outcomes after prolonged cardiac arrest: a large animal study. Crit Care. Sep 15 2015;19:328. doi:10.1186/s13054-015-1050-2 [PubMed: 26369409]

11. Reeder RW, Girling A, Wolfe H, et al. Improving outcomes after pediatric cardiac arrest - the ICU-Resuscitation Project: study protocol for a randomized controlled trial. Trials. Apr 3 2018;19(1):213. doi:10.1186/s13063-018-2590-y [PubMed: 29615134]

12. Sutton RM, Wolfe HA, Reeder RW, et al. Effect of Physiologic Point-of-Care Cardiopulmonary Resuscitation Training on Survival With Favorable Neurologic Outcome in Cardiac Arrest in Pediatric ICUs: A Randomized Clinical Trial. JAMA. Mar 8 2022;327(10):934–945. doi:10.1001/jama.2022.1738 [PubMed: 35258533]

13. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation. Dec 2004;63(3):233–49. doi:10.1016/j.resuscitation.2004.09.008 [PubMed: 15582757]

14. Nolan JP, Berg RA, Andersen LW, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Template for In-Hospital Cardiac Arrest: A Consensus Report From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia). Circulation. Oct 29 2019;140(18):e746–e757. doi:10.1161/CIR.0000000000000710 [PubMed: 31522544]

15. Morgan RW, Berg RA, Reeder RW, et al. The physiologic response to epinephrine and pediatric cardiopulmonary resuscitation outcomes. Crit Care. Mar 13 2023;27(1):105. doi:10.1186/s13054-023-04399-5 [PubMed: 36915182]

16. Fiser DH. Assessing the outcome of pediatric intensive care. J Pediatr. Jul 1992;121(1):68–74. doi:10.1016/s0022-3476(05)82544-2 [PubMed: 1625096]

17. Topjian AA, Scholefield BR, Pinto NP, et al. P-COSCA (Pediatric Core Outcome Set for Cardiac Arrest) in Children: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation. May 2021;162:351–364. doi:10.1016/j.resuscitation.2021.01.023 [PubMed: 33515637]

18. Alten JA, Klugman D, Raymond TT, et al. Epidemiology and Outcomes of Cardiac Arrest in Pediatric Cardiac ICUs. Pediatr Crit Care Med. Oct 2017;18(10):935–943. doi:10.1097/PCC.0000000000001273 [PubMed: 28737598]

19. Matos RI, Watson RS, Nadkarni VM, et al. Duration of cardiopulmonary resuscitation and illness category impact survival and neurologic outcomes for in-hospital pediatric cardiac arrests. Circulation. Jan 29 2013;127(4):442–51. doi:10.1161/CIRCULATIONAHA.112.125625 [PubMed: 23339874]

20. Meaney PA, Nadkarni VM, Cook EF, et al. Higher survival rates among younger patients after pediatric intensive care unit cardiac arrests. Pediatrics. Dec 2006;118(6):2424–33. doi:10.1542/peds.2006-1724 [PubMed: 17142528]

21. Morgan RW, Reeder RW, Meert KL, et al. Survival and Hemodynamics During Pediatric Cardiopulmonary Resuscitation for Bradycardia and Poor Perfusion Versus Pulseless Cardiac

Arrest. Crit Care Med. Jun 2020;48(6):881–889. doi:10.1097/CCM.0000000000004308 [PubMed: 32301844]

22. Samson RA, Nadkarni VM, Meaney PA, et al. Outcomes of in-hospital ventricular fibrillation in children. N Engl J Med. Jun 1 2006;354(22):2328–39. doi:10.1056/NEJMoa052917 [PubMed: 16738269]

23. Bhanji F, Topjian AA, Nadkarni VM, et al. Survival Rates Following Pediatric In-Hospital Cardiac Arrests During Nights and Weekends. JAMA Pediatr. Jan 1 2017;171(1):39–45. doi:10.1001/jamapediatrics.2016.2535 [PubMed: 27820606]

24. Berger JT, Maddux AB, Reeder RW, et al. Inhaled Nitric Oxide Use in Pediatric Hypoxemic Respiratory Failure. Pediatr Crit Care Med. Aug 2020;21(8):708–719. doi:10.1097/PCC.0000000000002310 [PubMed: 32195895]

25. Ong MS, Abman S, Austin ED, et al. Racial and Ethnic Differences in Pediatric Pulmonary Hypertension: An Analysis of the Pediatric Pulmonary Hypertension Network Registry. J Pediatr. Aug 2019;211:63–71 e6. doi:10.1016/j.jpeds.2019.04.046 [PubMed: 31176455]

26. Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. Jan 2019;53(1)doi:10.1183/13993003.01916-2018

27. Abman SH, Ivy DD, Archer SL, Wilson K, Committee AAJGfPPH. Executive Summary of the American Heart Association and American Thoracic Society Joint Guidelines for Pediatric Pulmonary Hypertension. Am J Respir Crit Care Med. Oct 1 2016;194(7):898–906. doi:10.1164/rccm.201606-1183ST [PubMed: 27689707]

28. Morell E, Gaies M, Fineman JR, et al. Mortality from Pulmonary Hypertension in the Pediatric Cardiac Intensive Care Unit. Am J Respir Crit Care Med. Apr 2 2021;doi:10.1164/rccm.202011-4183OC
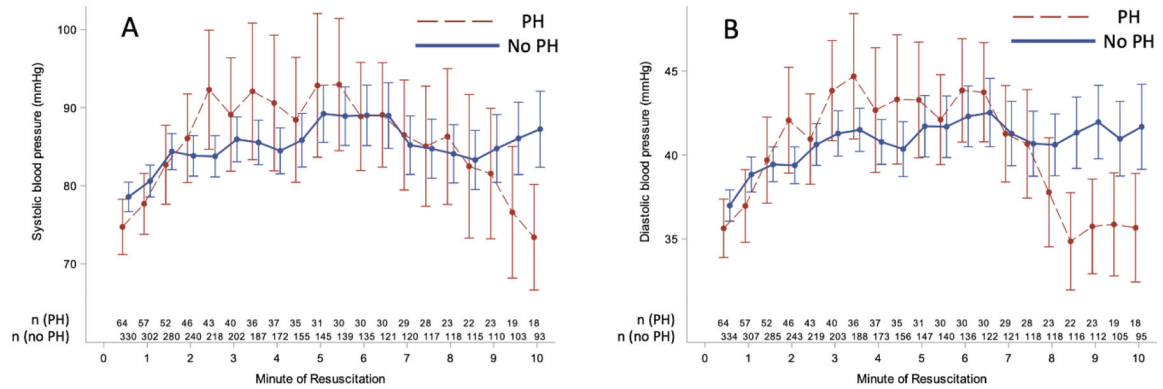
Figure 1. Blood Pressures During Cardiopulmonary Resuscitation in Patients with and without Pulmonary Hypertension.

Systolic (Panel A) and diastolic (Panel B) blood pressures during the first ten minutes of CPR depicted between patients with pulmonary hypertension (red dashed line) and patients without pulmonary hypertension (blue solid line). Values represent the mean blood pressure for each 30-second epoch of CPR and error bars represent one standard error above and below the mean. The number of patients with contributing data in each group at each time point is noted. There were no statistically significant differences between groups at any given time point.

Table 1.

Patient Characteristics

| Characteristic | Overall (N = 1129) | Pulmonary hypertension | | P-value |
		Yes (N = 184)	No (N = 945)	
Demographics				
Age				<0.001
1 month	181 (16.0%)	7 (3.8%)	174 (18.4%)	
1 month - < 1 year	475 (42.1%)	94 (51.1%)	381 (40.3%)	
1 year - < 8 years	269 (23.8%)	58 (31.5%)	211 (22.3%)	
8 years - < 19 years	204 (18.1%)	25 (13.6%)	179 (18.9%)	
Male	605 (53.6%)	99 (53.8%)	506 (53.5%)	1.000
Race				0.020
White	531 (47.0%)	71 (38.6%)	460 (48.7%)	
Black or African American	286 (25.3%)	60 (32.6%)	226 (23.9%)	
Other	66 (5.8%)	10 (5.4%)	56 (5.9%)	
Unknown or Not Reported	246 (21.8%)	43 (23.4%)	203 (21.5%)	
Preexisting medical conditions				
Respiratory insufficiency	974 (86.3%)	172 (93.5%)	802 (84.9%)	0.001
Hypotension	713 (63.2%)	111 (60.3%)	602 (63.7%)	0.404
Congenital heart disease	650 (57.6%)	140 (76.1%)	510 (54.0%)	<0.001
Sepsis	184 (16.3%)	26 (14.1%)	158 (16.7%)	0.445
Renal insufficiency	156 (13.8%)	32 (17.4%)	124 (13.1%)	0.130
Congestive heart failure	147 (13.0%)	40 (21.7%)	107 (11.3%)	<0.001
Pneumonia	141 (12.5%)	21 (11.4%)	120 (12.7%)	0.715
Malignancy	53 (4.7%)	5 (2.7%)	48 (5.1%)	0.187
Trauma	35 (3.1%)	0 (0.0%)	35 (3.7%)	0.004
Pre-arrest characteristics				
Illness category				<0.001
Medical cardiac	273 (24.2%)	55 (29.9%)	218 (23.1%)	
Medical non-cardiac	399 (35.3%)	47 (25.5%)	352 (37.2%)	
Surgical cardiac	383 (33.9%)	79 (42.9%)	304 (32.2%)	
Surgical non-cardiac	45 (4.0%)	3 (1.6%)	42 (4.4%)	
Trauma	29 (2.6%)	0 (0.0%)	29 (3.1%)	
Interventions in place				
Arterial catheter	574 (50.8%)	90 (48.9%)	484 (51.2%)	0.574
Central venous catheter	775 (68.6%)	131 (71.2%)	644 (68.1%)	0.436
Vasoactive infusion	591 (52.3%)	103 (56.0%)	488 (51.6%)	0.295
Non-invasive ventilation	206 (18.2%)	30 (16.3%)	176 (18.6%)	0.531
Invasive mechanical ventilation	802 (71.0%)	142 (77.2%)	660 (69.8%)	0.050
PRISM[1]	4.0 [0.0, 10.0]	3.0 [0.0, 10.0]	4.0 [0.0, 10.0]	0.306
Baseline PCPC score[2]				<0.001

| Characteristic | Overall (N = 1129) | Pulmonary hypertension | | P-value |
		Yes (N = 184)	No (N = 945)	
1 - Normal	690 (61.1%)	75 (40.8%)	615 (65.1%)	
2 - Mild disability	201 (17.8%)	47 (25.5%)	154 (16.3%)	
3 - Moderate disability	115 (10.2%)	34 (18.5%)	81 (8.6%)	
4 - Severe disability	111 (9.8%)	26 (14.1%)	85 (9.0%)	
5 - Coma/vegetative state	12 (1.1%)	2 (1.1%)	10 (1.1%)	
Baseline FSS[2]	6.0 [6.0, 10.0]	9.0 [6.0, 13.0]	6.0 [6.0, 10.0]	<0.001

PRISM = Pediatric RISk of Mortality; PCPC = Pediatric Cerebral Performance Category; FSS = Functional Status Scale.

[1] PRISM was evaluated 2 - 6 hours prior to the event.

[2] Baseline PCPC score and FSS score represent subject status prior to the event leading to hospitalization.

Table 2.

Pulmonary hypertension medications.

Table reflects frequency of medications prescribed or being administered to patients with pulmonary hypertension at the time of cardiac arrest.

Medication	Overall (N = 184)
Inhaled nitric oxide	101 (54.9%)
Primary indication for iNO initiation	
Pulmonary hypertension	32/101 (31.7%)
Other cardiac disease	45/101 (44.6%)
Congenital heart disease	40/77 (51.9%)
Heart transplant (post-operative)	5/77 (6.5%)
Respiratory disease	24/101 (23.8%)
Chronic lung disease / bronchopulmonary dysplasia	7/24 (29.2%)
Acute respiratory distress syndrome	6/24 (25.0%)
Sepsis	5/24 (20.8%)
Viral pneumonia / bronchiolitis / pneumonitis	3/24 (12.5%)
Bacterial pneumonia	2/24 (8.3%)
Asthma	1/24 (4.2%)
Non-iNO pulmonary vasodilators	97 (52.7%)
Phosphodiesterase inhibitors	
Sildenafil	91 (49.5%)
Tadalafil	2 (1.1%)
Endothelin receptor antagonists	
Bosentan	27 (14.7%)
Ambrisentan	5 (2.7%)
Prostacyclin agonists	
Treprostinil	14 (7.6%)
None	38 (20.7%)

iNO = inhaled nitric oxide.

Table 3.

Cardiac Arrest Characteristics

| Characteristic | Overall (N = 1129) | Pulmonary hypertension | | P-value |
		Yes (N = 184)	No (N = 945)	
Location of CPR Event				0.024
PICU	547 (48.4%)	75 (40.8%)	472 (49.9%)	
CICU	582 (51.6%)	109 (59.2%)	473 (50.1%)	
CPR time [1]				0.793
Weekday	597 (52.9%)	94 (51.1%)	503 (53.2%)	
Weeknight	222 (19.7%)	36 (19.6%)	186 (19.7%)	
Weekend	310 (27.5%)	54 (29.3%)	256 (27.1%)	
First documented rhythm				0.122
Pulseless electrical activity / asystole	455 (40.3%)	68 (37.0%)	387 (41.0%)	
Ventricular fibrillation / tachycardia	93 (8.2%)	10 (5.4%)	83 (8.8%)	
Bradycardia with poor perfusion	581 (51.5%)	106 (57.6%)	475 (50.3%)	
Immediate cause(s) of event				
Respiratory decompensation	612 (54.2%)	105 (57.1%)	507 (53.7%)	0.419
Hypotension	609 (53.9%)	84 (45.7%)	525 (55.6%)	0.015
Arrhythmia	195 (17.3%)	26 (14.1%)	169 (17.9%)	0.242
Cyanosis without respiratory decompensation	51 (4.5%)	14 (7.6%)	37 (3.9%)	0.033
Duration of CPR (minutes)				0.398
<6	520 (46.1%)	93 (50.5%)	427 (45.2%)	
6-15	228 (20.2%)	33 (17.9%)	195 (20.6%)	
16-35	191 (16.9%)	33 (17.9%)	158 (16.7%)	
>35	190 (16.8%)	25 (13.6%)	165 (17.5%)	
Interventions during CPR				
Epinephrine	895 (79.3%)	152 (82.6%)	743 (78.6%)	0.235
Number of epinephrine boluses	3.0 [1.0, 6.0]	2.0 [1.0, 4.0]	3.0 [1.0, 7.0]	0.025
Atropine	125 (11.1%)	19 (10.3%)	106 (11.2%)	0.798
Calcium	461 (40.8%)	62 (33.7%)	399 (42.2%)	0.033
Sodium bicarbonate	540 (47.8%)	83 (45.1%)	457 (48.4%)	0.468
Vasopressin	41 (3.6%)	5 (2.7%)	36 (3.8%)	0.666
Amiodarone	41 (3.6%)	7 (3.8%)	34 (3.6%)	0.831
Lidocaine	45 (4.0%)	6 (3.3%)	39 (4.1%)	0.685
Fluid bolus	291 (25.8%)	36 (19.6%)	255 (27.0%)	0.035
CPR Quality Metrics				
Chest compression depth (mm)	34.8 [25.3, 50.3]	29.3 [23.1, 52.2]	35.2 [25.7, 50.1]	0.551
Chest compression rate (min^{-1})	120.8 [111.8, 130.1]	120.0 [113.1, 126.5]	120.8 [111.6, 130.6]	0.592
Chest compression release velocity (mm/sec)	200.7 [150.4, 327.8]	172.8 [143.3, 328.9]	203.6 [155.8, 315.8]	0.573
Chest compression fraction	0.97 [0.92, 1.00]	0.98 [0.92, 1.00]	0.97 [0.92, 1.00]	0.429

CPR = Cardiopulmonary resuscitation; PICU = Pediatric intensive care unit; CICU = Cardiac intensive care unit.

*1*Weekday = 7AM - 11PM Monday - Friday. Weeknight = after 11PM Monday - Thursday. Weekend = 11PM Friday - 7AM Monday.

Table 4.

Survival and physiologic outcomes.

Outcome frequencies and unadjusted (univariate) and adjusted (multivariate) odds ratios / effect sizes between patients with and without pulmonary hypertension.

	Pulmonary hypertension		Unadjusted		Adjusted[2]	
	Yes (N = 184)	No (N = 945)	Odds ratio/ effect size[1] (CI)	P-value	Odds ratio/ effect size[1] (CI)	P-value
Survival outcomes						
Survival to hospital discharge with favorable neurologic outcome[3]	90 (48.9%)	514 (54.4%)	0.80 (0.58, 1.10)	0.173	0.82 (0.56, 1.20)	0.318
Survival to hospital discharge	101 (54.9%)	550 (58.2%)	0.87 (0.64, 1.20)	0.406	0.89 (0.65, 1.23)	0.484
Sustained ROSC	130 (70.7%)	651 (68.9%)	1.09 (0.77, 1.55)	0.636	1.07 (0.70, 1.65)	0.743
Hemodynamic measures						
Average DBP (mmHg)[4]	37.9 [30.1, 51.8]	38.9 [30.6, 49.0]	−1.45 (−6.24, 3.35)	0.553	−2.94 (−6.05, 0.16)	0.116
Adequate DBP[5]	55/67 (82.1%)	298/346 (86.1%)	0.74 (0.38, 1.54)	0.392	0.75 (0.46, 1.21)	0.240
Average SBP (mmHg)[4]	81.3 [58.8, 112.3]	81.6 [58.8,101.4]	−0.01 (−9.27, 9.24)	0.998	−3.58 (−9.93, 2.77)	0.311
Adequate SBP[6]	45/67 (67.2%)	234/341 (68.6%)	0.94 (0.54, 1.66)	0.815	0.93 (0.60, 1.44)	0.738
Average ETCO2 (mmHg)[4]	21.1 [15.0, 29.6]	22.3 [14.3,31.7]	−0.96 (−4.89, 2.96)	0.629	−1.29 (−4.88, 2.29)	0.515

ROSC = Return of spontaneous circulation; DBP = Diastolic blood pressur e; SBP = Systolic blood pressure; ETCO2 = End-tidal carbon dioxide.

[1] Odds/effect size of the survival outcome or physiologic measure for patients with pulmonary hypertension compared to patients without pulmonary hypertension.

Odds ratios for binary outcomes are based on logistic regression models. Effect sizes for continuous outcomes are based on linear regression.

[2] Adjusted results are based on models that control for age category, first d ocumented rhythm, illness category, and CPR time category.

[3] Favorable neurologic outcome is defined as Pediatric Cerebral Performance Category score of 1-3 (no more than moderate disability) or no worsening from baseline. Baseline refers to patient status prior to the event or illness leading to hospitalization.

[4] Average of available physiologic data from the first ten minutes of CPR.

[5] Average diastolic pressure was considered adequate if 25 mmHg for patients <1 year old or 30 mmHg for patients 1 year old.

[6] Average systolic pressure was considered adequate if 60 mmHg for subjects <1 year old or 80 mmHg for subjects 1 year old.