Clinical question.

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Peds-056A - For infants and children in cardiac arrest with pulmonary hypertension (PH) (prehospital [OHCA] or in-hospital [IHCA]) (P), do any specific modifications to resuscitation techniques (I) compared with standard resuscitation techniques (C), improve outcome (ROSC, survival to discharge, favorable neurologic survival) (O)?

**Is this question addressing an intervention/therapy, prognosis or diagnosis:** Intervention/therapy.

**State if this is a proposed new topic or revision of existing worksheet:** New topic

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? Ian Adatia is a member of the advisory committee to create a Canadian pediatric pulmonary hypertension data base funded by Actelion. Ian Adatia is a member of an advisory committee for the pediatric sildenafil trial and for the pediatric investigator protocol for sitaxsentan for Pfizer.

John Berger does not have any conflict of interests relevant to this worksheet. Dr. Wessel is a consultant to IKARIA, Inc.

**Search strategy (including electronic databases searched).**

We searched independently (via OVID and PubMed) MEDLINE, EMBASE, COCHRANE DATA BASE OF SYSTEMATIC REVIEWS, AHA Endnote database, ACP Journal Club, Cochrane Central Register of Controlled Trials, Cochrane Methodology Database, Database of Abstract Reviews of Effects, Health Technology Assessment Database, National Health Service Economic Evaluation Database.

We used also articles from our own knowledge bases and searched the reference lists in those articles. We used keywords cardiac resuscitation, CPR, pulmonary hypertension, pulmonary hypertensive crisis, nitric oxide therapy, epoprostenol, prostacyclin, iloprost, epinephrine, vasopressin, ECMO, ECLS. We searched also sudden death and pulmonary hypertension n=287.

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9 exp Resuscitation/ or exp Cardiopulmonary Resuscitation/ 62965
10 8 and 9 61
11 exp Heart Massage/ 2415
12 exp Cardiopulmonary Resuscitation/ 9337
13 11 or 12 11448
14 8 and 13 3

EMBASE
1 pulmonary hypertension.mp. or exp pulmonary hypertension/ 25403
2 heart arrest.mp. or exp heart arrest/ 17481
3 exp resuscitation/ or resuscitation.mp. 33942
4 heart massage.mp. or exp heart massage/ 914
AYERZA'S SYNDROME.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 0
5 1 or 5 25403
6 2 or 3 or 4 44908
7 6 and 7 426
8 limit 8 to infant <to one year> 18
9 8 not 9 408
10 limit 10 to (preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) 24
### EMBASE

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### Medline

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### Scopus

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<tr>
<td>child children pediatric* paediatric* infant* newborn* pregan*</td>
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Databases searched via OVID-Medline, ACP Journal Club (ACP), Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (COCH), Cochrane Methodology Register Database (CMR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), National Health Service Economic Evaluation Database (NHSEED), EMBASE.
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Explode death, sudden, cardiac  
Explode resuscitation  
Explode heart massage  
Explode respiration artificial  
Explode resuscitation orders  
Explode cardiopulmonary Resuscitation CPR keyword  
Explode heart arrest  
Explode death, sudden, cardiac  
Advanced cardiac life support  
Advanced cardiac life support keyword  
Pediatric cardiac life support keyword  
Chest compressions keyword  
Explode Epinephrine  
Explode norepinephrine  
Explode phenylephrine  
Explode Vasopressins  
Vasopressin keyword |
| **Pulmonary Hypertension Keyword** | Explode cardiopulmonary Resuscitation CPR keyword  
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Explode death, sudden, cardiac  
Advanced cardiac life support  
Advanced cardiac life support keyword  
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Chest compressions keyword  
Explode Epinephrine  
Explode norepinephrine  
Explode phenylephrine  
Explode Vasopressins  
Vasopressin keyword |
| **Explode PH or PH keyword** | Explode resuscitation  
Explode cardiopulmonary Resuscitation  
Explode heart massage  
Explode respiration artificial  
Explode resuscitation orders  
Congenital Heart defect |
| **Pulmonary heart disease** | Explode heart arrest  
Explode death, sudden, cardiac  
Explode cardiopulmonary Resuscitation  
Explode resuscitation  
Explode heart massage  
Explode respiration artificial  
Explode resuscitation orders  
CPR keyword  
Advanced cardiac life support  
Advanced cardiac life support keyword  
Pediatric cardiac life support keyword  
Asystole keyword  
Chest Compressions keyword  
Explode Epinephrine  
Explode norepinephrine  
Explode phenylephrine  
Explode Vasopressins  
Vasopressin keyword |
| **Cor pulmonale keyword** | Explode heart arrest  
Explode death, sudden, cardiac  
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Explode resuscitation  
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CPR keyword  
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Pediatric cardiac life support keyword  
Asystole keyword  
Chest Compressions keyword  
Explode Epinephrine  
Explode norepinephrine  
Explode phenylephrine |
| Explode Nitric oxide | Explode Heart Arrest  
| Explode death, sudden, cardiac  
| Explode Cardiopulmonary resuscitation  
| CPR keyword  
| Advanced cardiac life support  
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| Pediatric cardiac life support keyword  
| Asystole keyword  
| Chest Compressions keyword  
| Pulmonary Hypertension (Limited to Children Age 0-18) | Explode PH, PH keyword or  
| Explode Congenital heart defects |

SCOPUS

\[ ((\text{TITLE-ABS-KEY(cpr OR resuscit* OR "heart massage") AND TITLE-ABS-KEY("ayerza's syndrome" OR "pulmonary hypertension"))}) \text{AND (TITLE-ABS-KEY-AUTH(child OR children OR pediatric* OR paediatric*)) AND NOT (TITLE-ABS-KEY(infant* OR newborn OR pregnan*)) = 15} \]

• **State inclusion and exclusion criteria**
We included all studies and case reports that offered therapy for life threatening pulmonary hypertension and right ventricular failure in humans, adult and/or children.
We excluded articles that dealt exclusively with persistent pulmonary hypertension of the newborn or delivery room resuscitation, articles that were unavailable in English, French or German, animal studies. Single case reports were excluded if they did not deal with resuscitation of patients with pulmonary hypertension from cardiac arrest specifically. **We excluded consensus opinions, editorials and non systematic reviews.**
The date of the search was January 2010.

• **Number of articles/sources meeting criteria for further review:**
We considered 33 articles suitable for further review.
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
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<tr>
<td><strong>Evidence</strong></td>
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<td><strong>Khan, 2009:1417</strong></td>
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<td><strong>Miller, 2000:1464</strong></td>
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<td><strong>Morris, 2000:2974</strong></td>
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<td><strong>Namachivayam, 2006, 1042</strong></td>
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<td><strong>Atz, 1996:1759</strong></td>
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<td><strong>Cueto, 1997:1337</strong></td>
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<td><strong>Goldman, 1996:750</strong></td>
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<td><strong>Limsuwan, 2008:333</strong></td>
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<td><strong>Liu, 2009: 504 CE</strong></td>
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<td><strong>Matsui, 1997:17 E</strong></td>
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<td><strong>Miller, 1995;51 E</strong></td>
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<td><strong>Peiravian, 2007:113 E</strong></td>
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<td><strong>Rimensberger, 2001:544 E</strong></td>
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<td><strong>Carmosino, 2007:521</strong></td>
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<td><strong>King, 2000:628 C,D</strong></td>
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<td><strong>Turanlahti, 2000:46 B,E</strong></td>
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**Level of evidence**

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint
- *Italics = Animal studies*
### Evidence Neutral to Clinical question

<table>
<thead>
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Bizzarro, 2009:1 C,E

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Day, 2000:1907 B,E
Schranz, 1992:1243 E
Polderman, 2004:171 E
Sanatani, 2006:89 E

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</table>

**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint

*Italics = Animal studies*

### Evidence Opposing Clinical Question

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint

*Italics = Animal studies*
There are no studies that deal specifically with resuscitation from cardiac arrest in children with pulmonary hypertension. Sudden death and cardiac arrest may occur as the presenting event in pulmonary vascular disease or may complicate a patient with a known diagnosis of pulmonary hypertension (Polderman, Cohen et al. 2004; Sanatani, Wilson et al. 2006). Cardiac arrest may be due to arrhythmia, pulmonary hemorrhage, left main coronary compression by the pulmonary artery, pulmonary artery dissection, embolus or spontaneous pulmonary artery hypertensive crisis or crisis due to withdrawal of pulmonary artery specific medication. The reason for the cardiac arrest is usually acute right ventricular decompensation or failure often in a patient with little reserve. There is an association with an intercurrent illness usually respiratory tract infection or an association with a medical or surgical procedure. There are 4 case reports documenting successful resuscitation from cardiac arrest in patients with known pulmonary artery hypertension (Myles, Hall et al. 1994; Haas, Schulze-Neick et al. 1995; King, Esmail et al. 2000; Passarani, Vignati et al. 2004). Two adults were resuscitated with inhaled nitric oxide and infused prostacyclin (King, Esmail et al. 2000; Passarani, Vignati et al. 2004). One adult suffered a cardiac arrest during anesthetic induction for a lung transplant and failed to recover with CPR, epinephrine and intravenous prostacyclin at 5 ng/kg/min. He was cannulated for cardiac bypass and recovered well following lung transplant (Myles, Hall et al. 1994). One 15 yr old child failed to respond to inhaled NO, IV and aerosolized low dose prostacyclin but responded immediately to intra tracheal delivery of 1 µg/kg prostacyclin (Haas, Schulze-Neick et al. 1995). There are 2 retrospective reports of complications from cardiac catheterization in children with pulmonary hypertension (Carmosino, Friesen et al. 2007; Taylor, Derrick et al. 2007). In the report by Carmosino et al 6 patients suffered cardiac arrest or pulmonary hypertensive crisis. Four were resuscitated and therapy included inhaled NO in 3 and inhaled NO with epoprostenol in 1. Two died despite inhaled NO and epoprostanol administration (Carmosino, Friesen et al. 2007). In the second study 4 patients required CPR either during cardiac catheterization or within 24 hours. One patient died and 3 survived. Further details about the events and treatment used for resuscitation are not provided (Taylor, Derrick et al. 2007). There is one retrospective multicenter description of the outcome of cardiac arrest in adult patients with pulmonary artery hypertension. 513 out of 3,130 patients with pulmonary hypertension suffered cardiac arrest and CPR was attempted in 132. There was no return of circulation in 104 and only 8 patient survived longer than 90 days. all without neurological deficit. The majority (96%) was in hospital cardiac arrests with rapid institution of resuscitation efforts. Seven patients had a correctable cause for the cardiac arrest including tamponade during cardiac catheterization (1), digitalis toxicity (1), epilepsy (1) but of note 3 of the survivors either received inhaled nitric oxide or an intravenous bolus of 50µg of iloprost. CPR was ineffective, as observed by the authors, because in patients with a severely elevated pulmonary vascular resistance, chest compressions are unlikely to result in pulmonary blood flow or left ventricular preload (Hoeper, Galie et al. 2002). Therefore, treatment of the pulmonary hypertensive patient with cardiac arrest should concentrate on identifying a reversible acute component and then either decreasing pulmonary vascular resistance or supporting the RV or improving left ventricular preload. Pulmonary hypertensive crises are defined as acute often suprasystemic elevations in pulmonary artery pressure associated with a decrease in cardiac output and blood pressure and cause death from right ventricular failure if untreated. If one presumes this is a precursor to cardiac arrest then therapies that reverse pulmonary artery crises may be useful in resuscitation. In addition crises may be precipitated by withdrawal of pulmonary hypertensive specific therapy such as nitric oxide or prostacyclin and analogues and usually resolve with reinstitution of withdrawn therapy (Miller, Tang et al. 1995; Atz, Adatia et al. 1996; Lavoie, Hall et al. 1996; Cueto, Lopez-Herce et al. 1997). Thus we presume that drugs that provoke pulmonary hypertensive crises by withdrawal, and resolution, with reinstitution, may also prevent or treat a spontaneous crisis. There are numerous descriptions that demonstrate unequivocally that nitric oxide and prostacyclin are pulmonary vasodilators that can be used to treat a crisis (Atsumi, Gomi et al. 1996; Goldman, Delius et al. 1996; Murthy, Rao et al. 1996; Matsui, Yahagi et al. 1997; Murthy, Rao et al. 1999; Turanlhti, Laitinen et al. 2000; Journois, Baufreton et al. 2005; Khan, Schnickel et al. 2009) and that withdrawal may precipitate a crisis that is relieved with resumption of treatment (Miller, Tang et al. 1995; Atz, Adatia et al. 1996; Lavoie, Hall et al. 1996; Cueto, Lopez-Herce et al. 1997). Inhaled nitric oxide, inhaled prostacyclin or analogues and intravenous prostacyclin appear to be equally effective pulmonary vasodilators (Schranz, Zepp et al. 1992; Rimensberger, Spahr-Schopfer et al. 2001; Limsuwan, Wanitkul et al. 2008; Khan, Schnickel et al. 2009). Thus it seems reasonable to suggest that in a patient with known pulmonary hypertension who suffers a cardiac arrest that one should look for an interruption in pulmonary hypertensive specific therapy and treat with either nitric oxide or prostacyclin aerosolized or intravenously. One study by Day et al (Day, Hawkins et al. 2000) fails to show a benefit from inhaled NO in the treatment group. However, it is to be noted that in both control and treatment groups there were patients who on further evaluation had conditions that might not be expected to show benefit from inhaled NO and one patient in the control group who was according to the authors successfully treated and salvaged with inhaled NO. Sildenafil may effectively reduce NO withdrawal crises and prevent post operative pulmonary hypertension when given by NG tube and maybe an alternative (Namachivayam, Theilen et al. 2006; Peiravian, Amirghofran et al. 2007). However, there are no reports of sildenafil salvage during a cardiac arrest.
If the afterload imposed on the right ventricle cannot be relieved by pulmonary vasodilation and CPR is ineffective, then right ventricular support would be a logical alternative. Thus patients have been salvaged by the use of ECMO, ECLS or pumpless lung assist device (Dhillon, Pearson et al. 1995; Arpesella, Loforte et al. 2008; Liu, Tsai et al. 2009; Strueber, Hoeper et al. 2009). In addition, as conventional resuscitation with CPR and epinephrine (the latter causes pulmonary vasoconstriction) is rarely effective (Hoeper, Galie et al. 2002) it may be suggested that rapid consideration of ECMO or Nova lung may offer the best chances of salvage.

A Cochrane review (Bizzarro and Gross 2009) fails to find a survival benefit of NO therapy in patients with pulmonary hypertensive congenital heart disease. However, the studies were heterogeneous and most were not designed or powered to demonstrate improved survival. They did demonstrate improved pulmonary vascular hemodynamics.

Acknowledgements:
Sandy Campbell University of Alberta Librarian

Citation List


LOE 5. Poor. Supporting. Case series describing the use of ECMO to salvage patients with right ventricular failure. Included 2 patients with pulmonary hypertension.


LOE 5. Poor. Supportive. Case series describing effect of inhaled NO in patients with postoperative pulmonary hypertensive crises unresponsive to amrinone and prostaglandin E1.


LOE 5. Fair. Supportive. Case series describing the hemodynamic response to withdrawal of inhaled NO and precipitation of rebound pulmonary hypertension.


LOE 5. Good. Neutral. Review of inhaled NO in congenital heart disease fails to find a survival benefit of NO therapy in patients with pulmonary hypertensive congenital heart disease. However, the studies reviewed were heterogeneous and most were not designed or powered to demonstrate improved survival. They did demonstrate improved pulmonary vascular hemodynamics.


LOE 4. Fair. Supportive. Retrospective report of complications from cardiac catheterization in children with pulmonary hypertension. 6 patients suffered cardiac arrest or pulmonary hypertensive crisis. Four were resuscitated and therapy included inhaled NO in 3 and inhaled NO with epoprostenol in 1. Two died despite inhaled NO and epoprostenol administration.


LOE 5. Fair. Supportive. Case series describing the need for cardiopulmonary resuscitation of 11 patients with pulmonary hypertension following abrupt withdrawal of inhaled NO.

**LOE 5. Fair. Neutral.** Randomised controlled trial fails to show a benefit from inhaled NO in the treatment group. However, it is to be noted that in both control and treatment groups there were patients who on further evaluation had conditions that might not be expected to show benefit from inhaled NO and one patient in the control group who was according to the authors successfully treated and salvaged with inhaled NO.


**LOE5, poor, supportive. Case series describing 5 children with critical pulmonary hypertension salvaged with ECMO.**


**LOE5, fair, supportive cases series describing how inhaled NO may prevent the need for ECMO in some children with pulmonary hypertension.**


**LOE4, poor, supportive. Case report of a child in cardiac arrest due to idiopathic pulmonary hypertension resuscitated with intra tracheal prostacyclin after other measures failed.**


**LOE 5. Fair. Supportive. The only good description of the outcome of cardiac arrest in pulmonary hypertension.**

Retrospective multicenter description of the outcome of cardiac arrest in adult patients with pulmonary artery hypertension. 513 out of 3,130 patients with pulmonary hypertension suffered cardiac arrest and CPR was attempted in 132. There was no return of circulation in 104 and only 8 patient survived longer than 90 days, all without neurological deficit. The majority (96%) was in hospital cardiac arrests with rapid institution of resuscitation efforts. Seven patients had a correctable cause for the cardiac arrest including tamponade during cardiac catheterization (1), digitalis toxicity (1), epilepsy (1) but of note 3 of the survivors either received inhaled nitric oxide or an intravenous bolus of 50µg of Iloprost. CPR was ineffective, as observed by the authors, because in patients with a severely elevated pulmonary vascular resistance, chest compressions are unlikely to result in pulmonary blood flow or left ventricular preload


**LOE 5. Fair. Supportive. Observational study with historical controls. Suggests that pulmonary hypertensive crises are associated with a high mortality and that the crises and mortality can be reduced by use of inhaled NO.**


**LOE 5. Good. Supportive. Prospective randomized crossover study demonstrating equal efficacy and minimal side effect profile of inhaled NO and aerosolized prostacyclin on hemodynamics in pulmonary hypertension after cardiac transplant in adults.**


**LOE 5. Poor. Supportive. Case report describing resuscitation of an adult with pulmonary hypetension from cardiac arrest with inhaled NO.**

**LOE 5. Poor. Supportive.** Case series describing life threatening pulmonary hypertension following abrupt withdrawal of inhaled NO therapy.


**LOE 5. Fair. Supportive.** Case series describing hemodynamic efficacy of inhaled iloprost in children with post operative pulmonary hypertensive crises. Suggests iloprost may be useful if NO is unavailable.


**LOE 5. Fair. Supportive.** Inhaled NO treats and prevents pulmonary hypertensive crises after cardiac surgery in children.


**LOE 5. Fair. Supportive.** In children abrupt withdrawal of NO precipitates rebound pulmonary hypertension.


**LOE 5. Good. Supportive.** Prospective randomised comparison of inhaled NO and alkalotic hypeventilation on postoperative pulmonary hemodynamicks. Equal pulmonary hemodynamic efficacy is shown but hyperventilation reduces cardiac output and increases systemic vascular resistance.


**LOE 5. Poor. Supportive.** Case series. Inhaled NO acutely reduces pulmonary artery pressure in children and decreases crises.


**LOE 5. Poor. Supportive.** Case series describing efficacy and safety of inhaled NO in postoperative pulmonary hypertension and crises.


**LOE 5. Poor. Supportive.** Case report describing salvage of an adult from cardiac arrest with cardiopulmonary bypass and lung transplantation.


**LOE 5. Good. Supportive.** Randomized trial of sildenafil versus placebo. Sildenafil prevents rebound pulmonary hypertension after withdrawal of inhaled NO in children.

LOE 5. Poor. Supportive. Case report describing long term survival after cardiac arrest. Resuscitated with infused prostacyclin and inhaled NO


LOE 5. Fair. Supportive. Oral sildenafil improves pulmonary vascular hemodynamics and prevents crises in children with pulmonary hypertension compared with controls.


LOE 5. Neutral. Fair. Sudden death and cardiac arrest may occur as the presenting event in children with pulmonary vascular disease or may complicate a patient with a known diagnosis of pulmonary hypertension.


LOE 5. Fair. Neutral. Infused prostacyclin is an effective pulmonary vasodilator in children with pulmonary hypertension.


LOE 5. Poor. Supportive. Case series using novel pumpless lung assist to salvage 4 patients, including one child, from severe right heart failure and pulmonary hypertension.


LOE 4. Poor. Supportive. Retrospective report of complications from cardiac catheterization in children with pulmonary hypertension. 4 patients required CPR either during cardiac catheterization or within 24 hours. One patient died and 3 survived. Further details about the events and treatment used for resuscitation are not provided.
