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Review

Focused echocardiography, end-tidal carbon dioxide, arterial blood pressure or near-infrared spectroscopy monitoring during paediatric cardiopulmonary resuscitation: A scoping review

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Abstract

Aim: To evaluate the individual use and predictive value of focused echocardiography, end-tidal carbon dioxide ($EtCO_2$), invasive arterial blood pressure (BP) and near-infrared spectroscopy (NIRS) during cardiopulmonary resuscitation (CPR) in children.

Methods: This scoping review was undertaken as part of the continuous evidence evaluation process of the International Liaison Committee on Resuscitation (ILCOR) and based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for scoping reviews. PubMed, MEDLINE, CINAHL and EMBASE were searched from the last ILCOR reviews until September 2020. We included all published studies evaluating the effect of echocardiography, $EtCO_2$, BP or NIRS guided CPR on clinical outcomes and quality of CPR.

Results: We identified eight observational studies, including 288 children. Two case series reported the use of echocardiography, one in detecting pulmonary emboli, the second in cardiac standstill, where contractility was regained with the use of extracorporeal membrane oxygenation. The two studies describing $EtCO_2$ were ambivalent regarding the association between mean values and any outcomes. Mean diastolic BP was associated with increased survival and favourable neurological outcome, but not with new substantive morbidity in two studies describing an overlapping population. NIRS values reflected changes in $EtCO_2$ and cerebral blood volume index in two studies, with lower values in patients who did not achieve return of circulation.

Abbreviations: BP, blood pressure (invasive arterial); BVI, blood volume index; CA, cardiac arrest; CI, confidence interval; CoSTR, consensus on science with treatment recommendations; CPR, cardiopulmonary resuscitation; CSF, cerebrospinal fluid; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ED, emergency department; $EtCO_2$, end-tidal carbon dioxide; ICP, intracranial pressure; IHCA, in-hospital cardiac arrest; ILCOR, international liaison committee on resuscitation; NICU, neonatal intensive care unit; NIRS, near-infrared spectroscopy; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; PCICU, paediatric cardiac intensive care unit; PICU, paediatric intensive care unit; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PE, pulmonary emboli; RCT, randomized controlled trial; ROC, receiver operating characteristic; $rcSO_2$, regional cerebral oxygen saturations; ROSC, return of spontaneous circulation; RR, relative risk; RV, right ventricle; SD, standard deviation; USA, United States of America.

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Conclusion: Although there seems some beneficial effect of these intra-arrest variables, higher quality paediatric studies are needed to evaluate whether echocardiography, $EtCO_2$, BP or NIRS guided CPR could improve outcomes.

Keywords: Cardiopulmonary resuscitation, Near-infrared spectroscopy, End-tidal CO_2, Arterial blood pressure, Point-of-care ultrasound, Paediatric life support

Introduction

Cardiac arrest (CA) occurs infrequently in children, but still carries a poor prognosis particularly after out-of-hospital cardiac arrest (OHCA).[1,2] High quality cardiopulmonary resuscitation (CPR) improves outcomes, but what constitutes the best possible CPR for an individual patient is still based on limited evidence and probably differs between patients and aetiologies.[3] Real-time anatomical and physiological monitoring during CPR may allow rescuers to modify CPR itself, as well as other resuscitation interventions, or provide information to predict likelihood of return of spontaneous circulation (ROSC) and subsequent neurodevelopmental outcome and survival. Potential monitoring tools include focused echocardiography, end-tidal carbon dioxide ($EtCO_2$), invasive arterial blood pressure (BP) and near-infrared spectroscopy (NIRS).

During focused echocardiography, a generalized protocol with reduced views is used to quickly obtain information on general cardiac function and specific abnormalities to aid diagnosis and management of emergencies, including identification of reversible factors in CA.[4] However, there is a risk of delaying or increasing pauses in chest compressions. In adult CA, echocardiography is also used for prognostication of poor outcome when cardiac standstill is detected.[5] Although the use of focused echocardiography during CA is growing in the paediatric population and its use has been suggested by several international groups and guidelines, high certainty of evidence is lacking.[6–9]

$EtCO_2$ or capnography measures the clearance of CO_2 during exhalation and is therefore recommended to confirm endotracheal tube placement. In addition, it may provide an estimate of chest compression effectiveness and indirectly of cardiac output, pulmonary blood flow, and coronary perfusion pressure.[10] A rapid increase in $EtCO_2$ may be associated with ROSC, and sustained decline or persistently low values may be associated with the absence of ROSC.[11] In adult CA, $EtCO_2$ values of $\geq$10 mmHg post intubation or $\geq$20 mmHg after 20 min of CPR may be predictive of ROSC or survival to discharge.[12] However, there is insufficient evidence in paediatrics of a target $EtCO_2$ to guide resuscitation efforts.[13]

Arterial BP drives coronary and brain perfusion and therefore certain levels of systolic, diastolic or mean BP might be associated with improved outcome.[14] However, it is unknown if CPR with an individualized BP-goal directed protocol rather than the standard one-size-fits-all protocol could change outcome. Given the need for invasive monitoring, this intervention is presently limited to the in-hospital cardiac arrest (IHCA) subpopulation in an intensive care environment. At present there are no recommendations for target BP during adult or paediatric CA.[12,13]

NIRS is a non-invasive way of estimating regional cerebral oxygen saturations ($rcSO_2$) and can be detected in cardiac arrest state when flow is absent. It could therefore give an indication of the quality of CPR by giving feedback on the cerebral oxygenation achieved during CPR.[15,16] Although it has been used in paediatric and adult CA, a target range has not yet been validated.

In this scoping review, we evaluate evidence on the individual and combined use of focused echocardiography, $EtCO_2$, arterial BP monitoring and NIRS during paediatric cardiac arrest and their ability to guide resuscitation efforts and predict ROSC, survival, or neurological outcomes. This was initiated by the Paediatric Task Force of the International Liaison Committee on Resuscitation (ILCOR) as different methods of measuring intra-arrest variables are becoming more widely used in clinical practise. The literature was last reviewed in 2010 for echocardiography and 2015 for $EtCO_2$ and arterial BP with only animal studies and one small human study. This review was conducted as part of the continuous evidence update initiated by ILCOR to regularly review, and where needed update, the resuscitation guidelines and map out knowledge gaps for further research which are published in the international consensus on CPR and emergency cardiovascular care science with treatment recommendations (CoSTR).[17]

Methods

As part of the continuous evidence evaluation process, several different task forces review the available evidence by scoping reviews which are all subjected to a strict methodology. The Paediatric Task Force prioritised the most commonly used monitoring modalities during paediatric cardiac arrest, and selected focused echocardiography, $EtCO_2$, BP and NIRS for review.The methods for this scoping review were based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for scoping reviews,[18] which was overseen by members of the ILCOR scientific advisory committee. For all four monitoring variables we performed a separate search strategy.

Eligibility criteria

Any studies describing infants and children with IHCA or OHCA where intra-arrest variables that can provide physiologic feedback to guide resuscitation were measured to evaluate quality of CPR, predict ROSC, survival, or changes in functional outcome at discharge were included. The following intra-arrest variables were studied: focused echocardiography, $EtCO_2$, arterial BP monitoring and NIRS. All randomized controlled trials (RCTs) and non-randomized studies directly concerning the population and intervention described above were eligible for inclusion. As we anticipated that there would be insufficient studies from which to draw a conclusion, case series with 3 or more cases were included in the initial search; however, unpublished studies were excluded. Furthermore, we excluded all neonatal CA in the delivery room, animal studies, simulation or manikin studies, any pre- or post-arrest features or parameters and any studies evaluating the advanced life support interventions themselves (e.g. ventilation strategies, fluids, firm surface, medications given, extracorporeal CPR). Adults over 18 years old were excluded due to anatomical and physiological differences, in addition to differences in aetiology of cardiac arrest and underlying comorbidities. This makes it difficult to accurately extrapolate adult data to children. All languages were included if an English abstract was available. We searched articles from 2010 for echocardiography and articles from 2015 for $EtCO_2$ and arterial BP as those were the years the CoSTR was last reviewed. For NIRS all years were included as this was not previously reviewed.

Data information sources

PubMed, Medline, CINAHL and Embase databases were searched for all search strategies. The latest searches for each of the intra-arrest variables were performed on 11 September 2020.

Search strategy

The search strategies were performed by 3 of the authors (DA, PVV and MK). Additionally, the Paediatric Life Support ILCOR taskforce was part of the search identifying any ongoing or unpublished research across the world. We combined the following terms using Boolean operators: life support care, cardiopulmonary resuscitation, ROSC, heart arrest, cardiac arrest using both individual (ti,ab,kw) and related medical subject headings, as well as exploded terms within Embase and CINAHL. The following specific search strategies were added depending on the intra-arrest variable:

Echocardiography: Point-of-care systems; echocardiography; transesophageal; transoesophageal echocardiography, transthoracic; diagnostic imaging; echocardiography.

$EtCO_2$: end-tidal carbon dioxide; carbon dioxide end-tidal; end-tidal pCO2; $EtCO_2$; capnography.

BP: Blood pressure; diastolic; systolic; (mean) arterial pressure; coronary perfusion pressure; hemodynamic-directed; haemodynamic-directed.

NIRS: near-infrared spectroscopy; cerebral oximetry; regional cerebral oxygenation; regional cerebral oxygen saturation.

Details of full search strategies for each variable are included in the appendix A1.

Selection of sources of evidence

The titles and abstracts were independently screened by two reviewers, using Rayyan.qrci.org, who were blinded for each other's decisions until all titles were screened. For the subsequent screening by title, we excluded those studies that clearly did not have the intra-arrest variable as study focus, were not focused on values during

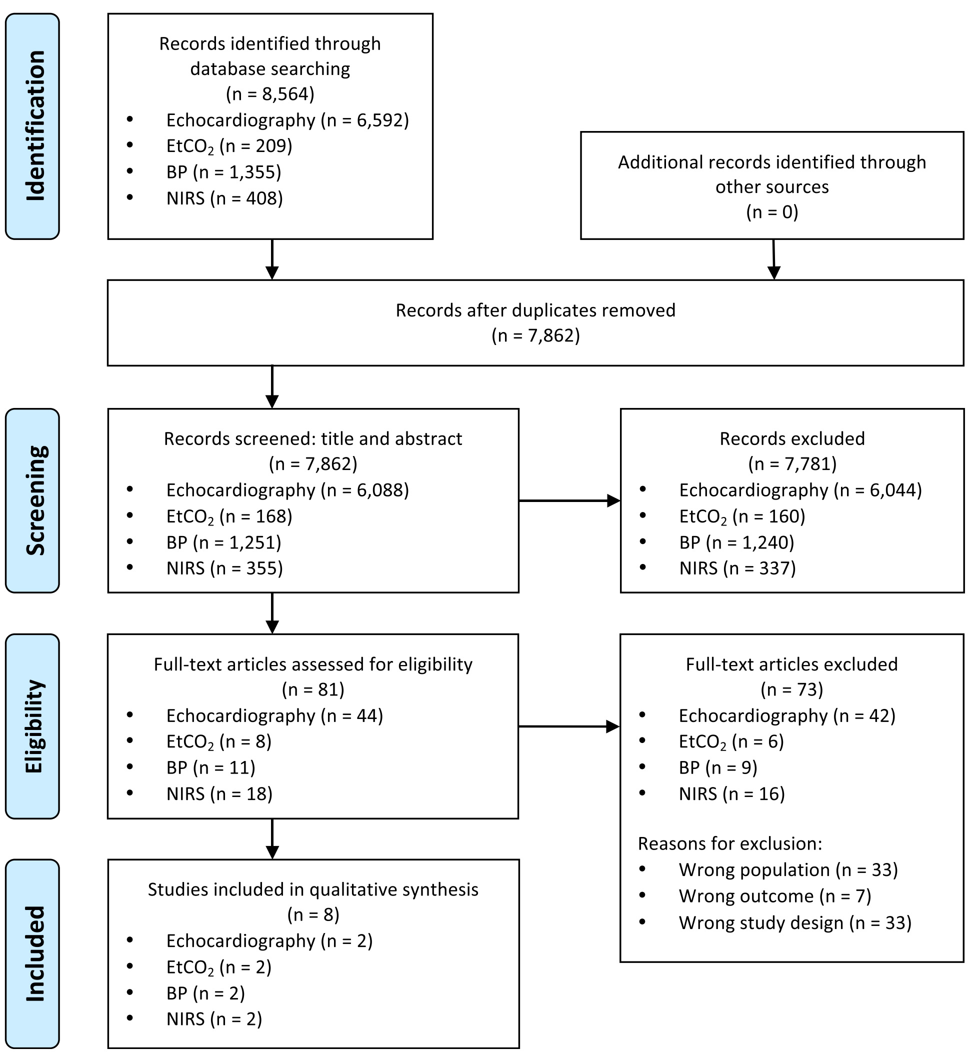

Fig. 1 – PRISMA diagram of echocardiography, $EtCO_2$, BP and NIRS during paediatric cardiac arrest.[19] $EtCO_2$ = End-tidal carbon dioxide, BP = Blood pressure, NIRS = Near-infrared spectroscopy.

cardiac arrest or obviously had one of the other pre-defined exclusion criteria. Consensus was reached for all inclusions and exclusions after discussions between the two reviewers.

Data extraction and charting process

Three authors (DA, PVV and MK) extracted data on different intra-arrest variables. This was then reviewed by co-authors (DA, PVV, BS). For echocardiography, we evaluated the literature specifically for diagnostic and prognostic abilities as well as the feasibility of reliably obtaining the measurements during CA. For all the other intra-arrest variables we evaluated the ability to assess CPR quality and predict any outcomes. In addition, for each of the intra-arrest variables the following data were collected as per ILCOR guidance: author and year of publication, study design and country, population, intervention and comparator, results of primary end points and summary of findings.

As per PRISMA guidelines for scoping reviews, we did not undertake a formal risk assessment of bias.[18]

Results

Our searches identified a total of 7862 articles after eliminating duplicates. Fig. 1 shows a full breakdown of the numbers in each stage as per PRISMA statement.[18,19] After full text review of 81 articles, 73 were excluded as the studies described the wrong population (n=33), the wrong outcome (n=7) or used the wrong study design (n=33). The remainder 8 studies were all observational, with four case series and four cohort studies, including a total of 288 children (Table 1).

Most studies were performed in the USA (n=7),[20–26] with one study taking place in Turkey.[27] The location of CA was mainly in-hospital (n=6),[20–25] where most arrests occurred within intensive care. Cardiac and respiratory disease were the most common causes of CA in the majority of studies, although two studies focused on patients with selected predispositions: high risk pulmonary emboli (PE) and cerebrospinal fluid (CSF) shunt obstruction.[21,26] The ages at arrest were variable with some studies describing mainly infants (n=4),[22–25] teenagers (n=1)[21] or a wider range of ages between birth and 18 years of age (n =3).[20,26,27]

Echocardiography

Only two paediatric case series were identified with a total of 8 patients and described patients during IHCA.[20,21] In the first study, bedside echocardiography was performed by intensive care physicians during CPR in teenagers at high risk of PE. Diagnosis of PE was suspected due to a large gradient between arterial carbon dioxide and $EtCO_2$, pulseless electrical activity during CA and echocardiographic findings of right ventricle (RV) dilatation and dysfunction. All patients were treated with thrombolysis and 80% survived to hospital discharge. One out of five was known to have PE prior to CA. PE accounted for 25% of all prolonged in hospital resuscitations of adolescents (12–17 years old).[21] The other case series reported on 3 patients in CA where focused echocardiography of subcostal views showed cardiac standstill during the 10s pulse check. However, with the use of extracorporeal membrane oxygenation (ECMO), contractility was regained. The study recognised that cardiac standstill during resuscitation may not indicate complete lack of resuscitation success.[20]

$EtCO_2$

Two observational studies from the USA where $EtCO_2$ was monitored during IHCA were included in analysis.[22,23] Berg et al. found no association between any mean $EtCO_2$ (as such or per CPR minute epoch) and any outcome. From the three patients with $EtCO_2$ below 10 mmHg during each minute of CPR, there was one survivor. There was a relationship of $EtCO_2$ with ventilation rate in that the mean $EtCO_2$ decreased 3.6 mmHg (95% confidence interval (CI): 1.3–6.0) for every 10 per minute increase in ventilation. There was no correlation of $EtCO_2$ with diastolic BP targets, which drives coronary perfusion.[22] Stine et al. reviewed $EtCO_2$ measurements to predict return of heart rate over 60 beats per minute in infants <6 months of age. $EtCO_2$ values between 17 and 18 mmHg corresponded to the highest sensitivity and specificity, with area under the curve of 0.835 ($p < 0.001$).[23]

BP

We identified two observational studies where diastolic BP was monitored during CPR, however, both studies were from the same research group using data with an overlapping study population.[24,25] Children admitted to paediatric intensive care and paediatric cardiac intensive care units, with invasive arterial BP monitoring prior to CA were included. More than 50% of this group was post cardiac surgery. Berg et al. found a significant association between the mean diastolic BP during the first 10 min (or less) of CPR and survival to hospital discharge and neurological outcome.[25] Wolfe et al. only studied a cohort of survivors, and did not find any association between any BP and new substantive morbidity.[24] Berg et al. were able to define optimal thresholds on the receiver operating characteristic (ROC) curve. The optimal thresholds without covariable consideration were 27 mmHg (infants) and 34 mmHg (children). These correlated with predicted survival rates of 63% (95%CI: 35%–84%) in infants and 67% (95%CI: 48%–82%) in children. A marked decrease in survival rates was shown in cubic spline analyses with thresholds below 20 mmHg (infants) and 25 mmHg (children). The lowest mean diastolic BP with survival to discharge was reported at 16 mmHg in infants and 18 mmHg in children.

NIRS

For NIRS we included one case series and one cohort study.[26,27] Abramo et al. published a case series of 14 patients with CSF shunts and raised intracranial pressure presenting in CA. They described NIRS values reflecting changes in observations e.g. $EtCO_2$, cerebral blood volume index.[26] The cohort study by Çağlar et al. of 10 OHCA patients, suggested minimum $rcSO_2$ were lower in the population who did not achieve ROSC.[27]

Discussion

Eight observational studies were included in this scoping review series. None of the studies specifically evaluated CPR quality, however, all reported the rate of ROSC and most studies also reported survival (n=7). Owing to the small sample sizes only the two studies on BP monitoring, although both covering essentially the same population, could comment on functional neurological outcomes.[24,25]

Table 1 – Summary of paediatric studies on each of the intra-arrest variables during CPR.

Author, year	Design, Country / Population	Intervention/Comparator	Results primary end points	Summary of findings
1. Echocardiography				
Author, year	**Design, Country**	**Intervention/Comparator**	**Results primary end points**	**Summary of findings**
Steffen, 2017[20]	Retrospective case series, single centre, USA **Population** Children <18 years old with IHCA (NICU, PICU and ED), year of admission not specified.(n=3)	Subcostal 4-chamber images obtained to assess for reversible causes of cardiac arrest.	Cardiac standstill noted in all 3 patients, all with ECPR. Cardiac contractility regained on ECMO.	Cardiac standstill during CPR may not indicate complete lack of resuscitation success.
Morgan, 2018[21]	Retrospective case series, single centre, USA **Population** Patients <18 years of age with IHCA due to PE, from 2013 to 2017. (n=5)	Bedside echocardiography during CPR in patients at high risk for PE.	PE suspected due to RV dilatation and systolic dysfunction, all associated with low $EtCO_2$. Embolus not directly seen on echocardiographic images.	Able to diagnose PE in high risk patients.
2. End-tidal carbon dioxide				
Author, year	**Design, Country**	**Intervention/Comparator**	**Results primary end points**	**Summary of findings**
Berg 2018[22]	Prospective multicentre observational study, USA **Population** Children >37 weeks gestation with IHCA requiring CPR > 1 min with $EtCO_2$ monitoring, from 2013 to 2016. (n=43 with 48 CPR events)	Association between mean $EtCO_2$>20 and any outcome. Comparison between survivors vs. non survivors.	No association was found between any mean $EtCO_2$ and ROSC, survival, and favourable neurological outcomes.	$EtCO_2$ decreased 3.6 mmHg for every 10/min increase in ventilation rate, no correlation with BP. No association between mean $EtCO_2$ and any outcome.
Stine 2019[23]	Retrospective single centre observational study; USA **Population** IHCA (PICU or PCICU) in infants ≤6 months old with $EtCO_2$ monitoring, from 2008 to 2012. (n=49)	$EtCO_2$ monitoring to predict heart rate >60. Comparison between patients with established vs. no established ROSC.	The highest positive predictive values (0.885) were seen for $EtCO_2$ between 17 and 18 mmHg.	$EtCO_2$ values of 17–18 predictive of heart rate >60.
3. Arterial blood pressure monitoring				
Author, year	**Design, Country**	**Intervention/Comparator**	**Results primary end points**	**Summary of findings**
Berg 2018[25]	Prospective multicentre observational study, USA **Population** Children >37 weeks gestation with IHCA (PICU or PCICU) requiring CPR > 1 min with invasive BP monitoring, from 2013 to 2016.(n=164)	Mean diastolic pressure, comparison was made between survivors vs. non survivors.	Maintenance of mean diastolic BP was significantly associated with increased survival (adjusted RR: 1.7, 95%CI: 1.2–2.6, $p = 0.007$) and favourable neurological outcome (adjusted RR: 1.6, 95%CI: 1.1–2.5, $p=0.02$).	Mean diastolic BP ≥ 25 mmHg in infants and ≥30 mmHg in children was associated with increased survival.

(continued on next page)

Wolfe 2019[24]	Prospective multicentre observational study, USA **Population** As above. Describing surviving population from Berg et al.[25] (n=77)	Mean diastolic and systolic BP comparison was made between patients with or without new substantive morbidity.	New substantive morbidity not related to either diastolic or systolic BP during CPR, only with baseline functional state scale.	No association between any BP and neurological outcome.
4. Near-infrared spectroscopy				
Author, year	**Design, Country**	**Intervention/Comparator**	**Results primary end points**	**Summary of findings**
Abramo, 2014[26]	Case series, single centre, USA **Population** CSF shunt patients in ED, requiring CPR, with $rcSO_2$ and BVI monitoring, from 2007 to 2013. (n=14)	NIRS monitoring compared with $EtCO_2$ and cerebral BVI.	All patients survived after surgical shunt revision and returned to their neurological baseline on discharge. Rise in rcSO2 and BVI was detected immediately after drainage of shunt with subsequent ROSC.	NIRS values reflected changes in observations ($EtCO_2$, BVI, ICP reduction).
Çağlar, 2017[27]	Prospective cohort study, single centre, Turkey **Population** Children <18 years old with OHCA, admitted to ED from 2014 to 2016. (n=10)	NIRS monitoring compared with pulse oximetry, ECG and $EtCO_2$.	Minimum $rcSO_2$ values during CPR were significantly higher in ROSC patient group (mean ± SD: 30.0 ± 1.0 in ROSC vs. 20.7 ± 5.7 in non ROSC population, p=0.02).	Minimum $rcSO_2$ lower in non ROSC patients.

CPR = cardiopulmonary resuscitation, USA = United States of America, IHCA = in-hospital cardiac arrest, NICU = neonatal intensive care unit, PICU = paediatric intensive care unit, ED = emergency department, ECPR = extracorporeal cardiopulmonary resuscitation, ECMO = extracorporeal membrane oxygenation, PE = pulmonary embolism, RV = right ventricle, $EtCO_2$ = end-tidal carbon dioxide, ROSC = return of spontaneous circulation, BP = blood pressure, PCICU = paediatric cardiac intensive care unit, RR = relative risk, CI = confidence interval, CSF = cerebrospinal fluid, $rcSO_2$ = regional cerebral tissue oxygen saturation, BVI = blood volume index, NIRS = Near-infrared spectroscopy, ICP = Intracranial pressure, OHCA = out-of-hospital cardiac arrest, ECG = electrocardiogram, SD = standard deviation.

Echocardiography during paediatric CA was last reviewed in the 2010 ILCOR paediatric advanced life support CoSTR which stated a potential use for echocardiography, if experienced health care providers were available, emphasizing minimal interruptions in high quality chest compressions.[9] In 2015, ILCOR evaluated the use of both $EtCO_2$ and arterial BP but was unable to make recommendations owing to limited studies of very low certainty of evidence, as only animal studies were available. It emphasised that maintaining high quality CPR is more important than securing invasive access to monitor arterial BP, however, where this was already in place at the time of resuscitation it could be used for targeting BP during CPR.[14] NIRS was not previously mentioned as an independent intra-arrest variable in any of the previous ILCOR recommendations.

Echocardiographic diagnosis of PE and cardiac tamponade are well documented in adult CA.[5,28] The diagnosis and treatment of PE in adolescents during CA was described in only one paediatric study. The study highlighted PE as an important differential diagnosis in the adolescent population with prolonged in-hospital resuscitation.[21] Several large adult studies have reported mortality rates of 94–100%, in patients with OHCA where cardiac standstill was demonstrated.[29–31] Nevertheless, the one published paediatric report of complete standstill revealed that cardiac contractility can be regained with the use of ECMO and is therefore not an absolute indicator of futility.[20]

Multiple adult CA studies demonstrate that both in-hospital and pre-hospital providers can adequately and quickly obtain images from which clinical decisions can be made, although there is concern about delay or longer pauses in chest compressions which will have deleterious effects on outcomes.[32–34] Different adult studies demonstrated that pauses in CPR increased from a median of 11 s to a median 17 s when echocardiography was used, although these pauses were shortened once a protocol was implemented.[35,36]

However, acquiring reliable images in children may be more difficult in children for several reasons. Firstly, the size of the chest is notably smaller, especially when defibrillator pads are attached. Additionally, the presence of abnormal cardiac anatomy with baseline abnormalities in ventricular size may compound difficulties in interpretation.[37] For example: diagnostic features of PE on echocardiogram are dilated RV with associated poor function, which may be a baseline finding in children with congenital heart disease. Finally, there is significant cost associated with purchase of equipment and training of users. This may limit its use, especially in limited resource settings.

A limitation to the use of $EtCO_2$ during CA is the requirement of an advanced airway. In children, as in adults, the desirable effects of placing an advanced airway during CPR needs to be balanced by the potential undesirable effects, as recent evidence has shown that intubation is not superior to bag valve mask ventilation and may even be harmful, particularly in OHCA.[38] Both identified paediatric studies only focused on patients in the intensive care unit, many of whom are already intubated before arrest. $EtCO_2$ is thought to relate to cardiac output and perfusion, however, it was not associated with diastolic BP or with any pre-defined outcomes in the Berg et al. study.[22] This might be because $EtCO_2$ is also affected by minute volume and ventilation perfusion matching. It is important to recognise that the study by Berg et al. was only descriptive and did not evaluate the outcomes associated with $EtCO_2$-directed CPR. As part of the ILCOR 2015 evidence evaluation process a systematic review (and meta-analysis) of the use of $EtCO_2$ in adult cardiac arrest was performed, showing only limited evidence (of at most low certainty) to suggest a relation of $EtCO_2$ above 10 mmHg and 20 mmHg respectively increased likelihood for ROSC.[11] Values of $EtCO_2$ below 10 mmHg after 20 min of CPR had a 0.5% likelihood of ROSC. Similar associations have been published in observational studies since then, however, cut off ranges varied considerably between the studies.[39–42] A few small paediatric animal studies suggested $EtCO_2$ directed CPR was superior to video/verbal feedback, although compression rates largely exceeded current guidelines to achieve $EtCO_2$ goals.[43,44]

Adequate myocardial and brain tissue perfusion is fundamental to outcome and (diastolic) BP could be useful as a clinically measurable surrogate for this. The identified evidence reports a possible relation between diastolic BP and patient outcome.[25] Only IHCA events were studied because of the need for invasive BP monitoring. Although Berg et al. were able to identify optimal ROC curve thresholds regarding test performance and identified thresholds below which no child survived, the evidence is too limited to consider diastolic BP in itself sufficient to identify CPR futility. A limitation to these studies is that both described overlapping populations although with different outcomes. A large prospective adult study (n=9096) showed that patient with monitoring in place (either EtCO2 or diastolic BP) had higher rates of ROSC (odds ratio (OR) 1.22, 95%CI: 1.04−1.43), although this did not translate in higher survival rates on discharge (OR 1.04, 95%CI: 0.91−1.18).[39] The study did not specifically look at diastolic BP and even for those with an arterial line in place, only about 1/3 reported using the diastolic BP to guide their CPR efforts. Importantly, most of the data in this register was collected before 2010. A systematic review in animal studies showed significantly superior outcomes in animals receiving haemodynamic directed feedback during resuscitation, but given the limited sample sizes and no human studies could be included, the authors did not feel the evidence to be sufficient to draw any conclusions.[45] This identified trend was also confirmed in more recent paediatric animal studies (mostly from the same research group).[46–50]

The potential value of truly personalised haemodynamic-directed CPR, where CPR efforts are adjusted in view of pre-defined (diastolic) BP goals and not limited by current 'standard' guidelines, has yet to be defined. Animal studies suggest a positive impact on outcome of such an approach but can only be seen as exploratory and hypothesis-generating.

There is limited paediatric evidence available for the use of NIRS during cardiac arrest. Many different NIRS devices were used throughout the studies which complicates comparisons as the saturation indices are not interchangeable.[16] At present, there is no consensus on a cut off threshold of $rcSO_2$ that can be used as an indicator to terminate CPR, or a single $rcSO_2$ value that can be used as a target during CPR or to continue CPR.

Two recent systematic reviews on NIRS monitoring during adult CA showed that a higher $rcSO_2$ is associated with a higher chance of ROSC and survival, whereas a lower $rcSO_2$ is linked with an increased mortality.[51,52] However, there seems to be no consensus on specific thresholds of $rcSO_2$ at which a prediction can be made regarding outcomes such as ROSC, survival or neurologic outcome.[51] Furthermore, there was a wide overlap of mean or median $rcSO_2$ values between patients with ROSC and patients where ROSC was not achieved. This was also reflected in subsequently published adult cohort studies.[53–56] However, an increasing trend in $rcSO_2$ seems more reliable as a predicting factor for ROSC, with suggested increase of at least 7−15% from baseline.[51,57,58]

There is inadequate data in the literature about the use of echocardiography, $EtCO_2$, arterial BP or NIRS monitoring during paediatric CA and their prognostic and diagnostic value. There is a significant difference in aetiology, pathophysiology and anatomy between children and adults, which may impact the usefulness and accuracy of these monitoring or diagnostic tools during CA, and extrapolations from adult literature should be done with caution. This scoping review series has not identified sufficient new evidence to prompt either a new systematic review for the use of these intra-arrest variables to predict outcomes or reconsideration of current resuscitation guidelines or treatment recommendations. Due to a disconnect between the amount of published literature and use of these monitoring variables in clinical practise, we recommend the use of international collaborations, such as PediRES-Q, for larger observational studies or RCT's to evaluate these modalities.

Strengths and limitations

This scoping review contributes to mapping the literature around the monitoring of echocardiography, $EtCO_2$, arterial BP and NIRS in resuscitation of children. A strength of this study is the comprehensive search strategy by multiple reviewers. A major limitation to this scoping review is the scarcity of evidence available. There were only few observational studies with small sample sizes. Furthermore, the populations studied were often highly preselected, e.g. children with high risk of thrombosis, cardiac arrests in intensive care only, or children with an advanced airway, arterial line or CSF shunt in place. Both studies on arterial BP monitoring described an overlapping population, further limiting the quality of evidence. However, as each of the studies described distinct outcomes which were deemed relevant, they were both included in our analysis.

A possible limitation to the methods is that our searches were limited to 2010 or 2015 for three of the variables. Although it is unlikely studies were missed, a more extensive systematic review may identify grey literature. Finally, we recognise there may be other monitoring modalities, such as transcranial doppler, that we have not evaluated in this scoping review but may be of use in paediatric resuscitation.

Conclusion

There is insufficient evidence to support the use of echocardiography, $EtCO_2$, arterial BP and NIRS monitoring in children during cardiac arrest at present. Adult and animal data suggest possible benefit and further research is needed.

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Conflicts of interest

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CRediT authorship contribution statement

Mirjam Kool: Writing - original draft. **Dianne Atkins:** Writing - original draft, Writing - review & editing. **Patrick Van de Voorde:** Writing - original draft, Writing - review & editing. **Ian Maconochie:** Writing - review & editing. **Barney Scholefield:** Supervision, Writing - review & editing. **PLS ILCOR Task Force:** Writing - review & editing.

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Appendix A. Search strategies

1. Echocardiography - Last updated 11 September 2020

1.1 PubMed

1 Echocardiography, Transesophageal"[Mesh] OR "Echocardiography"[Mesh] 136,373
2 Point-of-Care Systems"[Mesh] OR "Diagnostic Imaging"[Mesh] 2,658,482
3 echocardiography, transthoracic OR point of care ultrasound OR POCUS 189,883
4 1 or 2 or 3 (2,695,587)
5 "Life Support Care"[Mesh] (8835)
6 "Cardiopulmonary Resuscitation"[Mesh] (18226)
7 "Heart Arrest"[Mesh] (48239)
8 ((((life support) OR cardiopulmonary resuscitation) OR ROSC) OR return of spontaneous circulation) OR cardiac arrest (834771)
9 5 or 6 or 7 or 8 (834771)
10 (("Infant"[Mesh]) OR "Adolescent"[Mesh]) OR "Child"[Mesh] (3570670)
11 (infan* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab]) (4,970,579)
12 9 or 10 (4,970,579)
13 (animals [mh]) NOT humans [mh] (4,733,545)
14 (newborn* OR new-born* OR perinat* OR neonat* OR prematur* OR preterm*) (1,044,074)
15 4 and 9 and 12 not 13 not 14 (6,477)
16 Limit to studies from 2010 (4036)

1.2 MEDLINE

1 (MH "Echocardiography+") OR (MH "Echocardiography, Transesophageal") OR (MH "Point-of-Care Systems+") (149,226)
2 echocardiography, transthoracic OR point of care ultrasound OR POCUS or diagnostic imaging (3904)
3 1 or 2 (149,286)
4 (MH "Cardiopulmonary Resuscitation+") OR (MH "Heart Arrest+") (55395)
5 (MH "Life Support Care+") (8,789)
6 life support OR cardiopulmonary resuscitation OR ROSC OR return of spontaneous circulation OR cardiac arrest (71,094)
7 4 or 5 or 6 (88,836)
8 (MM "Adolescent") OR (MM "Infant+") OR (MM "Child+") ((69,673)
9 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school* (8,201,853)
10 8 or 9 (8,201,853)
11 3 and 7 and 10 (674)
12 Limit 11 to humans and year from 2010 (390)

1.3 CINAHL

1 (MH "Echocardiography+") OR (MM "Echocardiography, Transesophageal") (41,583)
2 Point-of-Care Systems or echocardiography, transthoracic OR point of care ultrasound OR POCUS or diagnostic imaging (50,589)
3 3.1 or 2 (81,758)
4 (MH "Life Support Care+") OR (MH "Resuscitation, Cardiopulmonary+") OR (MH "Heart Arrest+") (31,466)
5 life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest (31,777)

6 4 or 5 (31,466)
7 (MH "Child+") OR (MH "Child, Preschool") OR (MH "Adolescence +") OR (MH "Infant+") (968,527)
8 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*) (1,345,545)
9 7 or 8 (1,178,752)
10 3 and 6 and 9 (142)
11 Limit 10 to from 2010 (97)

1.4 Embase

1 exp transesophageal echocardiography/ or exp transthoracic echocardiography/ or exp echocardiography/ (345378)
2 (Point-of-Care Systems or echocardiography, transthoracic or point of care ultrasound or POCUS or diagnostic imaging).mp (200616)
3 1 or 2 (536394)
4 exp resuscitation/ (111222)
5 exp heart arrest/ or exp cardiopulmonary arrest/ or exp "out of hospital cardiac arrest"/ or exp sudden cardiac death/ (95175)
6 (life support care or life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest).mp (82355)
7 4 or 5 or 6 (194038)
8 exp child/ or boy/ or girl/ or infant/ or toddler/ (2627987)
9 exp adolescent/ (1526976)
10 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*).mp (4188146)
11 8 or 9 or 10 (4419827)
12 3 and 7 and 11 (2545)
13 Limit to humans and year 2010 (2064)

2. $EtCO_2$ - Last updated 11 September 2020
2.1 PubMed

1 Capnography [Mesh] (1370)
2 end tidal carbon dioxide OR carbon dioxide end tidal OR end tidal pCO2 OR EtCO2 (6939)
3 1 or 2 (7871)
4 "Life Support Care"[Mesh] (8835)
5 "Cardiopulmonary Resuscitation"[Mesh] (18226)
6 "Heart Arrest"[Mesh] (48239)
7 ((((life support) OR cardiopulmonary resuscitation) OR ROSC) OR return of spontaneous circulation) OR cardiac arrest (834771)
8 4 or 5 or 6 or 7 (834771)
9 (("Infant"[Mesh]) OR "Adolescent"[Mesh]) OR "Child"[Mesh] (3570670)
10 (infan* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab]) (4,970,579)
11 9 or 10 (4,970,579)
12 (animals [mh]) NOT humans [mh] (4,733,545)
13 (newborn* OR new-born* OR perinat* OR neonat* OR prematur* OR preterm*) (1,044,074)
14 3 and 8 and 11 not 12 not 13 (71)
15 Limit to studies from 2015 (25)

2.2 MEDLINE

1 (MM "Capnography") (836)
2 end tidal carbon dioxide OR carbon dioxide end tidal OR end tidal pCO2 OR EtCO2 (3904)
3 1 or 2 (4,541)
4 (MH "Cardiopulmonary Resuscitation+") OR (MH "Heart Arrest+") (55395)
5 (MH "Life Support Care+") (8,789)
6 life support OR cardiopulmonary resuscitation OR ROSC OR return of spontaneous circulation OR cardiac arrest (71,094)
7 4 or 5 or 6 (88,836)
8 (MM "Adolescent") OR (MM "Infant+") OR (MM "Child+") ((69,673)
9 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school* (8,201,853)
10 8 or 9 (8,201,853)
11 3 and 7 and 10 (128)
12 Limit 11 to humans and year from 2015 (32)

2.3 CINAHL

1 (MM "Capnography") (712)
2 end tidal carbon dioxide OR carbon dioxide end tidal OR end tidal pCO2 OR EtCO2 (1,149)
3 1 or 2 (1,719)
4 (MH "Life Support Care+") OR (MH "Resuscitation, Cardiopulmonary+") OR (MH "Heart Arrest+") (31,466)
5 life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest (31,777)
6 4 or 5 (31,466)
7 (MH "Child+") OR (MH "Child, Preschool") OR (MH "Adolescence +") OR (MH "Infant+") (968,527)
8 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*) (1,345,545)
9 7 or 8 (1,178,752)
10 3 and 6 and 9 (18)
11 Limit 10 to from 2015 (9)

2.4 Embase

1 exp Capnography / (3230)
2 (end tidal carbon dioxide OR carbon dioxide end tidal OR end tidal pCO2 OR EtCO2).mp (11113)

3 1 or 2 (13638)
4 exp resuscitation/ (111222)
5 exp heart arrest/ or exp cardiopulmonary arrest/ or exp "out of hospital cardiac arrest"/ or exp sudden cardiac death/ (95175)
6 (life support care or life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest).mp (82355)
7 4 or 5 or 6 (194038)
8 exp child/ or boy/ or girl/ or infant/ or toddler/ (2627987)
9 exp adolescent/ (1526976)
10 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*).mp (4188146)
11 8 or 9 or 10 (4419827)
12 3 and 7 and 11 (303)
13 Limit to humans and year 2015 (138)

3. BP - Last updated 11 September 2020

3.1 PubMed

1 Blood pressure [MESH] 99,310
2 Blood pressure, diastolic OR blood pressure, systolic OR mean arterial pressure OR arterial pressure OR coronary perfusion pressure OR hemodynamic directed OR haemodynamic directed 288,420
3 1 or 2 337,294
4 "Life Support Care"[Mesh] (8835)
5 "Cardiopulmonary Resuscitation"[Mesh] (18226)
6 "Heart Arrest"[Mesh] (48239)
7 ((((life support) OR cardiopulmonary resuscitation) OR ROSC) OR return of spontaneous circulation) OR cardiac arrest (834771)
8 4 or 5 or 6 or 7 (834771)
9 (("Infant"[Mesh]) OR "Adolescent"[Mesh]) OR "Child"[Mesh] (3570670)
10 (infan* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab]) (4,970,579)
11 9 or 10 (4,970,579)
12 (animals [mh]) NOT humans [mh] (4,733,545)
13 (newborn* OR new-born* OR perinat* OR neonat* OR prematur* OR preterm*) (1,044,074)
14 3 and 8 and 11 not 12 not 13 (71)
15 Limit to studies from 2015 (582)

3.2 MEDLINE

1 (MM "Blood Pressure+") OR (MM "Arterial Pressure") (87,985)
2 Blood pressure, diastolic OR blood pressure, systolic OR mean arterial pressure OR coronary perfusion pressure OR hemodynamic directed OR haemodynamic directed (37,989)
3 1 or 2 (118,036)
4 (MH "Cardiopulmonary Resuscitation+") OR (MH "Heart Arrest+") (55395)
5 (MH "Life Support Care+") (8,789)
6 life support OR cardiopulmonary resuscitation OR ROSC OR return of spontaneous circulation OR cardiac arrest (71,094)
7 4 or 5 or 6 (88,836)
8 (MM "Adolescent") OR (MM "Infant+") OR (MM "Child+") ((69,673)
9 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school* (8,201,853)
10 8 or 9 (8,201,853)
11 3 and 7 and 10 (371)
12 Limit 12 to humans and year from 2015 (58)

3.3 CINAHL

1 (MH "Blood Pressure+") OR (MH "Arterial Pressure+") (49,602)
2 Blood pressure, diastolic OR blood pressure, systolic OR mean arterial pressure OR coronary perfusion pressure OR hemodynamic directed OR haemodynamic directed (7203)
3 1 or 2 (49,603)
4 (MH "Life Support Care+") OR (MH "Resuscitation, Cardiopulmonary+") OR (MH "Heart Arrest+") (31,466)
5 life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest (31,777)
6 4 or 5 (31,466)
7 (MH "Child+") OR (MH "Child, Preschool") OR (MH "Adolescence +") OR (MH "Infant+") (968,527)
8 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*) (1,345,545)
9 7 or 8 (1,178,752)
10 3 and 6 and 9 (49)
11 Limit 10 to from 2015 (23)

3.4 Embase

1 exp blood pressure/ or exp mean arterial pressure(558197)
2 (Blood pressure, diastolic or blood pressure, systolic or coronary perfusion pressure or hemodynamic directed or haemodynamic directed).mp (5398)
3 1 or 2 (560001)
4 exp resuscitation/ (111222)
5 exp heart arrest/ or exp cardiopulmonary arrest/ or exp "out of hospital cardiac arrest"/ or exp sudden cardiac death/ (95175)
6 (life support care or life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest).mp (82355)
7 4 or 5 or 6 (194038)
8 exp child/ or boy/ or girl/ or infant/ or toddler/ (2627987)
9 exp adolescent/ (1526976)
10 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or

schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*).mp (4188146)
11 8 or 9 or 10 (4419827)
12 3 and 7 and 11 (1870)
13 Limit to humans and year 2015 (679)

4. NIRS - Last updated 11 September 2020

4.1 PubMed

1 Spectroscopy, Near-Infrared [Mesh] (13304)
2 ((cerebral oximetry) OR regional cerebral oxygenation) OR regional cerebral oxygen saturation (19218)
3 1 or 2 (31111)
4 "Life Support Care"[Mesh] (8835)
5 "Cardiopulmonary Resuscitation"[Mesh] (18226)
6 "Heart Arrest"[Mesh] (48239)
7 ((((life support) OR cardiopulmonary resuscitation) OR ROSC) OR return of spontaneous circulation) OR cardiac arrest (834771)
8 4 or 5 or 6 or 7 (834771)
9 (("Infant"[Mesh]) OR "Adolescent"[Mesh]) OR "Child"[Mesh] (3570670)
10 (infan* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab]) (4,970,579)
11 9 or 10 (4,970,579)
12 (animals [mh]) NOT humans [mh] (4,733,545)
13 (newborn* OR new-born* OR perinat* OR neonat* OR prematur* OR preterm*) (1,044,074)
14 3 and 8 and 11 not 12 not 13 (204)

4.2 MEDLINE

1 (MM "Spectroscopy, Near-Infrared") (6,936)
2 cerebral oximetry or regional cerebral oxygenation or regional cerebral oxygen saturation (1138)
3 1 or 2 (7886)
4 (MH "Cardiopulmonary Resuscitation+") OR (MH "Heart Arrest+") (55395)
5 (MH "Life Support Care+") (8,789)
6 life support OR cardiopulmonary resuscitation OR ROSC OR return of spontaneous circulation OR cardiac arrest (71,094)
7 4 or 5 or 6 (88,836)
8 (MM "Adolescent") OR (MM "Infant+") OR (MM "Child+") ((69,673)
9
(infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school* (8,201,853)
10 8 or 9 (8,201,853)
11 3 and 7 and 10 (65)
12 Limit 12 to humans (49)

4.3 CINAHL

1 (MM "Spectroscopy, Near-Infrared") (882)
2 cerebral oximetry or regional cerebral oxygenation or regional cerebral oxygen saturation (407)
3 1 or 2 (1,226)
4 (MH "Life Support Care+") OR (MH "Resuscitation, Cardiopulmonary+") OR (MH "Heart Arrest+") (31,466)
5 life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest (31,777)
6 4 or 5 (31,466)
7 (MH "Child+") OR (MH "Child, Preschool") OR (MH "Adolescence +") OR (MH "Infant+") (968,527)
8 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*) (1,345,545)
9 7 or 8 (1,178,752)
10 3 and 6 and 9 (6)

4.4 Embase

1 exp near infrared spectroscopy/ (22941)
2 (cerebral oximetry or regional cerebral oxygenation or regional cerebral oxygen saturation).mp (1791)
3 1 or 2 (23995)
4 exp resuscitation/ (111222)
5 exp heart arrest/ or exp cardiopulmonary arrest/ or exp "out of hospital cardiac arrest"/ or exp sudden cardiac death/ (95175)
6 (life support care or life support or cardiopulmonary resuscitation or ROSC or return of spontaneous circulation or cardiac arrest).mp (82355)
7 4 or 5 or 6 (194038)
8 exp child/ or boy/ or girl/ or infant/ or toddler/ (2627987)
9 exp adolescent/ (1526976)
10 (infan* or baby or baby* or babies or toddler* or minors or minors* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or juvenil* or youth* or teen* or under* age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school or school*).mp (4188146)
11 8 or 9 or 10 (4419827)
12 3 and 7 and 11 (184)
13 Limit to humans (146)

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