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New Methods of Monitoring Shock in Children

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Opinion statement

Shock in children is a cause of significant morbidity and mortality. Worldwide, most children dying from shock do not have the opportunity to benefit from advanced critical care support and we recommend to readers the World Health Organization ETAT guidelines [1]. For children treated in the intensive care environment, standard cardiovascular measures such as heart rate, pulse volume, perfusion/capillary refill, core-peripheral temperature gradient and blood pressure along with measures from other organ systems (e.g. urine output and consciousness level) remain vital. All are part of the global assessment of cardiovascular performance and shock in children, and none of the *new* techniques we describe replace the need for these assessments in critically ill children. Furthermore, evidence is lacking to mandate utilisation of any of the advanced methods we review and they should only be considered as adjuncts to the aforementioned assessments in critical care. We suggest that the optimal monitoring of the shocked child in the ICU, and those developing shock outside the ICU, should include measuring those hemodynamic parameters above together with assessment of preload responsiveness and organ perfusion. Early goal-directed therapy targeting shock reversal remains the consensus best practice position and includes optimization of several haemodynamic parameters [2]. Our personal practice remains to firstly target clearance of raised lactate and venous desaturation, measured by intermittent blood gas analysis and secondly to optimise preload, contractility and afterload guided by Doppler ultrasound or echocardiography. Both can be undertaken in both the emergency department as well as the ICU.

Introduction

Shock can be defined simply as failure to deliver oxygen to, and remove metabolites from, sites of cellular respiration. This leads to the development of an oxygen deficit and if untreated can lead to organ failure and death. Sepsis is a common cause of shock in children leading to alterations in vascular tone, cardiac

contractility and volume status. The American College of Critical Care Medicine (ACCM) consensus guidelines recommend time-sensitive rapid shock reversal as best practice [2].

Children in septic shock have been described as presenting with two distinct clinical pictures: high cardiac output with low systemic vascular resistance and low cardiac output with high systemic vascular resistance, so-called warm and cold shock, respectively [3]. Unlike the case in many adults with shock, these states are not fixed and children may move between them during treatment [4•]. Standard monitoring techniques such as heart rate, blood pressure and capillary refill time can fail to detect these shifts in hemodynamic status. They may also underestimate oxygen deficit and perform poorly as markers of circulatory failure [5]. Clinical examination alone is inaccurate [6], and the failure of standard monitoring techniques to differentiate between warm and cold shock can hinder optimisation of cellular perfusion.

An increasing number of novel measuring techniques are emerging into paediatric practice. Unfortunately, studies into cardiovascular monitors in children are almost entirely single-centre studies, with small numbers of patients (fewer than 50) and have often been conducted under steady-state conditions rather than during haemodynamic instability.

Measures of hemodynamics

Blood pressure (BP) is a product of cardiac output and systemic vascular resistance (SVR). Cardiac output (CO) = heart rate × stoke volume. Stoke volume depends on preload, contractility and afterload.

Unfortunately, trinomial equations cannot estimate variables in a dynamic state, ergo blood pressure monitoring alone cannot define adequate cardiac output (flow).

The American College of Critical Care Medicine (ACCM) advocates targeting cardiac index (CI = CO/body surface area) of 3.3–6.0 L/min/m^2 in children with catecholamine-resistant septic shock. In children, low CI rather than low SVR, particularly in septic shock, is associated with increased mortality [7].

Initial attempts to measure invasive hemodynamics in the critical care units of the 1970s focussed on use of the pulmonary artery catheter (PAC) [8] and exploitation of the Fick principle: total uptake or release of a substance (oxygen, carbon dioxide, dye or heat) is equal to blood flow (CO) to the organ and the arteriovenous concentration difference of the substrate [9]. This technique, and many others, is based upon the traditional catheter laboratory experiments and is the gold standard to which new hemodynamic monitors are compared [10]. However, PAC use in adults—let alone children—is controversial with safety concerns and limited availability of trained staff to place and manage PAC delaying data acquisition [11, 12]

Transpulmonary indicator dilution techniques

Transpulmonary indicator dilution (TPID) techniques involve injection of an indicator substance (heat or lithium) into a central venous line, and indicator concentration is measured at a large peripheral artery. The Stewart Hamilton equation describes calculation of an unknown volume (e.g. stroke volume) from a known mass of marker and its concentration over time (stroke volume (SV) = mass/concentration).

Concentration is the area under the curve (AUC) of a concentration/time graph with CO inversely proportional to the AUC. Two TPID techniques have been validated in children, thermodilution (PiCCO) [13–16] and lithium dilution (LiDCO) [17]. Avoiding pulmonary artery cannulation prevents complications such as line knotting in the tricuspid valve apparatus or pulmonary artery injury, but these newer techniques still require cannulation of a central vein and artery. Prolonged femoral artery cannulation with large calibre cannulae, although a common procedure in ICU, has significant risks [12]. Like PAC, TPID can only deliver intermittent hemodynamic estimations limiting its usefulness in situations of rapidly changing cardiovascular status. Both LiDCO and PiCCO overcome this limitation by incorporating a continuous measurement technique based upon arterial pulse pressure waveform analysis to estimate stroke volume.

Pulse pressure waveform analysis

In arteries, fluctuations in pressure around the MAP are a consequence of the volume of blood ejected into the artery during systole (SV). Pulse pressure is a function in magnitude of stroke volume [18]. Stroke volume estimations can therefore be made from pulse pressure wave (PPW) analysis—though we have expressed reservations ourselves about this technique [19].

Monitors that examine the PPW can be divided into those that analyse pulse contour morphology (PiCCO and LiDCO) and those that measure pulse power (LiDCO rapid and FloTrac) or pressure–time area's (pressure recording analytical method, PRAM). Measures of pulse contour calculate area under the systolic portion of the PPW and require regular calibration by another technique because arterial compliance and vascular resistance alter with pressure changes. Pulse power/pulse time measures such as LiDCO rapid, FloTrac and PRAM analyse both the systolic and diastolic portions of the PPW; they are not calibrated as the computational algorithms include compensation for arterial compliance changes with pressure. In adults, PPW analysis is a good surrogate for SV, but over time, changes in vascular tone reduces reliability [20]. An advantage for children of this technique is that PPW can be analysed from any in situ arterial line, reducing interventions. To date, studies to validate precision and accuracy of PPW monitors in children have been varied. PiCCO is validated for TPID but not pulse contour analysis [11, 21]. FloTrac failed to validate against PAC thermodilution [22]. PRAM failed to validate well against transpulmonary ultrasound dilution with the authors recommending that the current PRAM algorithm is not used in critically ill children [23]. The LiDCO algorithm has been validated in children, though the small study did not include those under 13 kg [24]. Understanding the limitations of these devices, summarised in Table 1, to give accurate data, PPW analysis can still be a useful guide of trends in CO.

Techniques to measure CO in children that rely upon insertion of invasive lines require skilled practitioners, and insertion can delay therapy. They have a place in ICU—especially if giving continuous readings, but utility is limited by cost, need for expertise, accuracy concerns and potential harm to patients. We suggest technologies that are easy to use and with good reproducibility that do not require specialist procedural skills are the future for paediatric goal-directed management of shock.

Table 1. Summary of limitations

	Pulse contour analysis	Pulse power analysis	Pressure time analysis
Market example	PiCCO	LiDCO rapid	PRAM
Arterial access	Specialised line, long length for central placement, large artery	Any arterial cannula in any artery	Any arterial cannula in any artery
Waveform accuracy	Need good arterial pressure trace with clear dicrotic notch	Any arterial waveform, even damped traces	Any arterial waveform, even damped traces
Calibrated	Yes	No	No
Validated PPW analysis in children	No	Partial	No

Partial carbon dioxide rebreathing indirect Fick

A non-invasive method of measuring CO exploiting the Fick principle, as described above, using carbon dioxide (CO_2) as the indicator has been developed. The partial pressure of end tidal CO_2 ($PETCO_2$) is measured at the tracheal tube. $PETCO_2$ during normal ventilation approximates the arterial content of CO_2 and $PETCO_2$ during a partial rebreathing exercise approximates mixed venous content of CO_2. The technique has been evaluated in children in a single small study, but only in children over the weight of 15 kg and those who are mechanically ventilated, limiting its use [25].

Doppler phenomenon

Exploitation of the Doppler phenomenon is an alternative method of CO monitoring that avoids cannulation of vessels and does not require intubation. Alterations in the frequency of transmitted sound waves as they are reflected from moving objects (e.g. blood cells) can be used to measure flow velocity across heart valves and vessels. These are no new techniques, but specific new devices have been investigated in children in recent years such as ultrasonic cardiac output monitor (USCOM) and cardioQP.

USCOM uses continuous-wave (CW) Doppler via a probe to produce velocity–time graphs of the high velocity flows across either the aortic or pulmonary valves. Estimations of valve diameter are made using an algorithm based on height, weight and gender [26] with hemodynamic data provided by automated calculations of velocity–time integral (distance travelled by a column of blood over a fixed time) to calculate stroke volume. Studies have suggested reliability for both physicians and non-physicians following a short training period with both good inter- and intra-user reliability [27, 28]. USCOM can be used in children outside ICU [29] permitting earlier hemodynamic information than traditionally available.

Comparing USCOM to PAC thermodilution demonstrated a 36 % mean error, falling outside acceptable criteria for device precision [30]. However, this methodology has itself been challenged and USCOM precision is comparable

to other non-invasive CO measurement techniques [17]. The precision of PAC itself is increasingly being questioned [31].

USCOM has been compared to echocardiography Doppler measures, 'estimated' (USCOM) and 'measured' left ventricular outflow tract diameters were not significantly different, but USCOM consistently 'overestimated' CO, particularly in children with septic shock [29]. It has been suggested this might be related to CW Doppler use which measures the highest velocity profile as opposed to pulsed-wave (PW) Doppler used in echocardiography where the user directs the Doppler beam [32]. Whilst some suggest limitations to achieving precise CO measurements with USCOM, multiple studies have used the technique to guide therapy in children suggesting USCOM can predict fluid responsiveness in shock [33] and track the evolution of sepsis in children managed in ICU [2, 34]. On-going USCOM studies are investigating potential cardiac inotropy measures but are not reported in children [35].

Oesophageal Doppler (CardioQP, Deltex) similarly directly measures flow, albeit in the descending aorta with a patient-specific inserted disposable probe. However, descending aorta pulsatility is of concern for accurate cross-section area calculation [36].

Transthoracic echocardiography

Transthoracic echocardiography (TTE) has appeal for monitoring hemodynamics in children with shock. Preload can be assessed using inferior vena cava diameter, discussed later, or by measuring end-diastolic left ventricular parameters. SV estimations can be made using PW Doppler directed across the left or right ventricular outflow tracts. More recently, dynamic global cardiac performance indices such as myocardial performance index have been developed. Transthoracic echocardiography traditionally required expert operators but recently 'targeted bedside echocardiography' by non-physicians has been suggested to be an effective technique for monitoring shock in children [37, 38].

Bioreactance

Several non-invasive techniques that require minimal training have recently been introduced into paediatric practice. Routine application of electrical velocimetry was compromised by electrical interference; however, bioreactance overcomes this by analysing phase shifts rather than signal change. A high-frequency (75 Hz) oscillating current is passed externally across the chest via four electrode stickers which also detect phase shifts in the current. Intra-aortic blood volume changes during the cardiac cycle are the primary source of phase shifts and can be analysed mathematically to estimate stroke volume. Comparison with PAC thermodilution, however, during cardiac catheterisation noted persistent over- and underestimation of cardiac output [39]. Comparing bioreactance estimation of CO to transthoracic echocardiogram in neonates with patent ductus arteriosus [40], paediatric cardiac patients [41] and paediatric neurosurgical patients [42], NICOM persistently underestimated SV. Studies in children have only been conducted in surgical patients, and comparison of bioreactance to thermodilution via PAC in critically ill adults with a variety of underlying pathologies also demonstrated poor correlation in values

[43]. In an animal model of paediatric haemorrhagic shock, again bioreactance consistently underestimated cardiac index [44].

Preload assessment

CO is a function of SV and HR but subject to changes in preload, cardiac contractility and afterload. Shock states in children whether due to diarrhoea and vomiting, sepsis or anaphylaxis often result in preload reduction, so preload optimisation is an important goal in managing paediatric shock.

Traditionally, PAC occlusion pressure and CVP are used to assess preload, but PAC use has declined in paediatric practice and static variables have shown limited utility in predicting fluid responsiveness in children [45]. TPID techniques to measure global end-diastolic volume have gained popularity in adults, but paediatric studies have demonstrated limited accuracy [36]. Alternative, non-invasive measures of preload assessment have been sought.

The inferior vena cava (IVC) is a highly compliant vessel, and variations in its size reflect changes in CVP and are easily assessed during transthoracic echocardiography or ultrasound [46]. Suggested measures include a collapsibility index, IVC diameter percent decrease with inspiration and the IVC to aortic diameter ratio (<0.8 suggested to be a measure of intravascular volume depletion). Whilst these measures have shown limited success diagnosing intravascular depletion in dehydrated children [47, 48] and recognising elevated CVP in children with cardiac disease [49], a single small study found these measures to be inaccurate when used to determine intravascular fluid status in critically ill children [50].

Perfusion and tissue oxygenation

Fundamentally, shock is the failure to deliver adequate oxygen to organs. This leads to increased extraction of oxygen from blood which reduces mixed venous oxygen saturations (SvO_2); therefore, SvO_2 is an indirect measure of oxygen delivery but requires sampling of blood from the pulmonary artery. In the absence of indwelling PACs, sampling of blood from the superior vena cava (central venous oxygen saturations, $ScvO_2$) has been shown to be a suitable surrogate [51]. Children are more likely to suffer from shock with low cardiac output than adults and to have lower ScvO2 [52]. Two recent studies of children with shock, albeit with relatively high background mortality, demonstrated that directing treatment to achieve a $ScvO_2$ greater than 70 % significantly reduced mortality, with a number needed to treat between 3.6 and 6 [53, 54]. Standard therapy was augmented in the intervention groups by a number of measures to improve shock, as quantified by venous desaturation, such as fluids, inotropes and transfusion. This parallels the landmark study by Rivers et al. recommending early goal-directed therapy in septic adults [55, 56, 57•].

Continuous measure of $ScvO_2$

PediaSat, a central venous catheter with in-line oximetry allowing continuous $ScvO_2$ measurement, has been developed to enable continuous targeting of venous desaturation in paediatric shock. Two studies in critically ill children

suggested that PediaSat accurately measured $ScvO_2$ [58, 59], but two separate studies in surgical patients [60, 61] failed to demonstrate accurate correlation with laboratory samples of $ScvO_2$. Like other devices discussed, PediaSat is an invasive monitor, reducing its early application in shocked children.

Near-infrared spectroscopy

Serum markers of globally poor perfusion such as lactate and base deficit are indirect and often late signs of poor organ perfusion in children who are in shock. Although lactate clearance has been shown to be a useful target for shock reversal therapies in adults and children. An alternative to non-specific global measures are methods of monitoring regional oxygenation.

Oxyhaemoglobin and deoxyhaemoglobin absorb light in the infrared region at different wavelengths. Passing infrared light through tissues and measuring relative absorptions permit estimation of haemoglobin saturation, known as regional saturation (rSO_2). This non-pulsatile signal is primarily a measure of capillary venous saturation, related but not equal to $ScvO_2$. Spatial resolution ensures that only deep tissue oxygenation is considered. Near-infrared spectroscopy (NIRS) is a continuous monitor of regional oxygenation. NIRS devices can monitor rSO_2 in cerebral, renal, mesentery and peripheral muscle circulations, as current devices have a field depth of 1–4 cm; multisite technology is most suitable in children under 10 kg.

Cerebral NIRS monitoring during and following cardiac surgery has been extensively discussed with some suggesting it ought to be a standard of care [62] though we cannot find outcome data to support widespread introduction in ICU. Multisite NIRS can theoretically measure regional and global organ perfusion in shock, but use is limited by the absence of a proven normal baseline rSO_2 and what might constitute a significant reduction. In addition, there are significant device and consumables costs. A reduction of 20 % from a suggested normal baseline rSO_2 of 70 % has been shown to predict risk of organ injury [63], but few studies have investigated the utility of multisite NIRS in shocked children. One small study suggests that average cerebral and renal rSO_2 of less than 65 % correlates with elevations in serum lactate—a marker of globally poor perfusion [64]. Whilst NIRS is non-invasive and does not require extensive specialist training, further studies are required before its use in any paediatric population.

Conclusion

Shock is a cause of significant mortality and morbidity in children, and early goal-directed therapy of shock states has been shown to improve outcomes with measures of hemodynamics, preload and tissue oxygenation successfully guiding therapy in paediatrics. Despite many years of development, no single measure of 'invasive hemodynamic performance' has been widely accepted in paediatric critical care practice. Whilst each technique has advantages and disadvantages, preference surely ought to be given to systems that can measure hemodynamics accurately, non-invasively, reproducibly and safely.

As early goal therapy with hemodynamic optimisation remains recommended treatment in paediatric shock, our personal practice remains targeting

of clearance of raised lactate and venous desaturation, measured by intermittent blood gas analysis, using optimisation of preload, contractility and afterload guided by Doppler ultrasound or echocardiography which can be undertaken in both the emergency department as well as the ICU.

Compliance with Ethics Guidelines

Conflict of Interest
Helen Turnham and Joe Brierley declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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The study demonstrated that type of shock (high CI with low SVR versus low CI with high SVR) optimising cellular perfusion requires monitoring of haemodynamics to titrate therapy

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