Measurement of cardiac output and tissue perfusion
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Recent technologic innovations have allowed a greater scope for cardiac output measurement in critically ill children. There is a move toward both less invasive and continuous methods, several of which also offer novel measures of preload. Many of the new methods are still undergoing preliminary evaluation in the pediatric population and will be summarized in this article. Curr Opin Pediatr 2002, 14:303–309 © 2002 Lippincott Williams & Wilkins, Inc.

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Abbreviations
CaO2 arterial oxygen content
CvO2 mixed venous oxygen content
DO2 tissue oxygen delivery
ICU intensive care unit
VO2 oxygen consumption

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Ensuring adequate tissue oxygen delivery (DO2) is a prerequisite for the maintenance of metabolic well-being, both in health and during critical illness. The components of DO2 include cardiac output, blood hemoglobin concentration, and degree of oxygen saturation of the hemoglobin molecule (ignoring the minimal contribution from dissolved oxygen in most clinical situations):

DO2 = cardiac output × (1.34 × hemoglobin concentration × oxygen saturation)

Critical illness often involves perturbation of DO2, and many of the common therapeutic interventions in the intensive care unit (ICU) (fluid administration, blood transfusion, inotropes, mechanical ventilation) augment this parameter. The hemoglobin-related components of DO2 are easily quantifiable by use of pulse oximetry, an arterial blood gas analyzer, and a Coulter counter; yet, DO2 is infrequently measured in pediatric practice. This is probably because of perceived difficulties, risks, and inaccuracies with the measurement of cardiac output in children. Over the past decade however, several technical innovations have allowed for a greater choice in the methods for cardiac output measurement, which are summarized in this review.

Why measure cardiac output?
It has yet to be convincingly shown that measurement of cardiac output improves patient outcome. Interestingly, the same can be said for many of the monitoring procedures that are “mandatory” for critically ill patients in a modern ICU, such as invasive arterial or central venous pressure measurement, blood gas analysis, and pulse oximetry. The perceived need to validate the prognostic aspect of cardiac output measurement over and above other parameters may stem from greater potential for misinterpretation of cardiac output data, resulting in inappropriate management strategies and thus harm to the patient. Interpretation of a low oxygen saturation provided by a pulse oximeter is relatively straightforward; correct acquisition followed by interpretation and assimilation of cardiac output, wedge pressure, pulmonary artery pressure, DO2, and systemic vascular resistance from a pulmonary artery catheter are not. Indeed, the pulmonary artery catheter has been the commonest method of measuring cardiac output in adults for nearly 30 years; yet, adequate knowledge of this modality is lacking among many ICU physicians [1,2], which may partly explain the poorer outcome associated with its use [3]. Understanding of the catheter and other aspects of measuring and interpreting cardiac output improves when
physicians are adequately trained, use it frequently, and supervise others [1,2]. This has prompted a suggestion that mandatory credentialing policies be in place before cardiac output measurement is taken [4].

Thus, any study attempting to answer prognostic aspects of cardiac output measurement must control for the accuracy of the technique used, require adequate training of clinicians taking part, and mandate careful consideration of the management decisions taken as a result of the cardiac output information acquired. The difficulty of orchestrating such a trial means it is unlikely to ever be performed.

Nonetheless, several studies have highlighted the utility of cardiac output measurement. Mimoz [5] studied 112 adult ICU patients and found improved outcome in a subgroup of shocked patients who had not responded to fluid and inotropes when cardiac output measurement prompted a change in therapy. In children with septic shock, a persistently low cardiac output carries a higher mortality [6,7]; in addition, the hemodynamic profile frequently changes over time, and cardiac output measurement commonly results in a change in therapy [7]. Mechanical ventilation, both conventional [8] and high-frequency oscillatory [9], can compromise cardiac output. In all these studies, poor cardiac output could not be predicted by the commonly measured hemodynamic parameters. Indeed, cardiac output cannot be estimated clinically in a reliable fashion in adults [5,10,11] or children [12]. The common thread in the above studies is that cardiac output measurement identifies low flow states and may allow for a more rational approach to the institution and monitoring of various therapies.

When to measure cardiac output?
The decision to measure cardiac output must be a balance between perceived risk and benefit to the patient. Thompson [13] has identified several areas where cardiac output measurement may be indicated: (1) congenital and acquired heart disease, (2) shock states, (3) multiple organ failure, (4) cardiopulmonary interactions during mechanical ventilation, and (5) clinical research that leads to a greater understanding of a disease process. We would add (6) assessment of selected new therapies (eg a novel inotrope) to this list.

It is important, however, that cardiac output and/or DO₂ not be treated as isolated variables or primary endpoints [14,15] but rather be used in conjunction with qualitative indicators of the adequacy of flow (eg blood lactate, central venous oxygen saturation, arteriovenous saturation difference, capillary refill, urine output), thus allowing adjustment to match the metabolic need of the individual patient [12].

How to measure cardiac output?
Over the past decade, there has been a gradual shift toward noninvasive (or less invasive) and continuous, rather than intermittent, methods of cardiac output measurement. As a general rule, noninvasive methods are easier to use, but they may suffer from a reduction in accuracy. However, a small calibration error is probably acceptable if the noninvasive method accurately follows changes in cardiac output, particularly when used in conjunction with indicators of adequacy of flow [16].

Invasive methods
Dilution techniques
Dilution techniques have existed for many years, evolving from principles developed by Stewart and Hamilton. Briefly, blood flow can be calculated after the central venous injection of an indicator by measuring the change in indicator concentration over time at a point downstream of the injection, provided a series of conditions are met. These include complete mixing of the indicator and blood, no loss of indicator between injection and measurement, no anatomic shunt, and minimal valve regurgitation. The earliest indicator used was dye [17]. Later, temperature [18] was followed by the introduction of the pulmonary artery catheter in the early 1970s.

Dye dilution Dye dilution, first described in 1932 by Hamilton et al. [17], may use a variety of indicators (indocyanine green, Evans blue, brilliant red). Dye is as accurate as the direct Fick method (see below) [19] and has the advantage of indicator measurement occurring in a peripheral artery rather than the pulmonary artery. Two main disadvantages exist: calibration of the densitometer used to measure indicator change can be time consuming, and the half-life of the dye used limits the frequency of measurements that can be performed over a given period. However, fiberoptic systems are now capable of dye analysis.

Pulmonary artery thermodilution This is the commonest clinical reference method against which new technologies are compared, and has been well described elsewhere [20,21]. Numerous sources of error exist [22,23], which can be reduced with meticulous attention to detail [24,25]. However, whether this happens in clinical practice remains to be seen [1,2]. An automated system to reduce human and methodologic error is attractive and has been recently evaluated in adults receiving mechanical ventilation [26]. The system uses an automated bolus injection over the whole respiratory cycle, with an algorithm to account for variations in baseline temperature.

Over the past decade, intermittent bolus thermodilution has been incorporated into a semicontinuous mode using a thermal filament [27]. Although commercially available devices perform comparatively in adults [28] with rea-
sonable accuracy at high and low flow states [29], they have yet to be evaluated in children.

Transpulmonary thermodilution Transpulmonary thermodilution differs from pulmonary artery thermodilution in that the thermistor is percutaneously placed in a large artery, usually the femoral or brachial artery. A commercially available system (COLD Z-021, Pulsion, Germany) uses a 1.3-French thermistor and can thus be sited in infants as small as 3 kg, via a 22G arterial cannula. The bolus injectate must be less than 10°C to account for the small and relatively constant indicator loss (heat gain) from passage through the lungs. This technique has been validated against pulmonary thermodilution and direct Fick [30,31]. The coefficient of variation is 4 to 6% [30,31], far less than the 10 to 20% seen with pulmonary artery thermodilution [23,25], probably because of the longer transit time allowing for variations in cardiac output caused by mechanical ventilation. We have used this technique in more than 200 infants and children and regard it as the closest to a clinical gold standard for pediatric cardiac output measurement.

Lithium dilution This novel indicator technique was first described in adults in 1993 [32]. The indicator sensor is attached to a preexisting peripheral arterial line and comprises a lithium-sensitive electrode encased in a disposable polycarbonate flow-through housing. After a central venous injection of lithium chloride, blood is pumped from the arterial line past the electrode, which converts the change in voltage to a change in lithium concentration using the Nernst equation, producing a typical indicator curve similar to dye. This technique is accurate in infants [33] and has the advantage of using preexisting monitoring lines. We have also found in infants that peripheral injection of lithium may produce reasonable curves, potentially negating the need for central venous access. The main limitations of this method are the need for blood sampling (≤3 ml) with each measurement and the need to avoid concomitant administration of medications containing electric charge (eg certain neuromuscular blocking agents).

Direct Fick

The Fick principle for flow measurement is now more than a century old. The equation states: cardiac output = VO\textsubscript{2} / (CaO\textsubscript{2} - CvO\textsubscript{2}). Where VO\textsubscript{2} is systemic oxygen consumption, and CaO\textsubscript{2} and CvO\textsubscript{2} represent oxygen contents in arterial and mixed venous blood respectively. The equation may also be modified using CO\textsubscript{2} production and content. Traditional techniques for measuring VO\textsubscript{2}, namely the Douglas bag, spirometry, and more recently mass spectrometry, have limited the clinical utility of this technique in the ICU. However, with the advent of portable metabolic monitors adapted for pediatric use, this technique is now possible in children [31,34–36]. For neonates, the mean of VO\textsubscript{2} measurements over 5 minutes is recommended [37*].

The numerous potential sources of error in the calculation of VO\textsubscript{2} with a metabolic monitor must be appreciated and minimized [31,38]. Also, the VO\textsubscript{2} measured with a metabolic monitor represents whole-body (ie lung plus systemic) VO\textsubscript{2} which can cause an overestimation of cardiac output in conditions of acute lung injury, where lung VO\textsubscript{2} may be considerable. [39*]

Noninvasive methods

Noninvasive Fick using CO\textsubscript{2}

The Fick principle using CO\textsubscript{2} can be used noninvasively if mixed venous CO\textsubscript{2} is estimated from expired CO\textsubscript{2}. This has traditionally involved rebreathing techniques needing CO\textsubscript{2} equilibration, which are impractical in the ICU setting. Arnold [40] described a single-breath modification of this technique in an animal model in 1996, with promising results. This was later extended to a lung injury model, with slightly less but acceptable accuracy [41]. To our knowledge, this has not yet been reported in pediatric ICU patients. A commercially available monitor has recently performed poorly in a porcine model of acute lung injury [42], with varying results in adults after cardiac surgery [43,44].

Bioimpedance

Bioimpedance, first described 35 years ago [45], involves the placement of voltage-sensing and current transmitting electrodes on the chest, which may be regarded as a conductor whose impedance is altered by changes in blood volume and velocity with each heart beat. Stroke volume is calculated from an equation involving baseline and maximum rate of change in impedance, ventricular ejection time, and thoracic segment length. Although several pediatric papers were published in the late 1980s and early 1990s, thoracic bioimpedance has not gained widespread clinical use in the pediatric ICU.

Bioimpedance has been used invasively to measure intracardiac impedance where the conductance catheter is placed inside the ventricle [46•]. This has recently been adapted to a less invasive form [47]. Here the current generating electrodes are placed in the superior vena cava and near the xiphisternal joint, with six epiphrenic electrodes on the chest wall to sense voltage differences. Several methodologic problems exist, such as interindividual and cardiac phase variability, along with the need to calibrate absolute stroke volume with another invasive method. However, this may be a promising new technique.

Echocardiography

Echocardiography can be used to measure cardiac output using a combination of Doppler to calculate the aortic velocity-time integral (stroke distance) with a two-
dimensional view to gauge aortic valve annulus dimensions. Errors in the estimation of aortic dimensions have prompted the development of a novel technique known as surface integration of velocity vectors [48]. Here, Doppler sampling is in multiple two-dimensional planes, which are reconstructed to represent three-dimensional flow. Measurements take 2 to 8 minutes, and the technique has yet to be described in children.

Echocardiography also supplies a vast amount of morphologic and functional information (e.g., indices of diastolic dysfunction, regional wall abnormalities, valve regurgitation, pericardial effusion). A load-independent parameter of cardiac function relating left ventricular wall stress to the velocity of circumferential fiber shortening has been advocated [49]. By use of this parameter, it was shown that the poor systolic cardiac performance seen in children with septic shock and after cardiac surgery is often secondary to diminished preload rather than to poor contractility [50,51]. A recent study demonstrated a greater reduction in contractility for a given increase in afterload in pediatric ICU patients [52•].

Automated border detection is an echocardiographic technique that allows estimation of ventricular area (related to volume) in unusually shaped ventricles. When it is used with invasive ventricular pressure readings, information on contractility is provided. Substitution of aortic for ventricular pressure may provide similar information, even on a single-beat basis [53•]. If so, the ability to monitor function in single-ventricle anatomy would be highly beneficial. Preliminary reports have also appeared on the myocardial performance index, which may be an alternative measure of ventricular function regardless of shape [54]. It has been suggested that this measure is both preload and afterload independent [55]. Three-dimensional echocardiography allows ventricular volume measurement without assumption of ventricular shape [56], and reduction in acquisition time has recently been reported [57].

However, the accuracy of any echocardiographic technique is largely a function of the skill of the user. Thus, the technique is ideally used by a pediatric cardiologist.

**Transesophageal Doppler**

Like echocardiography, this technique uses the Doppler principle to measure blood flow in the descending aorta via an esophageal probe [21]. The velocity-time integral (stroke distance) represents the distance traveled by a column of blood during one cardiac cycle. A pediatric nomogram now exists that allows derivation of stroke volume and cardiac output [58]. The assumptions inherent in the nomogram (aortic diameter is not directly measured) produce small errors in the estimate for absolute cardiac output in individual patients, however, changes in pediatric cardiac output are tracked accurately [58,59]. Interestingly, a new device that does measure aortic diameter does not improve the error for absolute cardiac output estimation [60].

Other benefits include minimal training of users [61], rapid initiation of cardiac output measurement, and the potential for other hemodynamic data from inspection of waveforms [62•]. The prognostic benefit from combined cardiac output and preload monitoring using transesophageal Doppler has been shown in adults [63].

**Pulse contour analysis**

Erlanger and Hooker [64] suggested a relation between cardiac output and arterial pulse contour nearly a century ago. A variety of methods for continuous pulse contour analysis exist, of which several have become commercially available with the advent of fast computer microprocessors [65,66•,67•]. Most methods provide only relative changes in stroke volume and cardiac output; hence, they must be combined with a method of calibration. The PiCCO method uses the area under the systolic portion of the pulse pressure waveform, and calibration is by transpulmonary thermodilution. Although accurate in adults [65], the combined system necessitates a 4-French arterial probe, which thus limits its use to the larger child.

The Modelflow method derives stroke volume by use of an extended Windkessel model comprising proximal aortic impedance, compliance, and total peripheral resistance. This model contains a self-adapting total peripheral resistance, which means that cardiac output can be calculated de novo; however, external calibration is still necessary to provide clinical accuracy [66•].

Another method, PulseCO (LiDCO, UK) is based on frequency analysis of aortic impedance, aorta-radial transfer function, aortic flow, and radial pressure [67•]. Analysis occurs via a radial arterial line, with calibration by lithium dilution [33•], making this an ideal method for infants and children. We are currently investigating the utility of this system.

**Other methods**

Several other noninvasive methods exist, including radionuclide techniques [68] and MRI [69]; however, none can be performed at the bedside, which limits their usefulness in ICU patients.

**Other aspects**

**Assessment of volume status**

Preload is an important contributor to cardiac output, but the commonly used pressure measures such as central venous pressure and pulmonary artery occlusion pressure are not good indicators of volume [70,71•]. Transpulmonary thermodilution can be used to calculate intrathoracic blood volume, using a technique that is not math-
ematically coupled to the derivation of cardiac output [72]. This parameter provides a good estimate of preload in adults [70,71].

Right ventricular end diastolic volume can be calculated with a suitably modified pulmonary artery catheter. A recent extension of this technique has been the estimation of right ventricular compliance by concurrently use of central venous pressure [73].

Variations in both arterial pulse pressure and aortic flow with mechanical ventilation show a great deal of promise as indicators of preload responsiveness (the change in stroke volume with fluid loading) [74,75,76].

Other markers of tissue perfusion

Capillary refill is a useful clinical parameter during the acute assessment and resuscitation phases. However, its meaning in the ICU is obscured by confounding factors such as fever and vasoactive medications [77]. Nonetheless, a dramatic change in this parameter should alert the clinician to the need for a more detailed hemodynamic assessment of the patient.

The prognostic value of serial blood lactate measurement has been well documented [78]; however, the exact relation between this parameter and tissue perfusion is not always well defined [79]. Mixed venous oxygen saturation is an indicator of oxygen extraction with a useful clinical role, but debate exists about whether central venous saturation can be used as a surrogate [80]. The oxygen excess factor, defined as the ratio of arterial oxygen saturation to the arterial-mixed venous oxygen saturation difference, is thought to reflect the DO₂:VO₂ (supply:demand) ratio [81]. This parameter can be used for sequential monitoring in univentricular hearts and may have prognostic value [82]. Finally, several techniques for measurement of flow in the microcirculation have been described, but they have primarily been used as research tools [83].

Conclusions

Many techniques for the measurement of cardiac output in critically ill children exist. There is a growing trend toward less invasive and continuous methods; however, some of them are not yet available or have yet to be adequately evaluated in children. With further refinement, cardiac output measurement may become more commonplace in the pediatric ICU.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
** Of outstanding interest


A preliminary report demonstrating the reduction in variability and hence error of thermomilution with an automated method. Several sources or error are minimized: temperature fluctuations are accounted for, injectate volume and rate are controlled and are spread across the whole ventilatory cycle.


38 Estable is a method to minimize VO2 and thus cardiac output error in neonates, by averaging VO2 measurements for 5 minutes.


41 Quantifies lung oxygen consumption in premature lung disease.


49 A nice synopsis of intracardiac impedance, explaining the method, clinical uses, and limitations.


56 This adds to earlier reports (see [50,51]) exploring the utility of this parameter in the ICU, providing food for thought as to future directions.


58 This report explores the translation of a useful invasive technique into a noninvasive form. If accurate, it can be used in patients with unusual ventricular dimensions, for example, univentricular hearts.


68 An attempt to evaluate preload responsiveness noninvasively. The authors conclude that corrected flow time (a Doppler parameter) can predict which patients are likely to be near the top of the Frank-Starling curve and thus unresponsive to volume loading. The superiority of this parameter over central venous pressure is shown.


73 Clinical validation of a pulse contour method in adults after cardiac surgery. Accuracy is improved greatly if the initial pulse contour calculation is calibrated with another method for CO measurement. Nonetheless, this represents a significant advance in minimally invasive, continuous cardiac output monitoring.


A study similar to [66], using a different model. The advantage to pediatrics is that here the calculation method is built in and has been validated in children (see [53]).


Demonstration of intrathoracic blood volume as a superior estimate of preload. This parameter is calculated using transpulmonary thermodilution (see [31]) but has not been investigated in children.


A small but interesting study highlighting the utility of respiratory cycle variation in aortic blood velocity as a predictor of preload responsiveness.


An approach similar to that in [76]. This study is commended for its thorough methodology and statistical analysis.


A very thorough synopsis of studies exploring the value of central venous oxygen saturation monitoring.


A preliminary report demonstrating prognostic value of the oxygen excess factor. This parameter represents the oxygen supply-demand ratio, is easy to calculate, and can be used in the setting of univentricular circulation.