

Advanced Hemodynamic Monitoring in the Neonatal Intensive Care Unit



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KEYWORDS

• Shock • Hemodynamic monitoring • Cardiac output

KEY POINTS

- Clinical assessment of systemic perfusion in critically ill newborn infants is rather inaccurate.
- Simultaneous assessment of blood pressure and cardiac output enables the identification of the earliest stage of shock.
- Comprehensive hemodynamic monitoring is pivotal for an individualized pathophysiology-based hemodynamic management.

INTRODUCTION

The continuous delivery of oxygen and nutrients via the circulation to the tissues is pivotal for the optimal functioning of all organ systems. Oxygen delivery (DO_2) is determined by the total oxygen concentration in the arterial blood (depending on hemoglobin concentration, oxygen saturation and, to a far lesser extent, partial pressure of oxygen) and the cardiac output.

Equation 1:

$$DO_2 = (Hb \times SaO_2 \times 0.98) + (PaO_2 \times 0.0004) \times CO$$

where CO is cardiac output (in L/min); DO_2 is oxygen delivery (in mmol/min); Hb is hemoglobin concentration (in mmol/L); PaO_2 is partial pressure of oxygen (kPa); and SaO_2 is oxygen saturation (in gradient).

It is not just the DO_2 ; it is above all the oxygen balance, that is, the relationship between DO_2 and the oxygen consumption (V_{O_2}), which must be taken into account and that reflects the adequacy of oxygenation. In a state of shock, DO_2 fails to meet the oxygen demand in the tissues, leading to cellular energy failure with subsequent dysfunction, injury, and eventually death of the cell. Oxygen balance can be evaluated

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on a macrocirculatory level, that is, total DO_2 in relation to total VO_2 , or on a more detailed level, such as regional or organ level, microcirculatory level, cellular level, or even mitochondrial level.

Everyone is very familiar with direct measurement of hemoglobin concentration and oxygen saturation, but cardiac output is usually indirectly assessed by interpretation of several clinical and biochemical variables, such as blood pressure, heart rate, capillary refill time, urine output, blood gas analysis, and serum lactate concentration. However, both the objectivity and the predictive value of most clinical signs and symptoms of circulatory failure are rather limited.¹ Moreover, the clinical estimation of cardiac output is unreliable. Only 26% of the patients in a true low cardiac output state, that is, less than 3.0 L/min/m^2 , is correctly categorized as such in a pediatric intensive care setting. This finding goes against the general perception that the patients with severe circulatory failure (“deep shock”) are recognized more easily² and emphasizes the need for objective cardiac output measurement in newborns infants in neonatal intensive care. The aims of cardiac output monitoring are as follows: (1) timely detection of low flow state; (2) understanding underlying pathophysiological mechanism; (3) enabling an individualized, pathophysiology-based therapeutic intervention; (4) monitoring the effect of the treatment and, if needed, reconsideration of treatment regimen.

METHODS OF CARDIAC OUTPUT MONITORING

In recent years many technologies have become available for cardiac output monitoring in critically ill patients, but the feasibility of many methods is limited in newborn infants because of size restraints, the presence of intracardiac and extracardiac shunts during transition, and the potential adverse effects. **Table 1** shows an overview of available advanced hemodynamic monitoring systems with information about feasibility in newborns, invasiveness, continuity of information, validation, and clinical application.^{3,4}

The methods for cardiac output monitoring that are feasible and (potentially) clinically applicable in critically ill newborn infants are transthoracic echocardiography (TTE), transcutaneous Doppler (TCD), electrical biosensing technologies, transpulmonary ultrasound dilution (TPUD), and arterial pulse contour analysis.

Transthoracic Echocardiography

Echocardiography can be used to longitudinally assess systemic and pulmonary blood flow and the presence of potential transductal and interatrial shunting. For the estimation of blood flow, one has to measure blood flow velocity using Doppler ultrasound in the area of interest (**Fig. 1**). The velocity-time integral is in fact the area under the Doppler spectral curve and represents the time distance, that is, the distance that a column of blood will travel during 1 heart cycle. When the cross-sectional area is known, stroke volume can be calculated, and by multiplying with heart frequency, cardiac output is calculated.

Left ventricular output (LVO), right ventricular output (RVO), and superior vena cava flow (SVCf) can be estimated by measuring Doppler flow velocity and cross-sectional area in the left or right ventricular outflow tract or in the superior vena cava, respectively. LVO and RVO are not interchangeable in the presence of intracardiac or transductal shunting. Transductal left-to-right shunting will increase LVO, whereas interatrial left-to-right shunting will increase RVO. Because the systemic blood flow is of most importance, that is, blood flow toward the organs, one must always interpret central blood flow estimates in the context of potential shunt flow across the fetal channels. SVCf is not biased by transductal or interatrial shunting; however, it does

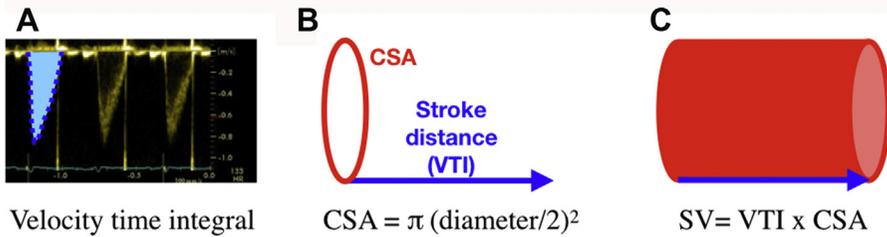
Table 1
Overview of advanced hemodynamic monitoring systems

Technology	Feasible in Newborns?	Invasive (I) or Noninvasive (N)	Continuous (C) or Intermittent (I)	Validated in Newborns?	Clinical Use (C) or Research Tool (R)
1. Macrocirculation					
1.1. Fick principle					
Oxygen Fick (O ₂ -F)	+	I	I	–	R
Modified carbon dioxide Fick (mCO ₂ -F)	+	I	I	–	R
Carbon dioxide rebreathing (CO ₂ -R)	–	N	I	–	–
1.2. Doppler ultrasound					
Transthoracic echocardiography (TTE)	+	N	I	+	C
Transcutaneous Doppler (TCD)	+	N	I	+	C
Transesophageal echocardiography (TEE)	±	N	I	–	C
Transesophageal Doppler (TED)	±	N	C/I	–	C
1.3. Indicator dilution technology					
Pulmonary artery thermodilution (PATD)	–	I	I	–	–
Transpulmonary thermodilution (TPTD)	–	I	I	–	–
Transpulmonary lithium dilution (TPLD)	–	I	I	–	–
Transpulmonary ultrasound dilution (TPUD)	+	I	I	–	C/R
Pulse dye densitometry (PDD)	+	I	I	–	R
1.4. Electrical biosensing technology (EBT)					
Transthoracic bioimpedance (TBI)	+	N	C	+	C/R
Transthoracic bioreactance (TBR)	+	N	C	+	C/R
Whole-body bioimpedance (WBI)	+	N	C	–	C/R
1.5. Arterial pulse contour analysis					
Pressure recording analytical method (PRAM)	+	I	C	+	C/R

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Table 1
(continued)

Technology	Feasible in Newborns?	Invasive (I) or Noninvasive (N)	Continuous (C) or Intermittent (I)	Validated in Newborns?	Clinical Use (C) or Research Tool (R)
Modelflow	+	N	C	–	C/R
Continuous CO monitoring in adjunction to and calibrated by invasive technologies	+	I		–	C/R
1.6. Cardiac MRI	+	N	I	+	R
2. Regional (organ) perfusion					
2.1. Near-infrared spectroscopy (NIRS)					
Cerebral	+	N	C	±	R
Somatic (splanchnic, renal, muscle)	+	N	C	±	R
3. Microcirculation					
3.1. Laser Doppler flowmetry	+	N	I	–	R
3.2. Optical methods					
Orthogonal polarization spectral imaging (OPS)	+	N	I	–	R
Sidestream darkfield imaging (SDF)	+	N	I	–	R
Incident dark field imaging (IDF)	+	N	I	–	R



Blood flow (mL/min) = $(\pi \times (D/2)^2 \text{ (cm}^2) \times \text{VTI (cm)} \times \text{HR (bpm))}$

Fig. 1. Doppler measurement of blood velocity in left ventricular outflow tract. (A) Assessment of the velocity time integral (VTI) by assessing the area under the Doppler spectral curve. (B) By multiplying the VTI, that is, the stroke distance, with the cross-sectional area (CSA), one calculates stroke volume (SV) (C). HR, heart rate.

not truly represent cardiac output. In fact, SVCf is partial cardiac input, because it indicates systemic venous return from the upper body.

For longitudinal follow-up of ventricular output, one may assume the outflow tract diameter to be constant and only assess the stroke distance (velocity time integral [VTI]) or so-called minute distance (VTI \times heart rate).

One should be aware that the precision of cardiac output assessment by echocardiography is limited with an error around $\pm 30\%$ in comparison with more accurate reference methods of cardiac output monitoring, such as dye dilution, Fick method, thermodilution technology, and cardiac phase contrast MRI.^{5,6} Despite this inaccuracy, combined with relatively high intraindividual and interindividual variability (coefficient of variation: 2.1%–22% and 3.1%–22%, respectively),⁵ echocardiographic-derived central blood flow assessment is considered by many the “gold-standard” clinical reference method, against which many innovative methods are validated. This approach is highly questionable, and validation studies using echocardiography as the standard reference method for cardiac output must be interpreted with caution. The imprecision of TTE is probably caused by the assumption of a perfect round shape of the outflow tract and therefore the difficulty in exact measurement of the cross-sectional area, the supposition of equal flow velocity from the center to the periphery of vessels, and the inaccuracy of tracking the Doppler velocity envelope for assessment of the velocity time integral. Moreover, cardiorespiratory interaction and errors secondary to angle of insonation hamper exact calculation of central blood flow.

As such, echocardiography is not the ideal (standard) method of continuous cardiac output monitoring, because it requires intensive training of the operator, its limited accuracy and precision, and influence of potential transductal and interatrial shunting. Given these restrictions, echocardiography, nevertheless, enables elucidation of underlying pathophysiologic causes of hemodynamic instability and the development of an individualized therapeutic approach.

Recently, the use of continuous, preferably noninvasive cardiac output monitors has gained much interest.

Transcutaneous Doppler

Cardiac output can be estimated by measuring blood flow velocity using continuous-wave Doppler aiming with an ultrasound probe at the assumed position of either the ascending aorta or the pulmonary artery (TCD; USCOM, Sydney, Australia).

Noteworthy, the area of interest and Doppler ultrasound sampling are not visualized (as in TTE); the probe is positioned in the sternal notch (LVO) or on the left hemithorax (RVO) and angled in such manner that an “optimal” Doppler spectral envelope is obtained on the monitor. This blind scanning also implies that the cross-sectional area of the respective outflow tract is not assessed directly, but derived from an algorithm based on height, weight, and age. Given this methodology, it is of no surprise that TCD is less accurate than TTE; moreover, validation studies have shown a low agreement between TCD and other techniques of cardiac output monitoring, such as TTE and thermodilution, with a bias% and error% of 0% to 21% and 43% to 65%, respectively.^{7–10}

Electrical Biosensing Technology

The first study of the application of impedance cardiography was published in Russia in 1949 by Kedrov and Liberman.¹¹ The technology was further developed by Kubicek and colleagues¹² in the 1960s to study the effects of weightlessness on cardiovascular function in astronauts.

For this truly noninvasive and easily applicable technology, surface electrodes are placed to apply and detect a high-frequency, low-magnitude current across the body. Because electrical conductivity of muscle, fat, and air is lower than of blood, the electrical current is mainly distributed to the blood. An increase in compartmental blood volume, higher blood flow velocity, and alignment of red blood cells during the systolic phase of the heart cycle will cause a reduction in electrical impedance. When the magnitude of the electrical current is kept constant, any periodic fluctuations in electrical impedance is assumed to be proportional to stroke volume. Several electrical biosensing monitors are available that differ in the methodology used to analyze these changes in electrical impedance, the algorithm to translate these alternations into stroke volume, and the placement of the biosensors. In transthoracic bioimpedance (TBI; Electrical cardiometry/ICON/Aesculon, Osypka Medical GmbH, Berlin, Germany) or whole-body bioimpedance (WBI; NICaS, NI Medical, Petah Tikva, Israel), the fluctuations in signal amplitude are analyzed, whereas in transthoracic bio-reactance (TBR; Starling/NICOM, Cheetah Medical Inc, Vancouver, WA, USA), alterations in phase shift are measured. Electrodes are either placed around the thorax for the transthoracic approach or on 1 wrist (radial artery) and the contralateral ankle (tibial artery) for WBI. Electrical biosensing cardiac output monitors have mainly been validated in studies using TTE as the reference method, which, as already mentioned, cannot be regarded as a gold-standard reference. Published bias% and error% are 1% to 9% and 25% to 60% for TBI and 32% to 39% and 23% to 31% for TBR, respectively.^{13–20} WBI has not been validated in newborn infants, but a validation study in children less than 16 years of age showed a bias% of 1.8% and an error% of ±29% in comparison with transesophageal Doppler technology.²¹

Transpulmonary Ultrasound Dilution

Indicator dilution technologies are based on the concept that when an indicator is injected in a known amount into the venous circulation and subsequently mixed and diluted in the heart, the detected concentration downstream over time will be related to cardiac output. The relation between the area under the indicator dilution curve and cardiac output is described by the so-called Stewart-Hamilton equation.

Equation 2:

$$CO = \frac{60 \times i}{\int C(t) dt}$$

where CO is cardiac output (in L/min); i is indicator (in mg); C is indicator concentration (in mg/L); and t is time (in seconds).

Pulmonary artery thermodilution (Swan-Ganz catheter) has been the clinical gold-standard method for cardiac output assessment for many years in adult intensive care. To overcome the disadvantage of directly sampling from the pulmonary artery with its associated risks, the concept of thermodilution has been modified with central venous injection of the indicator and measurement of indicator concentration in the arterial blood, the so-called transpulmonary indicator dilution technique. For obvious reasons it is not feasible to use pulmonary artery thermodilution in newborn infants. The need for a dedicated thermistor-tipped arterial catheter in transpulmonary thermodilution (TPTD; PiCCO, Pulsion Medical Systems, Feldkirchen, Germany) hampers its application in newborn infants because of size restraints. TPUD, however, is feasible in (preterm) newborn infants weighing greater than 600 g. Regular indwelling central venous and arterial catheters are used for this method (COstatus, Transonic Systems Inc, Ithaca, NY, USA) to interconnect an extracorporeal circuit. A small volume (0.5–1 mL/kg) of normal saline at body temperature is injected at the venous side as indicator and, because ultrasound velocity is slower through normal saline than blood, a decrease in ultrasound velocity can be detected at the arterial side. Cardiac output can be estimated by analysis of the acquired ultrasound dilution curve. This technique has extensively been validated in animal models and proved to be safe regarding systemic and cerebral hemodynamic and oxygenation with the use of the extracorporeal loop.^{22,23} Moreover, TPUD is also feasible in the presence of a significant transductal left-to-right shunt, in a state of hypovolemic shock, during volume resuscitation, and with severe lung injury.^{22–26} Agreement between TPUD and invasive pulmonary blood flow measurement with perivascular flow probe in an animal model is good, with an acceptable error% between 19% and 27%. Currently, clinical TPUD studies are mainly focused on (cardiac surgery) patients in a pediatric intensive care setting and are pending in neonatal care.^{27–32}

Arterial Pulse Contour Analysis

Since the first publication from Frank³³ in 1899, many efforts have been made to translate data from the arterial blood pressure curve into stroke volume or cardiac output using different algorithms. The assessment of stroke volume from the arterial pressure wave form is complicated by the fact that arterial blood pressure and stroke volume are not linearly related. This non-linear relationship is mainly due to the aortic impedance, that is influenced by aortic compliance, vascular resistance, and inductance (inertia of blood).

$$SV = \frac{\int dP/dt}{Z}$$

where SV is stroke volume; P is arterial pressure; t is time; and Z is aortic impedance.

It is the dependency of the aortic impedance on both stroke volume and aortic compliance that complicates accurate arterial pulse contour analysis. However, this technology might be promising with regards to trend monitoring, once the arterial pulse contour analysis (APCA) has been calibrated using an invasive method, such as TPTD or TPUD. APCA has only been validated in 3 studies in children and, to the authors' knowledge, not in newborns.^{34–36} There is an acceptable agreement from APCA (Pressure recording analytical method; MostCareUp, Vitec/Vigon, Padova, Italy) with TTE and the Fick method with an error percentage of 24 and 17, respectively.^{34,36}

WHAT IS A NORMAL LEVEL OF CARDIAC OUTPUT?

A ventricular output of 150 to 300 mL/kg/min is considered normal in (pre)term infants without transductal or interatrial shunting. A ventricular output less than 150 mL/kg/min or SVCf less than 40 to 45 mL/kg/min is associated with adverse outcomes. Although it would be preferred to measure cardiac output very accurately in absolute numbers, it might be more useful to categorize the level of cardiac output (low, normal, or high) for the purpose of understanding the underlying pathophysiology and when interpreted in conjunction with blood pressure for the classification of the stage of shock.³⁷ The combination of low cardiac output and normal blood pressure would suggest a compensated shock, whereas low cardiac output and low blood pressure is indicative of an uncompensated shock. In a hyperdynamic shock, one would expect high cardiac output and low blood pressure. The interpretation of simultaneously assessed cardiac output and blood pressure enables an individualized, pathophysiology-based approach toward cardiocirculatory failure in critically ill newborn infants.

COMPREHENSIVE HEMODYNAMIC MONITORING

Cardiac output measurement should not be considered the Holy Grail. The level of cardiac output, hence global DO_2 , should always be interpreted in relation to total oxygen demand. Oxygen demand is dependent on the level of basal metabolism, thermogenesis, and external work, and for example, influenced by work of breathing, growth, trauma (surgery), shivering, pain, discomfort, fever, and catecholamines, which means that even a cardiac output within the normal reference range could be insufficient to meet the increased metabolic demand in a specific postoperative anemic patient in distress on high doses of catecholamines with fever. On the other hand, a cardiac output of 120 mL/kg/min could be enough in a newborn infant with a relatively low oxygen demand.

Moreover, a normal level of cardiac output does not imply an adequate perfusion of all organs, because it only provides information about “global” blood flow. For this reason, comprehensive hemodynamic monitoring is indicated that also encompasses regional hemodynamic monitoring, such as near-infrared spectroscopy (NIRS), or technologies that assess the microcirculation, such as laser Doppler flowmetry, orthogonal polarization spectral imaging, sidestream darkfield imaging, or incident dark field imaging.

In a recent study it has been shown that an integrated hemodynamic approach, that is, the integration of results from clinical assessment, routine cardiovascular monitoring, TTE, NIRS, and cardiovascular biomarkers assessment, resulted in a reduction of time to clinical recovery in preterm infants with compromised hemodynamics.^{38,39} It must be stressed that it is not solely the monitoring that will improve outcome, because this also depends on an adequate interpretation of the acquired hemodynamic parameters and subsequent decisions about optimal therapeutic interventions. Therefore, instead of focusing on advanced hemodynamic monitoring alone, one should invest in high-quality hemodynamic consultation.⁴⁰

SUMMARY

Clinical assessment of cardiac output by interpretation of indirect parameters of cardiac output has proven to be inaccurate, irrespective of the level of experience of the clinician.

Objective cardiac output monitoring is feasible in newborn infants, and the most promising methods are TTE, TCD, electrical biosensing technologies, TPUD, and

arterial pulse contour analysis. Simultaneous assessment of blood pressure and cardiac output enables the identification of the earliest stage of shock. A normal level of cardiac output is no guarantee for an adequate perfusion in all tissues. Comprehensive hemodynamic monitoring, providing information on both global and regional perfusion, is pivotal for an individualized pathophysiology-based hemodynamic management.

DISCLOSURE

The author's research group received unrestricted research grants from or equipment has been put at their disposal by the following companies: Transonic Systems Inc, Ithaca, NY, USA; Pulsion Medical Systems, Feldkirchen, Germany; Osypka Medical, Berlin, Germany/San Diego, CA, USA; Cheetah Medical Inc, Maidenhead, UK, and NI Medical, Petah Tikva, Israel.

Best Practices

What is the current practice for the assessment of the hemodynamic status of newborn infants and the hemodynamic management of circulatory compromise?

- Assessment of systemic perfusion is mainly based on clinical estimation
- Hemodynamic management of newborn infants with cardiovascular failure is predominantly determined by blood pressure level

What changes in current practice are likely to improve outcome?

- Integrated longitudinal assessment of routine cardiovascular monitoring, blood pressure, cardiac output, TTE, cardiovascular biomarkers, regional perfusion
- Individualized, pathophysiology-based hemodynamic management

Major recommendations

- Delineate underlying pathophysiology to individualize hemodynamic management with tailor-made therapeutic interventions
- Concomitant assessment of cardiac output and blood pressure to categorize the stage of shock
- Monitor the response to the initiated hemodynamic management and reconsider if needed

Summary statement

Comprehensive hemodynamic monitoring encompassing the assessment of regular clinical cardiovascular variables, cardiac output, regional oxygenation and perfusion, and cardiovascular biomarkers will improve outcome after correct interpretation and the initiation of an individualized, pathophysiology-based hemodynamic management.

REFERENCES

1. de Boode WP. Clinical monitoring of systemic hemodynamics in critically ill newborns. *Early Hum Dev* 2010;86(3):137–41.
2. Tibby SM, Hatherill M, Marsh MJ, et al. Clinicians' abilities to estimate cardiac index in ventilated children and infants. *Arch Dis Child* 1997;77(6):516–8.
3. Vrancken SL, van Heijst AF, de Boode WP. Neonatal hemodynamics: from developmental physiology to comprehensive monitoring. *Front Pediatr* 2018;6:87.
4. de Boode WP, Osypka M, Soleymani S, et al. Chapter 14. Assessment of cardiac output in neonates. Techniques using the Fick principle, indicator dilution

- technology, Doppler ultrasound, thoracic electrical bioimpedance and arterial pulse contour analysis. In: Seri I, Kluckow M, Polin RA, editors. Hemodynamics and cardiology. 3rd edition. Philadelphia: Elsevier; 2018. p. 237–63.
5. Chew MS, Poelaert J. Accuracy and repeatability of pediatric cardiac output measurement using Doppler: 20-year review of the literature. *Intensive Care Med* 2003;29(11):1889–94.
 6. Ficial B, Finnemore AE, Cox DJ, et al. Validation study of the accuracy of echocardiographic measurements of systemic blood flow volume in newborn infants. *J Am Soc Echocardiogr* 2013;26(12):1365–71.
 7. Chong SW, Peyton PJ. A meta-analysis of the accuracy and precision of the ultrasonic cardiac output monitor (USCOM). *Anaesthesia* 2012;67(11):1266–71.
 8. Phillips RA, Paradisis M, Evans NJ, et al. Cardiac output measurement in preterm neonates: validation of USCOM against echocardiography [abstract]. *Crit Care* 2006;10(Suppl 1):144.
 9. Patel N, Dodsworth M, Mills JF. Cardiac output measurement in newborn infants using the ultrasonic cardiac output monitor: an assessment of agreement with conventional echocardiography, repeatability and new user experience. *Arch Dis Child Fetal Neonatal Ed* 2011;96(3):F206–11.
 10. Meyer S, Todd D, Shadboldt B. Assessment of portable continuous wave Doppler ultrasound (ultrasonic cardiac output monitor) for cardiac output measurements in neonates. *J Paediatr Child Health* 2009;45(7–8):464–8.
 11. Kedrov AA, Liberman TU. Rheocardiography. *Klin Med (Mosk)* 1949;27(3):40–6.
 12. Kubicek WG, Karnegis JN, Patterson RP, et al. Development and evaluation of an impedance cardiac output system. *Aerosp Med* 1966;37(12):1208–12.
 13. Noori S, Drabu B, Soleymani S, et al. Continuous non-invasive cardiac output measurements in the neonate by electrical velocimetry: a comparison with echocardiography. *Arch Dis Child Fetal Neonatal Ed* 2012;97(5):F340–3.
 14. Song R, Rich W, Kim JH, et al. The use of electrical cardiometry for continuous cardiac output monitoring in preterm neonates: a validation study. *Am J Perinatol* 2014;31(12):1105–10.
 15. Grollmuss O, Gonzalez P. Non-invasive cardiac output measurement in low and very low birth weight infants: a method comparison. *Front Pediatr* 2014;2:16.
 16. Torigoe T, Sato S, Nagayama Y, et al. Influence of patent ductus arteriosus and ventilators on electrical velocimetry for measuring cardiac output in very-low/low birth weight infants. *J Perinatol* 2015;35(7):485–9.
 17. Boet A, Jourdain G, Demontoux S, et al. Stroke volume and cardiac output evaluation by electrical cardiometry: accuracy and reference nomograms in hemodynamically stable preterm neonates. *J Perinatol* 2016;36(9):748–52.
 18. Hsu KH, Wu TW, Wu IH, et al. Electrical cardiometry to monitor cardiac output in preterm infants with patent ductus arteriosus: a comparison with echocardiography. *Neonatology* 2017;112(3):231–7.
 19. Weisz DE, Jain A, McNamara PJ, et al. Non-invasive cardiac output monitoring in neonates using bioreactance: a comparison with echocardiography. *Neonatology* 2012;102(1):61–7.
 20. Weisz DE, Jain A, Ting J, et al. Non-invasive cardiac output monitoring in preterm infants undergoing patent ductus arteriosus ligation: a comparison with echocardiography. *Neonatology* 2014;106(4):330–6.
 21. Beck R, Milella L, Labellarte C. Continuous non-invasive measurement of stroke volume and cardiac index in infants and children: comparison of Impedance Cardiography NICaS® vs CardioQ® method. *Clin Ter* 2018;169(3):e110–3.

22. de Boode WP, van Heijst AFJ, Hopman JCW, et al. Cardiac output measurement using an ultrasound dilution method: a validation study in ventilated piglets. *Pediatr Crit Care Med* 2010;11(1):103–8.
23. de Boode WP, van Heijst AFJ, Hopman JCW, et al. Application of ultrasound dilution technology for cardiac output measurement: cerebral and systemic hemodynamic consequences in a juvenile animal model. *Pediatr Crit Care Med* 2010;11(5):616–23.
24. Vrancken SL, de Boode WP, Hopman JC, et al. Cardiac output measurement with transpulmonary ultrasound dilution is feasible in the presence of a left-to-right shunt: a validation study in lambs. *Br J Anaesth* 2012;108(3):409–16.
25. Vrancken SL, de Boode WP, Hopman JC, et al. Influence of lung injury on cardiac output measurement using transpulmonary ultrasound dilution: a validation study in neonatal lambs. *Br J Anaesth* 2012;109(6):870–8.
26. Vrancken SL, van Heijst AF, Hopman JC, et al. Hemodynamic volumetry using transpulmonary ultrasound dilution (TPUD) technology in a neonatal animal model. *J Clin Monit Comput* 2015;29(5):643–52.
27. Floh AA, La Rotta G, Wermelt JZ, et al. Validation of a new method based on ultrasound velocity dilution to measure cardiac output in paediatric patients. *Intensive Care Med* 2013;39(5):926–33.
28. Lindberg L, Johansson S, Perez-de-Sa V. Validation of an ultrasound dilution technology for cardiac output measurement and shunt detection in infants and children. *Pediatr Crit Care Med* 2014;15(2):139–47.
29. Crittendon I 3rd, Dreyer WJ, Decker JA, et al. Ultrasound dilution: an accurate means of determining cardiac output in children. *Pediatr Crit Care Med* 2012;13(1):42–6.
30. Saxena R, Krivitski N, Peacock K, et al. Accuracy of the transpulmonary ultrasound dilution method for detection of small anatomic shunts. *J Clin Monit Comput* 2015;29(3):407–14.
31. Boehne M, Baustert M, Paetzel V, et al. Feasibility and accuracy of cardiac right-to-left-shunt detection in children by new transpulmonary ultrasound dilution method. *Pediatr Cardiol* 2017;38(1):135–48.
32. Boehne M, Baustert M, Paetzel V, et al. Determination of cardiac output by ultrasound dilution technique in infants and children: a validation study against direct Fick principle. *Br J Anaesth* 2014;112(3):469–76.
33. Frank O. Die Grundform des arteriellen Pulses. Erste Abhandlung. *Mathematische Analyse. Z Biol* 1899;37:483–526.
34. Calamandrei M, Mirabile L, Muschetta S, et al. Assessment of cardiac output in children: a comparison between the pressure recording analytical method and Doppler echocardiography. *Pediatr Crit Care Med* 2008;9(3):310–2.
35. Garisto C, Favia I, Ricci Z, et al. Pressure recording analytical method and bio-reactance for stroke volume index monitoring during pediatric cardiac surgery. *Paediatr Anaesth* 2015;25(2):143–9.
36. Alonso-Inigo JM, Escriba FJ, Carrasco JI, et al. Measuring cardiac output in children undergoing cardiac catheterization: comparison between the Fick method and PRAM (pressure recording analytical method). *Paediatr Anaesth* 2016;26(11):1097–105.
37. de Boode WP, van der Lee R, Eriksen BH, et al. The role of neonatologist performed echocardiography in the assessment and management of neonatal shock. *Pediatr Res* 2018;84(S1):57–67.

38. Elsayed YN, Amer R, Seshia MM. The impact of integrated evaluation of hemodynamics using targeted neonatal echocardiography with indices of tissue oxygenation: a new approach. *J Perinatol* 2017;37(5):527–35.
39. Elsayed YN, Louis D, Ali YH, et al. Integrated evaluation of hemodynamics: a novel approach for the assessment and management of preterm infants with compromised systemic circulation. *J Perinatol* 2018;38(10):1337–43.
40. Hebert A, Lavoie PM, Giesinger RE, et al. Evolution of training guidelines for echocardiography performed by the neonatologist: toward hemodynamic consultation. *J Am Soc Echocardiogr* 2019;32(6):785–90.