European Journal of Pediatrics
https://doi.org/10.1007/s00431-021-04307-5

CLINICAL ALGORITHM

A new physiologic-based integrated algorithm in the management of neonatal hemodynamic instability

Yasser Elsayed[1] · **Muzafar Gani Abdul Wahab**[2]

Received: 10 March 2021 / Revised: 27 October 2021 / Accepted: 28 October 2021

Abstract

Physiologic-based management of hemodynamic instability is proven to guide the logical selection of cardiovascular support and shorten the time to clinical recovery compared to an empiric approach that ignores the heterogeneity of the hemodynamic instability related mechanisms. In this report, we classified neonatal hemodynamic instability, circulatory shock, and degree of compensation into five physiologic categories, based on different phenotypes of blood pressure (BP), other clinical parameters, echocardiography markers, and oxygen indices. This approach is focused on hemodynamic instability in infants with normal cardiac anatomy.

Conclusion: The management of hemodynamic instability is challenging due to the complexity of the pathophysiology; integrating different monitoring techniques is essential to understand the underlying pathophysiologic mechanisms and formulate a physiologic-based medical recommendation and approach.

What is Known:
• *Physiologic-based assessment of hemodynamics leads to targeted and pathophysiologic-based medical recommendations.*

What is New:
• *Hemodynamic instability in neonates can be categorized according to the underlying mechanism into five main categories, based on blood pressure phenotypes, systemic vascular resistance, and myocardial performance.*
• *The new classification helps with the targeted management and logical selection of cardiovascular support.*

Keywords Integrated hemodynamics · Neonatal hemodynamic instability · Circulatory shock

Abbreviations

BP	Blood pressure
DBP	Diastolic blood pressure
DO_2	Oxygen delivery
FOE	Fractional oxygen extraction
PDA	Patent ductus arteriosus
PP	Pulse pressure
PVR	Pulmonary vascular resistance
MABP	Mean arterial blood pressure
NIRS	Near-infrared spectroscopy
POCUS	Point of care ultrasound
StO_2	Tissue oxygen saturation
VO_2	Oxygen consumption
SBP	Systolic blood pressure
SpO_2	Arterial oxygen saturation
SVR	Systemic vascular resistance

Communicated by Daniele De Luca

✉ Yasser Elsayed
yelsayed@exchange.hsc.mb.ca

Muzafar Gani Abdul Wahab
amgani@npmmcmaster.ca

[1] Division of Neonatology, Department of Pediatrics and Child Health, Rady Faculty of Health Sciences, University of Manitoba, Women's Hospital, 820 Sherbrook Street, Winnipeg, MB R2016, R3A0L8, Canada

[2] Division of Neonatology, Department of Pediatrics and Child Health, McMaster University, Hamilton, Canada

Stepwise compensatory mechanisms from stability to decompensation

During any temporary period of instability, the first and foremost compensatory mechanism that takes place within a fraction of a second is autoregulation, and it happens with fluctuations or changes of the parameters affecting oxygen

Published online: 08 November 2021

delivery, for example, fluctuation of oxygen saturation, carbon dioxide, blood flow, or blood pressure [1–4]. Autoregulation is typically a local release of nitric oxide by red blood cells with subsequent local vasodilatation of blood vessels at any specific area of reduced oxygen delivery or when oxygen demand exceeds delivery [5]. If the oxygen delivery is less than the demand at any time beyond the capacity of autoregulation, then tissues extract more oxygen than usual to maintain aerobic metabolism; this can be detected in real-time on near-infrared spectroscopy (NIRS) as low regional tissue oxygen saturation (StO_2) and increased the calculated fractional oxygen extraction (FOE), assessment of blood pressure, and tissue oxygen trends; and histograms are helpful for early detection of the decompensation [6–11]. Anaerobic metabolism is the last mechanism to compensate if decreased oxygen delivery is lower than the maximum capacity of the tissue to extract the oxygen required to maintain aerobic metabolism; Fig. 1 demonstrates the impact of different mechanisms of shock on oxygen delivery (DO_2), oxygen consumption (VO_2), and FOE [12]. We conducted a systematic approach to explore the current literature and the available knowledge regarding hemodynamic instability through an appraisal of the most common practices in neonatal intensive care units. This systematic approach reflects the gap in knowledge regarding the management of hemodynamic instability; the result of this systematic approach is provided as a supplemental Table 1. Most practitioners are still considering an empiric start of one drug for cases with hemodynamic instability, usually dopamine or dobutamine. However, many randomized control trials for the last two decades could not provide any supporting evidence for this concept that one approach can fit everyone. These trials also could not provide evidence of improving any of the short- or long-term outcomes [13]. The physiologic approach is the

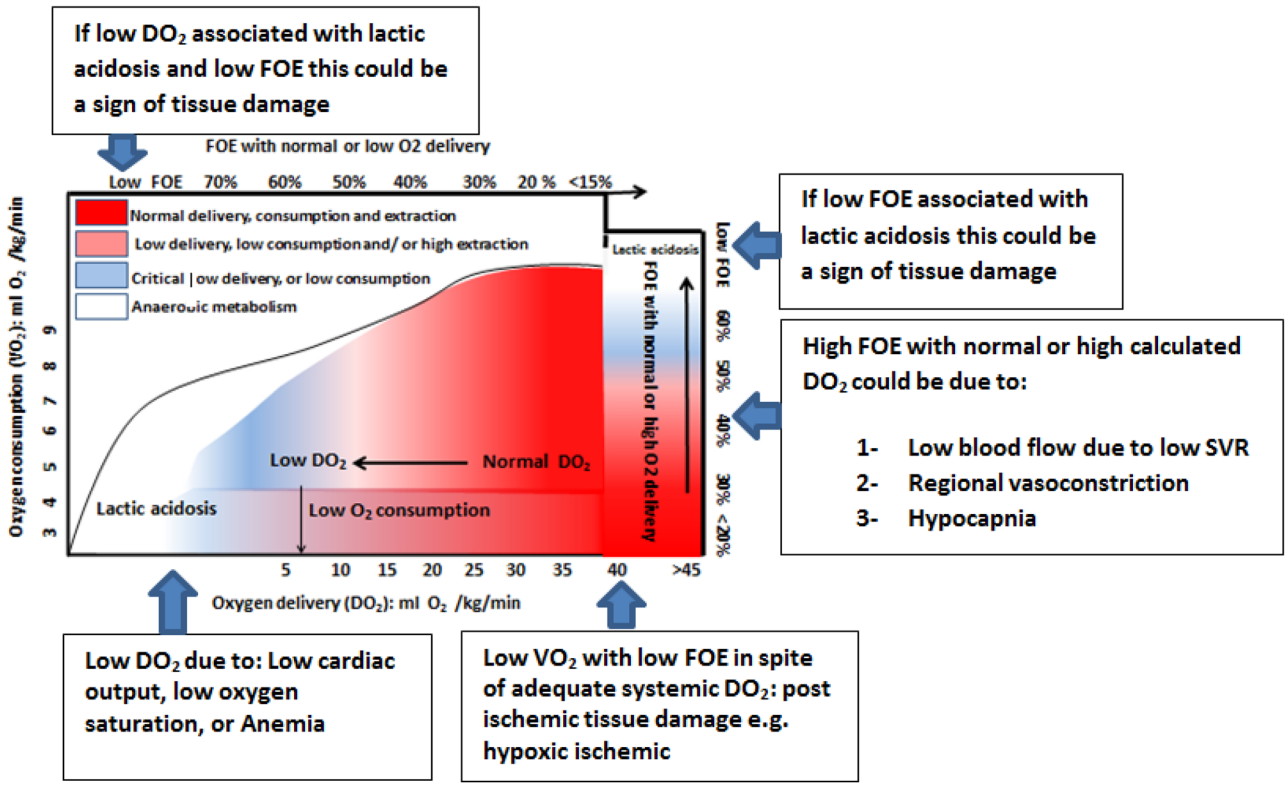

Fig. 1 This multidimensional graph is simplifying the 3 main mechanisms of hypoxia in neonates [1–3], and the decompensated stage with anaerobic metabolism [4]. The 3 calculated oxygen indices are oxygen delivery (DO_2), oxygen consumption (VO_2), and fractional oxygen extraction (FOE): the lower *X* axis is representing the trend of DO_2, left side direction means decreasing DO_2 (lower *X* axis), the left *Y* axis is representing the VO_2 and downward direction is decreasing VO_2, the right *Y* axis and upper *X* axis are representing the FOE as percent. Mechanism 1: Low capacity of tissue to extract oxygen due to prolonged hypoxemic ischemic injury, although DO_2 is adequate but both VO_2 and FOE are low. Mechanism 2: Low oxygen delivery due to severe anemia, hypoxemia, or low cardiac output, represented as low DO_2 and subsequently low VO_2 and high FOE to compensate for low DO_2. Mechanism 3: Although calculated DO_2 is normal or high and cardiac output is normal or high, the FOE is high due to low SVR which is not included in DO_2 equation, or regional vasoconstriction and hypocapnia is one of the common causes of cerebral vasocontraction which can be detected on NIRS as high FOE. Mechanism 4: if situation 2 or 3 continued and the DO_2 is insufficient to maintain aerobic metabolism, then anaerobic metabolism with lactic acidosis takes place to maintain energy production, but at the same time FOE decreases to low levels due to exhaustion of aerobic metabolism

logical alternative to the empirical selection of cardiovascular support, which in many situations is unsuccessful due to the complexity and heterogeneity of the underlying mechanisms of the hemodynamic instability [14].

Important definitions and concepts

Oxygen delivery

The amount of oxygen delivered per minute at the tissue level depends on maintained and steady blood flow, adequate hemoglobin, its saturation with oxygen, pressure gradient of oxygen between tissues and plasma, and the position of the oxyhemoglobin dissociation curve, and the main gaol of maintaining stable hemodynamics is to maintain tissue oxygen delivery [15].

Hemodynamic instability

Non-specific fluctuation of one or more hemodynamic markers outside the normative ranges; this hemodynamic instability may or may not affect end-organ blood flow and hence the oxygen delivery [16].

Hypotension

Low BP should not be used synonymously with shock; BP is one of the hemodynamic markers that may or may not be associated with decreased blood flow and hence shock [17]. Relying on mean blood pressure (MABP) adds more limitation to hypotension as a surrogate marker of shock, as MABP might be normal or high in vasoconstrictive physiology [18].

Shock

It is a state of imbalance between oxygen delivery and oxygen requirement by end organs. The body autoregulatory mechanisms are working in sequence to compensate and maintain aerobic metabolism [19, 20]. The first mechanism is hypoxic vasodilatory autoregulation which is a localized mechanism at tissues with higher demand than oxygen delivery, and it is also different from organ to organ [7, 21]. The next compensatory phase is characterized by neuroendocrine mechanisms with increased tissue oxygen extraction, which can be detected by decreased StO_2 by NIRS [22, 23]. If the increased oxygen extraction cannot maintain aerobic metabolism, the production of lactic acidosis will temporarily compensate for energy failure, but prolonged tissue ischemic hypoxia results in end-organ dysfunction and cellular damage [24].

Physiologic determinants of cardiovascular performance

Preload

It refers to the volume of blood present in the ventricle at end-diastole, and it reflects the blood from venous return added to the residual blood in the ventricle at the end of systole. Preload is dependent on three factors: the intravascular blood volume (about 80% is present in the venous compartment), diastolic compliance of the ventricle, and changes in pulmonary vascular resistance (PVR) which oppose venous return if increased above the physiologic levels [25, 26]. Low preload results from decreased vascular volume such as acute hemorrhage, excessive fluid losses occurring with conditions such as open gastroschisis, or third space losses in septic shock [27]. Increased PVR may also decrease the left heart preload by reducing the amount of blood returning to the left atrium from the lungs [28].

Afterload

It refers to the vascular resistance that the myocardium must overcome to move blood to either pulmonary or systemic circulation. In neonates, systemic afterload is affected by the systemic vascular tone, and it increases in arterial hypertension or volume overload [28].

Systolic myocardial performance

It is the intrinsic ability of the myocardium to contract. The poor myocardial performance or ineffective contraction against normal or even low SVR occurs in conditions such as transient myocardial ischemia seen in infants with hypoxic-ischemic encephalopathy (HIE), viral myocarditis, cardiomyopathy, and secondary to arrhythmias [29].

Heart rate

It determines together with stroke volume and cardiac output. As the heart rate increases, cardiac output is also increasing. However, in the presence of significant tachycardia, the filling time decreases and hence the stroke volume is reduced [16].

Persistence of the physiologic fetal shunts

Particularly in preterm infants, fetal shunt considerably affects cardiovascular performance by shifting systemic ventricular output or venous return to the pulmonary circulation through left to right ductus arteriosus or patent foramen ovale, causing pulmonary over-circulation and lung edema [30].

Normal vascular tone

It results from a balance between local vasoconstrictors such as thromboxane and vasodilators such as tissue nitric oxide regulated by nitric oxide synthetase (NOS). Low peripheral vascular resistance may result when this balance is disturbed. Clinical examples of lost balance include systemic inflammatory response syndrome (SIRS), neonatal sepsis, and necrotizing enterocolitis, where circulating cytokines with systemic-induced NOS lead to reduced SVR [28].

Physiology of blood pressure components

Diastolic blood pressure (DBP) is the baseline arterial pressure initiated by systolic heart performance and elastic recoil of the great arteries, then maintained by the vascular tone of the arterioles under many neuronal and humoral vasopressors, which are responsible for maintaining SVR. The SVR and blood volume in the arterial compartment are responsible for maintaining normal DBP [12]. Ejection of stroke volume is the direct function of the myocardial systolic performance which creates an increase of pressure from the baseline diastolic to the peak systolic; this is the pulse pressure. Systemic afterload directly affects myocardial systolic performance, so increased afterload may impair the myocardial systolic performance, particularly in preterm infants during the postnatal transition [14]. The stroke volume is also affected by two other essential components, such as end-diastolic ventricular volume or preload and the heart rate. The DBP and PP are relatively independent compared to SBP and MABP, the systolic pressure (SBP), which is the sum of both DBP and PP, and both define the MABP, which is the area under the curve, and it can be calculated in many different ways, e.g., 2/3 DBP + 1/3 SBP [1, 31, 32]. We provided the normative blood pressure values in supplemental Table 2.

Critical parameters for assessment of hemodynamics, oxygen delivery, and consumption:

1. Left ventricular output (LVO), expressed as ml/kg/min:

The gold standard for assessing systemic blood flow is by an invasive cardiac catheter which is not practical for routine clinical assessment. Still, the cardiac output can be measured by multiple non-invasive methods, like electrical cardiometry, which has been validated as surrogate markers for systemic blood flow [33]. Methods relying on echocardiography, Doppler technique, and electrical cardiometry have been validated in neonates with normative values [33, 34]. The most used method in clinical practice is measuring both left and right ventricular outputs by echocardiography and Doppler as follows: The velocity-time integral (VTI) of aortic flow is measured using pulse-wave Doppler from an apical five-chamber view by placing the sampling gate at the level of the hinge point of the aortic valve. Trans-aortic root diameter is measured at the hinge points of the valve from the parasternal long-axis view in the 2D image. LVO can be then calculated as (Ao CSA × VTI × heart rate) / weight in kg, where Ao CSA = cross-sectional area of the aortic valve, the normative values of LVO have been validated in many references, and right ventricular output (RVO) can be calculated similarly [12]. This method is operator-dependent as it is affected by the accuracy of echo measurement of valvular cross-sectional area and Doppler assessment of VTI. Also, the presence and direction of shunts may significantly impact the calculated values. For this reason, it is important to consider RVO as a surrogate marker of systemic blood flow in the presence of hemodynamically significant PDA [12, 14]. The normal LVO in stable preterm infants > 29 weeks at birth is a mean of 230 (with 10th and 90th percentiles of 174–321) ml/kg/min [12].

2. Systemic vascular resistance can be measured invasively by either thermodilution or through an aortic catheter by using diastolic flow time constant as a surrogate marker [35, 36]. SVR index can also be measured by electrical cardiometry, as published by Boet et al. [33]. It can also be calculated by dividing the LVO by MABP-CVP; the results should be considered an estimated value, not the absolute SVR. The normal SVR in the stable preterm infant has been published as a mean of 192 (with 10th and 90th percentile of 149–246) mmHg/L/kg/min [12].

3. Monitoring of tissue oxygenation:

Providing sufficient oxygen to the tissues is the primary goal of maintaining normal hemodynamics. Early prediction of impaired oxygen delivery might prevent irreversible shock before proceeding to significant hypoxia and ending with anaerobic metabolism [12, 24]. This prediction requires calculating the difference between oxygen delivery and oxygen consumption. To accurately measure these parameters, we need an invasive arterial catheter and pulmonary arterial catheter to accurately measure both systemic oxygen saturation and mixed venous saturation to calculate body tissue oxygen extraction; however, this technique has been used in adult intensive care units for a long time, but most practitioners are currently shifting to the non-invasive assessment of tissue oxygen extraction [11, 37]. Arterial oxygen saturation (SpO_2) can be monitored by a pulse oximeter and tissue oxygen saturation StO_2 by NIRS, and fractional oxygen extraction FOE calculated as the ratio between SpO_2 and StO_2 [12].

Calculation of DO_2:

$DO_2 = LVO \times \text{oxygen content} = LVO\ (\text{ml/kg/min}) \times 1.39 \times Hb\ (\text{g/ml}) \times SpO_2$ (expressed as a fraction)

Right ventricle output should be used in cases of a hemodynamically significant patent ductus arteriosus (HSPDA) for a more accurate representation of systemic blood flow as

LVO, in this case, is more representative of the pulmonary over-circulation [38].

FOE calculated as = $(SpO_2 - StO_2) / SpO_2$ (all expressed as fractions)

VO_2 calculation:

Since FOE = VO_2 / DO_2, then organ-specific VO_2 (ml of oxygen kg/min) = systemic $DO_2 \times$ organ-specific FOE [12].

Elsayed et al. [12] published the centile values for end-organ oxygen indices in stable non-ventilated preterm infants with gestational age 30 ± 3 weeks as follows:

1. The mean of the cerebral tissue oxygen saturation (ScrO2) is 76% (with 10th and 90th percentile of 69–81%), and cerebral FOE is 0.23 (with 10th and 90th percentile of 0.14–0.29).
2. The mean of the mesenteric oxygen saturation (SmsO2) is 74% (with 10th and 90th percentile of 68–79%), and mesenteric FOE is 0.22 (with 10th and 90th percentile of 0.19–0.27).
3. The mean of renal oxygen saturation (SrnO2) is 79% (with 10th and 90th percentile of 73–88%), and renal FOE is 0.2 (with 10th and 90th percentile of 0.13–0.24).
4. The mean of total body oxygen delivery is 32.5 ml/kg/min (with 10th and 90th percentile of 22–42 ml/kg/min).

4. Other clinical parameters:

Other clinical parameters are essential but limited if interpreted in isolation from other hemodynamic components, including urine output (UOP), metabolic acidosis, perfusion index, heart rate variability, perfusion pressure (MAP-CVP), and superior vena cava flow (SVCF) [39–42]. Combination of multiple parameters has been shown higher predictability to end-organ hypoperfusion and subsequent hypoxia compared to isolated parameters [5]. Figure 2 demonstrates the expected abnormal trends of different hemodynamic parameters according to the underlying category of hemodynamic instability.

Categorized evaluation and management of hemodynamic instability

Category I, hemodynamic instability due to vasodilatory physiology

Many diseases and factors may decrease SVR and cause hemodynamic instability manifested as vasodilatory physiology, which might progress or decompensate to shock. This is the most common cause of shock in the neonatal age group. It is commonly expected in neonatal septicemia or systemic inflammatory response syndrome to circulating cytokines; it is also the common mechanism of hemodynamic instability in preterm infants beyond postnatal transition (late-onset hemodynamic instability) [24]. Vasodilatory physiology might be associated with hypoxemia secondary to hypoxemic respiratory failure, pulmonary hypertension, or congenital heart diseases [6]. It is also reported in metabolic acidosis. Vasodilatory physiology could be iatrogenic secondary to vasodilator medications, e.g., anesthesia, milrinone, and opioids [43]. The DBP decreases below the baseline average level or trending down over time as shown on the monitor trends; or as represented on BP histograms, pulse pressure (PP) usually stays normal, SBP and MABP decrease secondary to decrease in DBP, and tachycardia is commonly associated [24].

The systolic cardiac functions are normal or hyperdynamic, the calculated SVR is low, and oliguria or decrease in urine output < 1 ml/kg/h for at least 12 h beyond the first 12 h after birth is also common. An increase in end-organ oxygen extraction measured by NIRS is a sign of compromised autoregulation and low oxygen delivery, and if increased extraction reached the maximum capacity, then lactic acidosis is a late sign before progression to end-organ dysfunction [24].

Management should be directed to treat the underlying etiology, e.g., septic shock, and with an appropriate dose of vasopressor to maintain both vascular resistance and oxygen delivery, norepinephrine is commonly used as a vasopressor; alternatively, epinephrine can be used at a starting dose of 0.1 μg/kg/min, vasopressin or its analogue terlipressin can also be considered, and hydrocortisone may also increase receptor sensitivity to circulating catecholamines, a summary of mechanism of action and the indication of different cardiovascular drugs are demonstrated in Table 1 [44].

Category II, hemodynamics instability due to vasoconstrictive physiology

This category is characterized as a state of relatively high afterload with failure of myocardial systolic performance against SVR; it usually happens with a sudden increase of SVR or with relatively immature myocardium [28]. The most common causes in neonates are a premature infant with failure of postnatal circulatory adaptation, hypoxic-ischemic encephalopathy, post-PDA ligation cardiovascular compromise, and post arteriovenous malformation (AVM) embolization, and it can also be associated with pulmonary hypertension [31, 32]. The DBP is normal to high or trending higher than the baseline; the PP is narrow or below the baseline level, low SBP, and normal MABP. This category is commonly misdiagnosed if the neonatal team relies solely on MABP for monitoring hemodynamic instability [32]. The cardiac systolic performance is usually impaired, and the calculated SVR is high [24]. This condition could be complicated with oliguria; lactic acidosis and NIRS assessment are similar to category I [2].

Table 1 The mechanism of action, pharmacologic, and physiologic characteristics of the commonly used cardiovascular medications in neonatal age group. Although doses of all drugs are variable according to the severity and the physiologic category of shock, and all drugs should be titrated cautiously as per desired effect, but if undesired effects occur or the case is unresponsive to the selected medication, then an advice from a neonatologist or pediatric intensivist expert in hemodynamics should be considered. The impact of most of these drugs on brain development in preterm infants is still unknown, but at least the impact of dopamine—which still the most used drug—is known to be negative on the brain blood flow and cerebral autoregulation, so titration of doses of these drugs should be considered cautiously and guided by the physiologic algorithm as explained in this article [84]. Unresponsiveness may be related to wrong selection of a drug that does not fit the pathophysiology, coexisting severe acidosis, coexisting suprarenal dysfunction, or overlap of multiple physiologic mechanisms, e.g., vasodilator physiology and hypovolemic shock secondary to sepsis. Abbreviations: *cAMP*, cyclic adenosine monophosphate; *SVR*, systemic vascular resistance; *PVR*, pulmonary vascular resistance

Cardiovascular drugs	Mechanism of action	Physiologic effects on:				Half-life	Side effects	Recommended indications as per the underlying pathophysiology	Dosage
		Myocardium	Systemic vasoactivity	Pulmonary vasoactivity	Systemic and end-organ blood flow				
Dopamine (Natural catecholamine precursor to norepinephrine) [66, 67]	Adrenoreceptor stimulation and cAMP	Inotropy at dose of 5–10 µg/kg/min (β1 and β2)	Increase SVR (α1) at 10–20 µg/kg/min	Increase PVR at 10–20 µg/kg/min	Stimulates dopaminergic receptors in the coronary, renal, and mesenteric systems at 2–4 µg/kg/min	2–5 min	May worsen pulmonary hypertension May impair brain autoregulation in preterm infants May increase myocardial oxygen consumption	Dopamine is a non-specific medication with potential negative impact on wide range of organs including brain and heart; its use should be limited in our targeted physiologic approach	The negative impact on other organs is expected in dose > 10 µg/kg/min
Dobutamine (Synthetic catecholamine) [68, 69]	Adrenoreceptor stimulation and cAMP Mainly β1 and β2 effects with some α1	Dose-related inotropic and chronotropic	Peripheral vasodilation	Unknown	Better than dopamine in improving blood flow, no proven effect on cerebral blood flow	2–5 min	High dose may worsen diastolic filling, if used with normal myocardial contractility	Best indicated in cardiogenic shock, and vasoconstrictive physiology	Dose ranges as per desired effect
Epinephrine [45, 70]	Adrenoreceptor stimulation and cAMP	Inotropic at dose 0.01 to 0.1 µg/kg/min	Peripheral vasodilation at low doses Peripheral vasoconstriction at > 0.1 µg/kg/min	Unknown	Unknown	2–5 min	Increase lactate and hyperglycemia due to β2-adrenoreceptors in the liver and skeletal muscle	Inotropic effect in cardiogenic shock Vasopressor effect with higher doses in vasodilatory physiology	Dose ranges as per desired effect
Norepinephrine naturally occurring sympathomimetic amine [71, 72]	Adrenoreceptor stimulation and cAMP strong α agonist	Weak β agonist	Potent vasoconstrictor	Pulmonary vasodilation	Unknown	2–5 min	Tachycardia	Effective in refractory vasodilator physiology And vasodilatory shock with pulmonary hypertension	Dose ranges as per desired effect

Table 1 (continued)

Cardiovascular drugs	Mechanism of action	Physiologic effects on:				Half-life	Side effects	Recommended indications as per the underlying pathophysiology	Dosage
		Myocardium	Systemic vasoactivity	Pulmonary vasoactivity	Systemic and end-organ blood flow				
Vasopressin naturally occurring hormone [62, 73, 74]	V1 (vascular), V2 (renal), V3 (CNS)	Negative inotropic effect	Potent vasoconstrictor	Pulmonary vasodilator	Renal and coronary vasodilator	10–30 min	Hyponatremia May impact myocardial performance in higher doses Unknown long-term safety in preterm infants	Effective in refractory vasodilatory physiology And vasodilatory shock with pulmonary hypertension Vasopressin has been shown to increase SVR, and urine output in patients with vasodilatory shock and unresponsiveness to catecholamines	Dose ranges as per desired effect 0.0003 to 0.0012 IU/kg/min
Terlipressin [40, 75]	Long-acting form of vasopressin	Negative inotropic effect	Potent vasoconstrictor	Pulmonary vasodilator	Renal and coronary vasodilator	6 h	Similar to vasopressin	Long-acting form of vasopressin has been reported to reverse vasodilatory shock	0.04 mg/kg followed by 0.02–0.04 mg/kg every 4–6 h
Milrinone [76]	Phosphodiesterase-III inhibition and cAMP	Inotropy (enhances myocardial contractility) and lusitropy (promotes myocardial relaxation)	Systemic vasodilator	Pulmonary vasodilator	Unknown	4 h in term infant 10 h in preterm infants	Hypotension It should be used with caution in very preterm, renal failure, and HIE due to long half-life and impaired renal excretion	Left and right myocardial dysfunction, pulmonary hypertension refractory to inhaled nitric oxide Vasoconstrictor physiology Post-PDA ligation low cardiac output syndrome	Dose ranges as per desired effect 0.3 to 0.9 µg/kg/min

Table 1 (continued)

Cardiovascular drugs	Mechanism of action	Physiologic effects on:				Half-life	Side effects	Recommended indications as per the underlying pathophysiology	Dosage
		Myocardium	Systemic vasoactivity	Pulmonary vasoactivity	Systemic and end-organ blood flow				
Levosimendan [77, 78]	Calcium sensitization	Inotropy	Systemic vasodilator	Pulmonary vasodilator (Limited evidence)	Unknown	60 min	Hypotension	Limited evidence in neonates Postoperative myocardial dysfunction in CHD	Infusion: 0.05 to 0.2 µg/kg/min
Volume expansion [46, 79, 80]	Increase cardiac output	Improve performance only if impaired performance is secondary to underfilling	-	-	Transient increase in blood flow	Variable	Excessive volume expansion in preterm babies may be associated with higher mortality No sustainable significant effect on cerebral blood flow May cause volume overload on euvolemic infants	Indicated with evidence of volume depletion. Fluid volume > 20 ml during the first week of life may increase incidence of IVH and BPD, unless guided by echocardiography	> 20 ml/kg should be given with caution
Hydrocortisone [81–83]	Increase number and sensitization of adrenoreceptors to circulating catecholamines	No effect	Increase PVR	Unknown	Unknown	1.7 h	Increased risk of gastrointestinal perforation, particularly when hydrocortisone is used in conjunction with indomethacin	Better than placebo in refractory hypotension Should not be used routinely because of unknown long-term safety	Variable, dose ranges as per desired effect May start at 2 mg/kg as loading then 0.5 mg/kg/dose q 6–8 h

Management should be directed to treat the underlying etiology together with an appropriate dose of inotrope without systemic vasoconstrictive effect, but with potential vasodilator effect, so the logical selection is dobutamine after a bolus of volume expander. Lusitropic with inodilator effect like milrinone or levosimendan (insufficient data for use in neonatal population) might be considered to decrease both SVR and hence afterload; refer to Table 1 for more details.

Category III, cardiogenic shock

This category is characterized as a state of circulatory failure due to impaired myocardial systolic performance as a primary mechanism with normal or low SVR. The most common causes in neonates are hypoxic-ischemic encephalopathy, cardiac arrhythmias, and myocarditis [16, 29]. All BP components are low, including narrow pulse pressure. The cardiac systolic performance is impaired, and the calculated SVR is normal or low [16]. This condition could be complicated with oliguria; lactic acidosis and NIRS assessment are similar to category I [1].

Management should be directed to treat the underlying etiology and an appropriate dose of inotropic with a vasopressor effect like epinephrine after a bolus of volume expander. Refer to Table 1 for more details [45]. In refractory postnatal shock due to LV dysfunction, prostaglandin might be considered to promote a temporary shift of blood flow from pulmonary to the systemic circulation; this mechanism is similar to augmenting systemic blood flow in coarctation of the aorta [16].

Category IV, left to right shunt physiology

It is a state of decreased blood flow in diastole due to blood shunts through PDA from the aorta to the pulmonary artery, mainly in preterm infants [46]. It is diagnosed primarily by echocardiography and characterized later by low DBP, wide pulse pressure, and low MABP. Besides PDA diameter, the parameters reflecting left heart volume overload and pulmonary over-circulation should be assessed, including the ratio of left atrial diameter to aortic root diameter (LA/Ao): measured from the short-axis parasternal view at the level of the aortic valve, using m-mode. The ratio of mitral inflow E wave peak velocity to A wave peak velocity: interrogation of transmitral valve flow using pulse-wave Doppler at the tips of the mitral valve leaflets from an apical 4-chamber view [47]. LVO, left ventricular end-diastolic dimension (LVEDD): measured at the tips of the mitral valve leaflet using m-mode from a parasternal long-axis view of the left ventricle [48]. Biochemical markers can help together with echocardiographic evaluation; one of them is a brain-type natriuretic peptide (BNP) secreted by ventricular myocytes in response to volume overload of the ventricles [47]. BNP measurements are reported useful for evaluating PDA significance in preterm infants and its impact on pulmonary blood flow [49]. Parameters of systemic hypoperfusion: should include diastolic flow in descending aorta distal to PDA, celiac or mesenteric, renal, and middle or anterior cerebral arteries: Absent or retrograde (negative) diastolic flow is considered as an indicator of significant PDA shunt, suggestive of diastolic "steal" from the systemic circulation [50]. Assessment of regional systemic blood flow by NIRS can also be used as a model of integrated evaluation with echocardiography, and it has been validated in literature before and after medical and surgical interventions [23]. Management: when and who require either medical treatment or invasive intervention is still an area of controversy [1].

Category V, volume depletion

Depletion of intravascular volume, or underfilling of the heart due to excessive losses either outside the body, e.g., high urine output; or gastrointestinal losses, or third space losses secondary to capillary leak syndrome, which could be due to infection or systemic inflammatory process [51]. Venous return could be depleted in severe pulmonary hypertension or with applying high mean airway pressure. Restricted heart filling with low cardiac output could be secondary to myocardial hypertrophy, either idiopathic or with infant of diabetic mother [16]. The use of echocardiography to evaluate volume status in a critically ill pediatric patient is recommended, however, with the recognition that preload assessment in neonates and infants can be limited in the context of mechanical ventilation. Assessment of end-diastolic volume in the 4-chamber view and parasternal by m-mode is also useful in more accurate determination of the need for fluid resuscitation. Pulse-wave Doppler of the left ventricular outflow tract in the 5-chamber apical view has been utilized to predict hemodynamic responsiveness in critically ill patients. Variation in peak VTI of $>15\%$ was consistent with predicting volume responsiveness [26, 52]. Underfilling of the heart can be semi-quantitatively assessed by measuring inferior vena-cava (IVC) variation of diameter during the cardiorespiratory cycle. During this evaluation, the eventual presence of pulmonary hypertension or high abdominal and thoracic pressures should be considered. In non-ventilated children with normal right atrium pressure, IVC collapse during inspiration is $>50\%$. A dilated IVC with collapsibility $<50\%$ could be a sign of increased right atrial pressure (above 10 mmHg) [26]. Management should be directed to treat the underlying cause and fluid resuscitation until the intravascular volume is restored, inotropic support should be avoided in this category, but vasopressor may be used if low BP is unresponsive to volume expanders, and Fig. 2 demonstrates the changes in different hemodynamic parameters in the five categories of hemodynamic instability

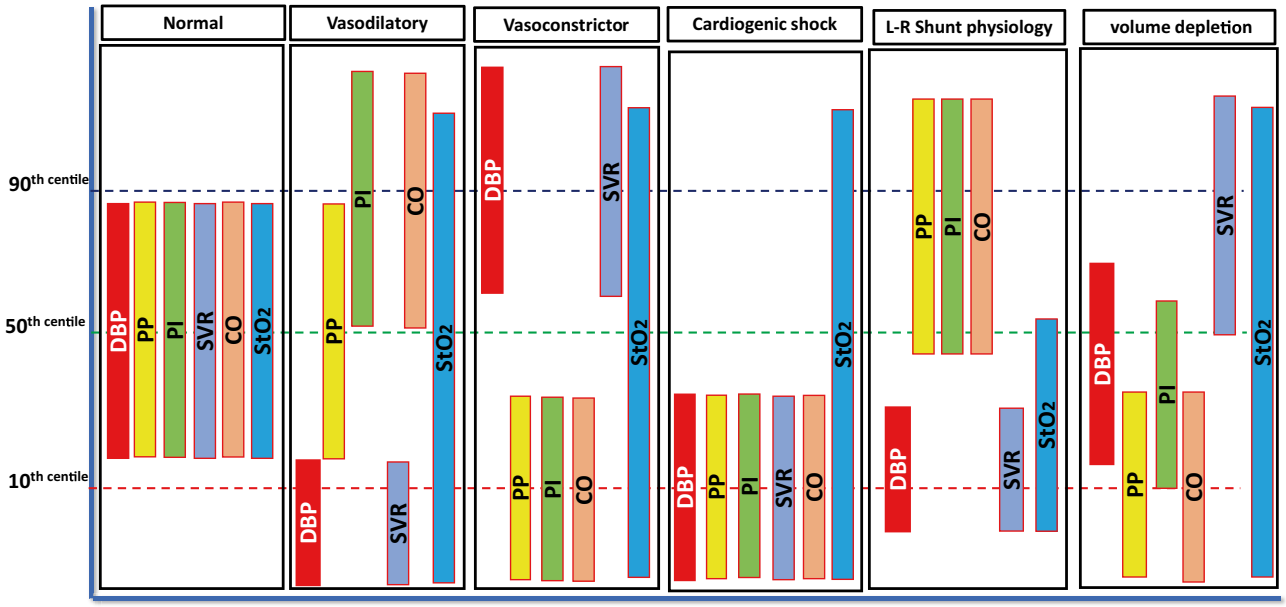

Fig. 2 The parameters that can be used to differentiate different categories of hemodynamic instability are DBP, diastolic blood pressure; PP, pulse pressure; PI, perfusion index; SVR, systemic vascular resistance; CO, cardiac output; StO_2, tissue oxygen saturation. All parameters are expected to be physiologically fluctuating within 10th and 90th of the normative values, and fluctuation of parameters beyond the normative values occurs in hemodynamic instability but they are trending low or high according to the underlying mechanism as in the illustrated figure

[16]. The recommended empiric volume should not exceed 20 ml/kg during the first week of life, as it may increase the risk of IVH or lung injury, and up to 30 ml/kg after that, an extra volume may be considered as guided by echocardiography and with evidence of volume losses either third space losses of outside the body [27]. There is no clear evidence that supports colloid over crystalloids in neonates [53].

Management of hemodynamic instability in specific disease conditions

Preterm infant

Postnatal cardiovascular adaptation is a complex transition from parallel fetal circulation circuits to sequential postnatal pulmonary and systemic circulation. Once the lung starts to function for gas exchange and PVR decreases with an increase in SVR, followed by gradual closure of fetal shunts in the term infants [30]. But in preterm infants, these shunts frequently remain open and complicate already compromised hemodynamics and autoregulatory mechanisms [52]. Systemic vascular resistance increases after removal of the low resistance placental circulation, a change that is usually well-tolerated in term and late preterm infants. In very premature infants, this change in SVR can result in impaired cardiac output because it increases the afterload of the myocardium. Systemic flow can be further compromised if the ductus arteriosus remains open, allowing shunting from left to right, shifting more blood away from systemic flow to recirculate within the pulmonary circulation [16]. Systemic compromise can be more complex in the presence of poor autoregulation of cerebral blood flow during the first 12–36 h after birth [30]. Autoregulation gradually improves over the first 3 days of life [54]. Early postnatal hemodynamic instability might be commonly presented as vasoconstrictive or less commonly as vasodilatory physiology; detailed assessment of the hemodynamics parameters as explained is essential for the logical selection of the cardiovascular support, as significant hemodynamic instability might result in intraventricular hemorrhage (IVH) [55]. Delayed cord clamping has been proven to decrease the requirement of postnatal cardiovascular support [56].

Septic shock

Hemodynamic instability and shock might follow systemic infection in neonates; this is usually through the direct effect of bacterial toxins or release of inflammatory mediators into the circulation, affecting mainly vasoactivity, and it is generally vasodilatory, but it can be vasoconstrictive too [27, 40]. These inflammatory processes might also affect capillary bed integrity, causing capillary leak and loss of vascular volume [27, 57]. The cellular dysfunction might occur directly secondary to lipopolysaccharides and bacterial toxins without shock [58]. The management then should be directed according to the underlying pathophysiological mechanism.

Hypoxic-ischemic encephalopathy

Perinatal hypoxic-ischemic injury results in myocardial ischemia in about one-third of the cases, but the injury is usually transient. This injury might result in impaired systolic performance, and therapeutic hypothermia may result in systemic vasoconstriction, which increases afterload and impact systemic blood flow [29]. The expected mechanism then is vasoconstrictive physiology, so increased DBP and hence normal MABP in this situation might mask the hemodynamic instability, and PP is vital to assess in all cases with HIE. Additionally, hypoxia–ischemia is associated with other pathophysiologic mechanisms of hemodynamic instability, including vasodilatory physiology, particularity with significant acidosis, excessive use of sedation or anticonvulsant drugs, pulmonary hypertension, and adrenal insufficiency [59]. Management should be considered after careful assessment of the underlying pathophysiologic mechanism, dobutamine is the logical choice in vasoconstrictive physiology, and milrinone is better to be avoided due to relatively long half-life and an expected impaired renal clearance. Vasopressor is the logical choice in vasodilatory physiology, either norepinephrine, vasopressin, or terlipressin, and cautious use of volume expanders, only if there is evidence of heart underfilling. Steroids can be considered when there is evidence of suprarenal dysfunction or in resistant cases [29].

Pulmonary hypertension

Systemic blood flow might be compromised in pulmonary hypertension secondary to several mechanisms, increased PVR may limit left heart preload, dilated right ventricle may compress the left ventricle, decreasing the end-diastolic filling volume, also right ventricular failure is associated with low cardiac output, and associated hypoxia may decrease SVR and cause vasodilatory shock [60]. Management should be considered according to the underlying mechanism; milrinone is a useful drug if pulmonary hypertension is associated with RV dysfunction; it is also an inodilator, so it should be used cautiously in the presence of low SVR. If pulmonary hypertension is associated with low SVR, then norepinephrine, vasopressin, or terlipressin may be used [61, 62].

Infant of diabetic mother

Infants of diabetic mothers have an increased risk of pulmonary hypertension and hypertrophic cardiomyopathy; septal hypertrophy may cause diastolic dysfunction and may negatively impact LV filling [16]. Augmenting preload by giving

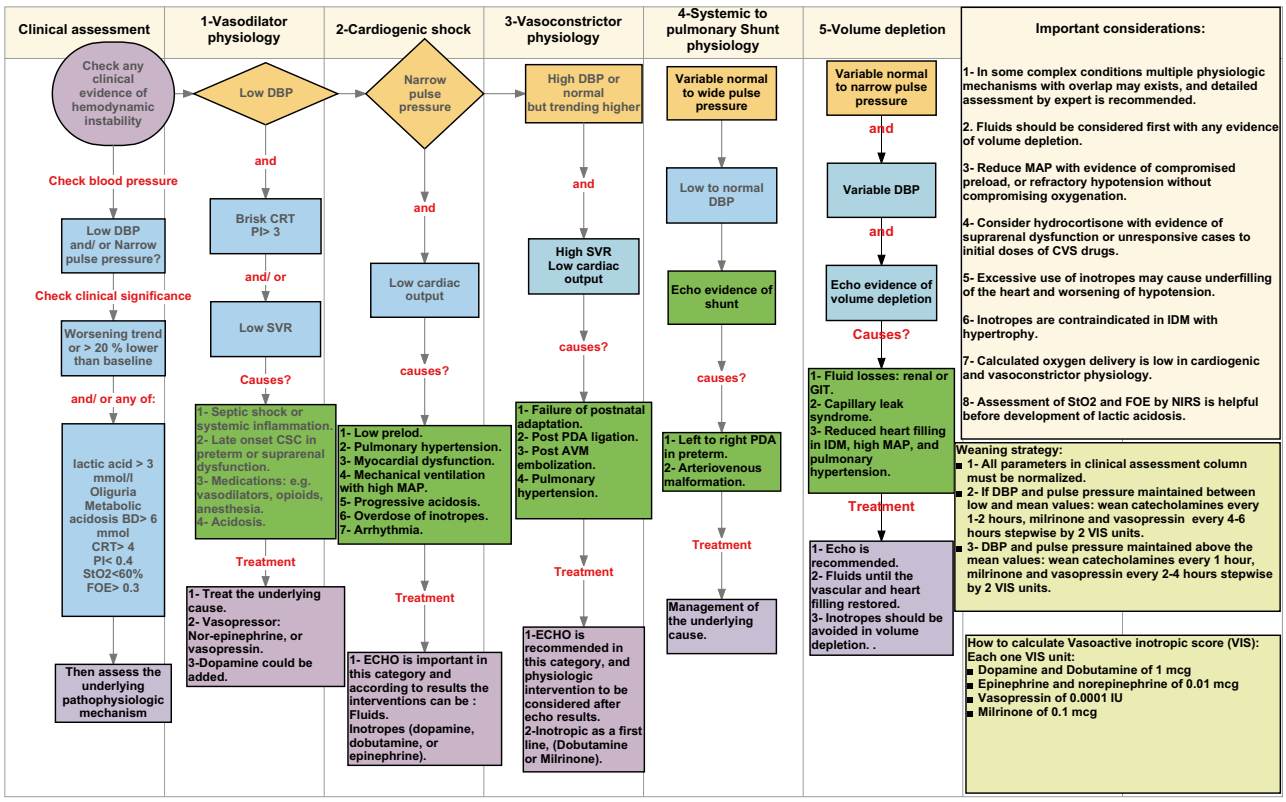

Fig. 3 Algorithm to guide integrated physiologic management of neonatal hemodynamic instability; CRT, capillary refile time; PI, perfusion index; StO_2, tissue oxygen saturation; HSPDA, hemodynamically significant PDA; GIT, gastrointestinal tract; VIS, vasoactive inotropic score

adequate volume expanders is the main line of managing associated hemodynamic instability; lowering heart rate by B blockers might be considered in resistant cases. Inotropes should not be used as they may further compromise diastolic filling. Vasopressors may augment preload and improve associated low systemic BP [63].

Post-PDA ligation

After ligation of a hemodynamically significant PDA, a rapid change in both preload and afterload in neonates with high volume shunt, PDA ligation is followed by rapid reduction of left atrial filling pressure together with a compensatory increase in systemic afterload and the resultant increase in LV systolic wall stress leads to LV myocardial dysfunction [14]. The clinical decompensation usually occurs in 6–12 h post-PDA ligation; this phenomenon is clinically presented with narrow PP, normal to high DBP, increased FOE, and lactic acidosis if not treated. Echocardiography assessment is recommended post-PDA ligation; if low LVO is associated, considering volume expanders with dobutamine or milrinone is recommended [64].

Challenges in hemodynamic management

Some case scenarios might have multiple underlying pathophysiologic mechanisms, for instance, a preterm infant with vasodilatory physiology and significant shunt at the same time, or an infant with pulmonary hypertension and low systemic blood flow due to left ventricular dysfunction; in these challenging conditions, it is essential to prioritize the lines of treatment, and it is better to be directed by an expert in neonatal hemodynamics. Figure 3 is a comprehensive algorithm to guide management of neonatal hemodynamics instability, and we included a quick approach to the five categories and the weaning strategies of the cardiovascular medications in this algorithm [1, 3]. Hemodynamic instability might be related to worsening of other organ performance, e.g., hypoxemic respiratory failure secondary to parenchymal lung diseases with the resultant impact of pulmonary hypertension and mechanical ventilation on hemodynamics, and the other example is loss of blood volume, and anemia secondary to intracranial or abdominal bleeding, this complexity of multiorgan failure is highlighting the importance of integrating other point of care ultrasound (POCUS) applications (lung, cranial, and abdominal ultrasound) to delineate any other undetectable pathologies in other organs as recommended in the international consensus on POCUS [65].

The future directions

The researchers are currently working on understanding autoregulation, earlier prediction of shock, and data acquisition to develop innovative machine learning that can give a predictive clinical score which can then be accessed by the clinical team in real-time and respond accordingly. The possibility of developing a clinical decision support system to support the clinicians for critical decision-making and a physiologic-based approach in management.

Conclusion

The management of hemodynamic instability is challenging due to the complexity of the pathophysiology; integrating different monitoring techniques is essential to understand the underlying pathophysiologic mechanisms and formulate a physiologic-based medical recommendation and approach; more research is still needed to validate this physiologic approach.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00431-021-04307-5.

Authors' contributions YE and MA conceptualized the article. YE and MA conducted the background literature search. YE devised the manuscript, and both authors agree to the formatting and contents.

Funding No funding was received.

Availability of data and material Yes.

Code availability N/A.

Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate N/A.

Consent for publication Yes.

Conflict of interest The authors declare no competing interests.

References

1. Burton VJ, Gerner G, Cristofalo E, Chung S en, Jennings JM, Parkinson C et al (2015) A pilot cohort study of cerebral autoregulation and 2-year neurodevelopmental outcomes in neonates with hypoxic-ischemic encephalopathy who received therapeutic hypothermia. BMC Neurol 15(1):1–13

2. Chock VY, Ramamoorthy C, Van Meurs KP (2012) Cerebral autoregulation in neonates with a hemodynamically significant patent ductus arteriosus. J Pediatr [Internet]. [cited 2012 May 5] 160(6):936–42. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0022347611012285
3. Eriksen VR, Hahn GH, Greisen G (2015) Cerebral autoregulation in the preterm newborn using near-infrared spectroscopy: a comparison of time-domain and frequency-domain analyses. J Biomed Opt 20(3):037009
4. Votava-Smith JK, Statile CJ, Taylor MD, King EC, Pratt JM, Nelson DP et al (2017) Impaired cerebral autoregulation in preoperative newborn infants with congenital heart disease. J Thorac Cardiovasc Surg [Internet] 154(3):1038–44. Available from: https://doi.org/10.1016/j.jtcvs.2017.05.045
5. Allen BW, Stamler JS, Piantadosi CA (2009) Hemoglobin, nitric oxide and molecular mechanisms of hypoxic vasodilation. Trends Mol Med 15(10):452–60
6. Hickok RL, Spaeder MC, Berger JT, Schuette JJ, Klugman D (2016) Postoperative abdominal NIRS values predict low cardiac output syndrome in neonates. World J Pediatr Congenit Hear Surg [Internet] 7(2):180–4. Available from: https://doi.org/10.1177/2150135115618939
7. Chock VY, Kwon SH, Ambalavanan N, Batton B, Nelin LD, Chalak LF et al (2020) Cerebral oxygenation and autoregulation in preterm infants (early NIRS study). J Pediatr 227:94-100.e1
8. Bozzetti V, Paterlini G, Meroni V, DeLorenzo P, Gazzolo D, Van Bel F et al (2012) Evaluation of splanchnic oximetry, Doppler flow velocimetry in the superior mesenteric artery and feeding tolerance in very low birth weight IUGR and non-IUGR infants receiving bolus versus continuous enteral nutrition. BMC Pediatr [Internet] 12(1):106. Available from: BMC Pediatrics
9. Martini S, Corvaglia L (2018) Splanchnic NIRS monitoring in neonatal care: rationale, current applications and future perspectives. J Perinatol [Internet] 1–13. Available from: https://doi.org/10.1038/s41372-018-0075-1
10. Verhagen EA, Hummel LA, Bos AF, Kooi EMW (2014) Near-infrared spectroscopy to detect absence of cerebrovascular autoregulation in preterm infants. Clin Neurophysiol [Internet] 125(1):47–52. Available from: http://www.clinph-journal.com/article/S1388245713009280/fulltext
11. Tortoriello TA, Stayer SA, Mott AR, McKenzie ED, Fraser CD, Andropoulos DB et al (2005) A noninvasive estimation of mixed venous oxygen saturation using near-infrared spectroscopy by cerebral oximetry in pediatric cardiac surgery patients. Paediatr Anaesth 15(6):495–503
12. Elsayed YN, Louis D, Ali YH, Amer R, Seshia MM, Patrick J et al (2018) Integrated evaluation of hemodynamics: a novel approach for the assessment and management of preterm infants with compromised systemic circulation. J Perinatol (1)
13. Dempsey EM, Barrington KJ, Marlow N, O'Donnell CPF, Miletin J, Naulaers G et al (2021) Hypotension in preterm infants (HIP) randomised trial. Arch Dis Child Fetal Neonatal Ed
14. Elsayed YN, Amer R, Seshia MM (2017) The impact of integrated evaluation of hemodynamics using targeted neonatal echocardiography with indices of tissue oxygenation: a new approach. J Perinatol
15. Seear M, Wensley D, MacNab A (1993) Oxygen consumption-oxygen delivery relationship in children. J Pediatr 123(2):208–214
16. Giesinger RE, McNamara PJ (2016) Hemodynamic instability in the critically ill neonate: an approach to cardiovascular support based on disease pathophysiology. Semin Perinatol [Internet] 40(3):174–88. Available from: https://doi.org/10.1053/j.semperi.2015.12.005
17. Barrington KJ (2008) Hypotension and shock in the preterm infant. Semin Fetal Neonatal Med 2008:16–23
18. Alderliesten T, Lemmers PMA, van Haastert IC, de Vries LS, Bonestroo HJC, Baerts W et al (2014) Hypotension in preterm neonates: low blood pressure alone does not affect neurodevelopmental outcome. J Pediatr [Internet] 164(5):986–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24484771
19. Parker MM (2014) Hemodynamics in preterm neonates with septic shock. Pediatr Crit Care Med [Internet] 15:494–5. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00130478-201406000-00015
20. Perera P, Mailhot T, Riley D, Mandavia D (2010) The RUSH exam: rapid ultrasound in shock in the evaluation of the critically lll. Emerg Med Clin North Am [Internet] 28(1):29–56. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0733862709001175
21. Thewissen L, Caicedo A, Lemmers P, Van BF, Van HS, Naulaers G (2018) Measuring near-infrared spectroscopy derived cerebral autoregulation in neonates: from research tool toward bedside multimodal monitoring. Front Pediatr 6(May):1–21
22. Tweddell JS, Ghanayem NS, Hoffman GM (2010) Pro: NIRS is "standard of care" for postoperative management. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu [Internet] 13(1):44–50. Available from: https://doi.org/10.1053/j.pcsu.2010.02.008
23. Sood BG, McLaughlin K, Cortez J (2015) Near-infrared spectroscopy: applications in neonates. Semin Fetal Neonatal Med [Internet] 20(3):164–72. Available from: https://doi.org/10.1016/j.siny.2015.03.008
24. Amer R, Kalash R, Seshia MM, Elsayed YN (2017) The impact of integrated evaluation of hemodynamics on management of preterm infants with late-onset compromised systemic circulation. Am J Perinatol
25. van Vonderen JJ, Roest AW, Siew ML, Walther FJ, Hooper SB, Te Pas AB (2014) Measuring physiological changes during the transition to life after birth. Neonatology [Internet]. [cited 2014 Mar 24] 105(3):230–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24504011
26. Singh Y (2017) Echocardiographic evaluation of hemodynamics in neonates and children. Front Pediatr 5(September):1–14
27. Wynn JL, Wong HR (2010) Pathophysiology and treatment of septic shock in neonates. Clin Perinatol [Internet] 37(2):439–79. Available from: https://doi.org/10.1016/j.clp.2010.04.002
28. Elsayed Y, Fraser D (2016) Integrated evaluation of neonatal hemodynamics program optimizing organ perfusion and performance in critically ill neonates, part 1 : understanding physiology of neonatal hemodynamics. Neonatal Netw 143–50
29. Giesinger RE, Bailey LJ, Deshpande P, McNamara PJ (2016) Hypoxic-ischemic encephalopathy and therapeutic hypothermia: the hemodynamic perspective. J Pediatr [Internet] 1–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27742125
30. Fraser D (2017) Patent ductus arteriosus in preterm infants, part 1 : understanding the pathophysiologic link between the patent ductus arteriosus and clinical complications. 36(5):265–72
31. Giesinger RE, Elsayed YN, Castaldo MP, McNamara PJ (2019) Targeted neonatal echocardiography-guided therapy in vein of galen aneurysmal malformation: a report of two cases with a review of physiology and approach to management. AJP Rep 9(2):E172–E176
32. Selim A, El Wahab AA, Salem H, Yahmadi MA, Al Aisary S, Malviya M et al (2020) Perioperative management of arteriovenous malformation guided by integrated evaluation of hemodynamics. Eur J Pediatr
33. Boet A, Jourdain G, Demontoux S, De Luca D (2016) Stroke volume and cardiac output evaluation by electrical cardiometry: accuracy and reference nomograms in hemodynamically stable preterm neonates. J Perinatol 36(9):748–752
34. Noori S, McCoy M, Anderson MP, Ramji F, Seri I (2014) Changes in cardiac function and cerebral blood flow in relation to peri/

intraventricular hemorrhage in extremely preterm infants. J Pediatr [Internet] 164(2):264–270.e3. Available from: http://linkinghub.elsevier.com/retrieve/pii/S002234761301216X
35. Jones P (1999) Haemodynamic measurements (continuous cardiac output and systemic vascular resistance) in critically ill patients: transoesophageal Doppler versus continuous thermodilution. Crit Care 1(1):33–37
36. Abbas AE, Fortuin FD, Patel B, Moreno CA, Schiller NB, Lester SJ (2004) Noninvasive measurement of systemic vascular resistance using Doppler echocardiography. J Am Soc Echocardiogr 17(8):834–838
37. Cerussi A, Van Woerkom R, Waffarn F, Tromberg B (2005) Noninvasive monitoring of red blood cell transfusion in very low birthweight infants using diffuse optical spectroscopy. J Biomed Opt [Internet] 10(5):051401. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16292938
38. Amer R, Elsayed YN, Graham MR, Sikarwar AS, Hinton M, Dakshinamurti S (2019) Effect of vasopressin on a porcine model of persistent pulmonary hypertension of the newborn. J of pediatr pulmonology (December 2018):319–32
39. Wynn JL, Wong HR (2010) Pathophysiology and treatment of septic shock in neonates. Clin Perinatol 37(2):439–479
40. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC et al (2017) American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. Crit Care Med 45:1061–1093
41. Limperopoulos C, Gauvreau KK, O'Leary H, Moore M, Bassan H, Eichenwald EC et al (2008) Cerebral hemodynamic changes during intensive care of preterm infants. Pediatrics [Internet] 122(5):e1006–13. Available from: https://pediatrics.aappublications.org/content/122/5/e1006/tab-e-letters. https://doi.org/10.1542/peds.2008-0768
42. Elsayed YFD (2016) Integrated evaluation of neonatal hemodynamics, part 2: systematic bedside assessment. Neonatal Netw 192–203
43. Dempsey E, Cabañas F, De Boode WP, Vrancken SL, Van Heijst AF (2018) Neonatal hemodynamics: from developmental physiology to comprehensive monitoring. Front Pediatr 687(6):1–15
44. Fortas F, Di Nardo M, Yousef N, Humbert M, De Luca D (2021) Life-threatening PPHN refractory to nitric oxide: proposal for a rational therapeutic algorithm. Eur J Pediatr 180(8):2379–2387
45. Manouchehri N, Bigam DL, Churchill T, Rayner D, Joynt C, Cheung PY (2013) A comparison of combination dopamine and epinephrine treatment with high-dose dopamine alone in asphyxiated newborn piglets after resuscitation. Pediatr Res [Internet]. [cited 2014 Mar 5] 73(4 Pt 1):435–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23344679
46. Bonestroo HJC, Lemmers PMA, Baerts W, van Bel F (2011) Effect of antihypotensive treatment on cerebral oxygenation of preterm infants without PDA. Pediatrics 128(6):e1502–10.
47. Elsayed Y, Seshia M, Soni R, Buffo I, Baier RJ (2016) Presymptomatic prediction of morbitidies in preterm infants with patent ductus arteriosus by targeted neonatal echocardiography and brain-type natriuretic peptide. J Pediatr Neonatal Individual Med 5(2):1–10
48. Farooqui MA, Elsayed YN, Jeyaraman MM, Dingwall O, Tagin M, Zarychanski R et al (2019) Pre-symptomatic targeted treatment of patent ductus arteriosus in preterm newborns: a systematic review and meta-analysis. J Neonatal Perinatal Med 12(1)
49. Elsayed Y, Seshia M, Baier RJ, Dakshinamurti S (2017) Serial serum brain-type natriuretic peptide (BNP) identifies compromised blood flow in infants with hemodynamically significant patent ductus arteriosus. J Pediatr Neonatal Individual Med 6(2):1–10
50. El-khuffash A, James AT, Corcoran JD, Dicker P, Franklin O, Elsayed YN et al (2015) A patent ductus arteriosus severity score predicts chronic lung disease or death before discharge. J Pediatr [Internet] 167(6):1354–1361.e2. Available from: https://doi.org/10.1016/j.jpeds.2015.09.028
51. Singh Y, Katheria AC, Vora F (2018) Advances in diagnosis and management of hemodynamic instability in neonatal shock. Front Pediatr 6(January):1–12
52. Singh Y, Tissot C (2018) Echocardiographic evaluation of transitional circulation for the neonatologists. Front Pediatr [Internet] 6(May):140. Available from: http://journal.frontiersin.org/article/https://doi.org/10.3389/fped.2018.00140/full
53. So KW, Fok TF, Ng PC, Wong WW, Cheung KL (1997) Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants. Arch Dis Child Fetal Neonatal Ed 76(1):46–49
54. Banerjee J, Leung TS, Aladangady N (2016) Cerebral blood flow and oximetry response to blood transfusion in relation to chronological age in preterm infants. Early Hum Dev [Internet] 97:1–8. Available from: https://doi.org/10.1016/j.earlhumdev.2015.10.017
55. Elsayed YN, Fraser D (2017) Patent ductus arteriosus in preterm infants, part 1: understanding the pathophysiologic link between the patent ductus arteriosus and clinical complications. Neonatal Netw 36(5)
56. Vesoulis ZA, Rhoades J, Muniyandi P, Conner S, Cahill AG, Mathur AM (2018) Delayed cord clamping and inotrope use in preterm infants. J Matern Neonatal Med [Internet] 31(10):1327–34. Available from: https://doi.org/10.1080/14767058.2017.1315663
57. Rivers EP, Kruse JA, Jacobsen G, Shah K, Loomba M, Otero R et al (2007) The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock*. Crit Care Med [Internet] 35(9):2016–24. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00003246-200709000-00002
58. Opal SM, Scannon PJ, Vincent JL, White M, Carroll SF, Palardy JE et al (1999) Relationship between plasma levels of lipopolysaccharide (LPS) and LPS-binding protein in patients with severe sepsis and septic shock. J Infect Dis 180(5):1584–1589
59. Giesinger RE, El Shahed AI, Castaldo MP, Breatnach CR, Chau V, Whyte HE et al (2019) Impaired right ventricular performance is associated with adverse outcome after hypoxic ischemic encephalopathy. Am J Respir Crit Care Med 200(10):1294–1305
60. Mohamed A, Nasef N, Shah V, Mcnamara PJ (2013) Pulmonary hypertension in neonates: case series. 1–7
61. Bidegain M, Greenberg R, Simmons C, Dang C, Cotten CM, Smith PB (2010) Vasopressin for refractory hypotension in extremely low birth weight infants. J Pediatr [Internet] 157(3):502–4. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0022347610003380
62. Mohamed A, Nasef N, Shah V, McNamara PJ (2014) Vasopressin as a rescue therapy for refractory pulmonary hypertension in neonates: case series. Pediatr Crit Care Med [Internet] 15(2):148–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24141655
63. Evans N, Kluckow M, Currie A (1998) Range of echocardiographic findings in term neonates with high oxygen requirements. Arch Dis Child Fetal Neonatal Ed [Internet] 78(2):F105–11. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1720754&tool=pmcentrez&rendertype=abstract
64. Sehgal A, Francis JV, James A, Mcnamara PJ (2010) Patent ductus arteriosus ligation and post-operative hemodynamic instability: case report and framework for enhanced neonatal care. Indian J Pediatr [Internet] 77(8):905–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20740386
65. Singh Y, Tissot C, Fraga MV, Yousef N, Cortes RG, Lopez J et al (2020) International evidence-based guidelines on point of care ultrasound (POCUS) for critically ill neonates and children issued by the POCUS Working Group of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). Crit Care 24(1):1–16
66. Sasidharan R, Gupta N, Chawla D (2019) Dopamine versus epinephrine for fluid-refractory septic shock in neonates. Eur J Pediatr 178(1):113–114

67. Gupta S, Donn SM (2014) Neonatal hypotension: dopamine or dobutamine? Vol. 19, Seminars Fetal Neonatal Med
68. Hallik M, Ilmoja ML, Standing JF, Soeorg H, Jalas T, Raidmäe M et al (2020) Population pharmacokinetics and pharmacodynamics of dobutamine in neonates on the first days of life. Br J Clin Pharmacol 86(2):318–328
69. Mahoney L, Shah G, Crook D, Rojas-Anaya H, Rabe H (2016) A literature review of the pharmacokinetics and pharmacodynamics of dobutamine in neonates. Pediatr Cardiol 37(1):14–23
70. Pryds O, Christensen NJ, Friis-Hansen B (1990) Increased cerebral blood flow and plasma epinephrine in hypoglycemic, preterm neonates. Pediatrics 85(2):172–176
71. Tourneux P, Rakza T, Bouissou A, Krim G, Storme L (2008) Pulmonary circulatory effects of norepinephrine in newborn infants with persistent pulmonary hypertension. J Pediatr [Internet] 153(3):345–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18534241
72. Rizk MY, Lapointe A, Lefebvre F, Barrington KJ (2018) Norepinephrine infusion improves haemodynamics in the preterm infants during septic shock. Acta Paediatr Int J Paediatr 107(3):408–413
73. Acker SN, Kinsella JP, Abman SH, Gien J (2014) Vasopressin improves hemodynamic status in infants with congenital diaphragmatic hernia. J Pediatr [Internet] 165(1):53–58.e1. Available from: https://doi.org/10.1016/j.jpeds.2014.03.059
74. Budniok T, ElSayed Y, Louis D (2020) Effect of vasopressin on systemic and pulmonary hemodynamics in neonates. Am J Perinatol
75. Filippi L, Gozzini E, Daniotti M, Pagliai F, Catarzi S, Fiorini P (2011) Rescue treatment with terlipressin in different scenarios of refractory hypotension in newborns and infants. Pediatr Crit Care Med 12(6):237–241
76. McNamara PJ, Shivananda SP, Sahni M, Freeman D, Taddio A (2013) Pharmacology of milrinone in neonates with persistent pulmonary hypertension of the newborn and suboptimal response to inhaled nitric oxide. Pediatr Crit Care Med [Internet] 14(1):74–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23132395
77. Lechner E, Hofer A, Leitner-Peneder G, Freynschlag R, Mair R, Weinzettel R et al (2012) Levosimendan versus milrinone in neonates and infants after corrective open-heart surgery: a pilot study. Pediatr Crit Care Med 13(5):542–548
78. Lechner E, Moosbauer W, Pinter M, Mair R, Tulzer G (2007) Use of levosimendan, a new inodilator, for postoperative myocardial stunning in a premature neonate. Pediatr Crit Care Med 8(1):61–63
79. Kobayashi S, Fujimoto S, Koyama N, Fukuda S, Iwaki T, Tanaka T et al (2008) Late-onset circulatory dysfunction of premature infants and late-onset periventricular leukomalacia. Pediatr Int 50:225–231
80. Osborn DA (2005) Diagnosis and treatment of preterm transitional circulatory compromise. Early Hum Dev 81(5):413–22
81. Seri I, Tan R, Evans J (2001) Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. Pediatrics 107(5):1070–1074
82. Noori S, Friedlich P, Wong P, Ebrahimi M, Siassi B, Seri I (2006) Hemodynamic changes after low-dosage hydrocortisone administration in vasopressor-treated preterm and term neonates
83. Ng PC (2006) A double-blind, randomized, controlled study of a "stress dose" of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. Pediatrics [Internet] 117(2):367–75. Available from: http://pediatrics.aappublications.org/cgi/https://doi.org/10.1542/peds.2005-0869
84. Eriksen VR, Hahn GH, Greisen G (2014) Dopamine therapy is associated with impaired cerebral autoregulation in preterm infants. Acta Paediatr 103(12):1221–1226