



Neonatal hemodynamics and management of hypotension in newborns

Türk Neonatoloji Derneği yenidoğanın hemodinamisi ve yenidoğanlarda hipotansiyona yaklaşım rehberi

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Abstract

Hemodynamic instability is frequent in high-risk infants admitted to neonatal intensive care units. However, monitoring and treatment strategies of those conditions might show variations among the units. Different factors can compromise hemodynamic status in preterm/term infants. Treatment options mostly include volume replacement, inotropes and/or vasopressors (dopamine, dobutamine, epinephrine and milrinone) and hydrocortisone. In general, these treatments are driven by predetermined protocols, which are not patient-based. According to the current knowledge, a physiology-driven approach that takes the individual characteristics of the newborn into consideration is accepted to be more suitable. In neonatal hemodynamics, important determinants are cardiac output, systemic vascular resistance, blood pressure, regional tissue perfusion and oxygenation. The novel technological methods, "targeted neonatal echocardiography" and "near-infrared spectroscopy" can help to delineate the underlying pathophysiology better, when added to the clinical assessment. In this review, strategies for the assessment of neonatal hemodynamics, as well as etiology, monitoring, and treatment of hemodynamic instability in preterm and term infants are presented.

Keywords: Hemodynamics, management, monitoring, newborn

Öz

Yenidoğan yoğun bakım biriminde yatan riskli yenidoğanlarda hemodinamik bozukluklara sık rastlanır. Bununla birlikte izlem ve tedavi stratejileri birimden birime değişkenlik gösterebilmektedir. Prematüre ve term yenidoğanlarda hemodinamik bozulma çeşitli nedenlere bağlı olabilir. Tedavide sıvı replasmanı, inotrop ya/ya da vazopressör ilaçlar (dopamin, dobutamin, adrenalin ve milrinon) ve hidrokortizon sıklıkla yer alır. Bu tedaviler, genellikle önceden belirlenmiş, hasta bazlı planlanmamış protokollere göre uygulanmaktadır. Güncel bilgilere göre yenidoğanın bireysel özelliklerini dikkate alan fizyoloji temelli yaklaşımın daha uygun olduğu kabul edilmektedir. Yenidoğan döneminde hemodinaminin en önemli belirleyicileri kardiyak debi, sistemik vasküler direnç, kan basıncı, bölgesel doku perfüzyonu ve oksijenasyonudur. Yeni teknolojik araçlardan "hedefe yönelik ekokardiyografi" ve "yakın kızılötesi spektroskopisi" klinikle birlikte kullanıldığında patofizyolojinin daha iyi aydınlanmasını sağlamaktadır. Bu derlemede yenidoğanda hemodinaminin değerlendirme yöntemleri ile birlikte prematüre ve term yenidoğanlarda görülen hemodinamik bozulma nedenleri, izlem ve tedavileri anlatılmaktadır.

Anahtar sözcükler: Hemodinami, izlem, tedavi, yenidoğan

Introduction

In the neonatal period, hemodynamics is normal functioning of the target organ enabled by the cardiovascular system (CVS), the capacity of the blood to carry oxygen, and the autoregulation ability of the tissue in association. In the neonatal period, hemodynamic disruption may be caused by various conditions including mainly perinatal

asphyxia, patent ductus arteriosus (PDA), sepsis, and necrotizing enterocolitis (NEC). Currently, the physiology-based approach, which considers the individual characteristics of the newborn, is recommended in the management of hemodynamics (1-4). In recent years, specification of cardiac functions with 'targeted neonatal echocardiography' and calculation of oxygen consumption in tissues using

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near-infrared spectroscopy (NIRS) have opened new horizons in the evaluation of hemodynamics (5, 6, 8).

Criteria used in the evaluation of hemodynamics in the neonatal period

1.1 Clinical evaluation criteria

Findings specific for each system (clinical, laboratory and radiologic) should be evaluated carefully (2, 8-10). While evaluating these findings, the effector factors (e.g., temperature of the environment, light, gestational week and postnatal age of the baby, medications used, accompanying problems) should be considered.

Lung functions: Respiratory pattern, respiratory function tests, pulse oxymeter arterial oxygen saturation (SpO₂), transcutaneous carbon dioxide (CO₂), arterio-alveolar oxygen gradient, and lung radiography and computed tomography (CT).

Cardiovascular functions: Cardiac murmur, presence of tachycardia/bradycardia or arrhythmia, non-invasive and invasive assessment methods.

Noninvasive methods: Heart rate and heart rate variability, oscillometric blood pressure (BP), SpO₂, perfusion index (PI), transcutaneous CO₂, echocardiography (ECO), impedance cardiography, and functional cardiac magnetic resonance imaging (MRI).

Invasive methods: Arterial BP measurement, arterial/capillary blood gases measurement, complete blood count, biochemical markers [serum cardiac troponin, brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) levels] and cardiac catheterization.

Renal functions: Urine output rate (oliguria: <1 mL/kg/hour), serum electrolytes, blood urea nitrogen (BUN) and creatinine level, glomerular filtration rate (GFR), fractional excretion of sodium (FeNa), renal ultrasonography (USG), and Doppler USG.

Hepatic functions: Liver dimensions, serum bilirubin (direct and indirect) and liver enzyme levels, prothrombin time, and hepatobiliary USG.

Adrenal functions: Inotrope-resistant hypotension, serum glucose, cortisol, and electrolyte levels.

Cerebral functions: Lethargy or agitation, amplitude

electroencephalography (aEEG), electroencephalography (EEG), and tissue oxygenation with NIRS.

Tissue perfusion: Capillary filling time (prolonged: >3 s), paleness/coldness, cutis marmorata, metabolic acidosis, arterial blood gases lactate level (increased: >2.8 mmol/L), laser Doppler, and microcirculation assessment methods.

1.2 Targeted echocardiography

Targeted echocardiography (TE) is an application that helps physicians who care for newborns in their decisions by providing instantaneous and physiology-based information, and which is gradually gaining functionality. Use of TE in association with clinical observation and laboratory findings in evaluation of hemodynamics increases diagnostic accuracy and treatment success. It should be kept in mind that functional evaluation is made with TE; anatomic evaluation should be performed by a pediatric cardiologist (4, 6).

1.2.1 Principles of targeted echocardiography

Evaluation with TE is recommended if the patient has been evaluated using echocardiography (ECHO) by a pediatric cardiologist and one or more of the following conditions have emerged in the follow-up (6):

- a) Persistent pulmonary hypertension (PPH) is present and no or little response has been obtained to nitric oxide treatment;
- b) Clinical or radiologic suspicion of pericardial effusion;
- c) Hypotension and signs of disruption in the systemic circulation (tachycardia, oliguria, lactic acidosis);
- d) Hypoxic ischemic encephalopathy (HIE) and signs of disruption in the systemic circulation in the first 72 hours of life;
- e) No urine output despite volume loading;
- f) Right heart failure or PPH due to bronchopulmonary dysplasia (BPD);
- g) Hemodynamically significant suspicion of PDA;
- h) Monitoring following patent ductus arteriosus ligation;
- i) Follow-up of a patient with a diagnosis of congenital diaphragm hernia (CDH);
- j) Evaluation of the position of central venous catheter or umbilical catheter.

1.3 Near-infrared spectroscopy

NIRS is a non-invasive method that measures tissue oxygen-hemoglobin levels. In recent years, NIRS has become a widespread method in neonatal units. The device operates according to the principle of transmission and reflection.

tion of near-infrared light (700-1000 nm wavelength). It does not require pulsatile blood flow in contrast to pulse oxymetry. It indicates the oxyhemoglobin concentration as percentage (0-100%) in tissues 8 cm below the skin surface (especially in the venous compartment) (venous; 70%, artery; 25%, capillary; 5%) (11, 12). The numeric value measured gives regional oxygen saturation (rSO₂) and is called the 'tissue oxygenation index (TOI)' (normal values: 55-85%) (11). Figure 1 shows the management algorithm in a case of hypoxemia (TOI<55%).

1.3.1 Indications for use of near-infrared spectroscopy (13)

- In the weaning period in infants who receive oxygen treatment (>30%);
- In the assessment of tissue oxygenation (especially brain) in association with TE in the presence of cardiovascular failure;
- In the assessment of results at the tissue level in patients in whom an oxygen tolerance test is to be performed;
- In the assessment of cerebral autoregulation by correlating with BP in hypoxic ischemic encephalopathy;
- In the follow-up of patent ductus arteriosus;
- In the assessment of mesenteric and splanic circulation in preterms;
- In the follow-up of patients with congenital heart disease (CHD) during and after surgery;
- In specifying indications for transfusion.

2. Criteria used in the assessment of the cardiovascular system and their physiologic mechanisms

Organization of the CVS, which is included in hemodynamic balance, is shown in Figure 2.

2.1 Blood pressure:

Blood pressure is a numeric measure constituted by cardiac output and systemic vascular resistance (SVR) in association, and a significant indicator of sufficient circulation (14).

$$BP = \text{Cardiac output} \times SVR$$

Accordingly, BP may increase, decrease or stay stable depending on the compensation level of cardiac output and SVR. There are different opinions related with the critical BP limit affecting short-term and long-term morbidity and mortality in newborns (15-18).

Blood pressure shows an increase with gestational week

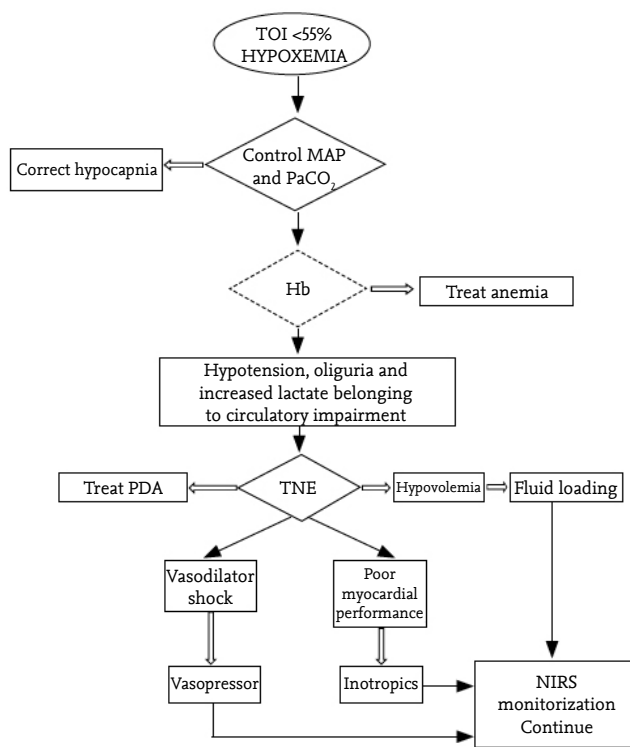


Figure 1. Management algorithm in low tissue oxygenation (12)

Hb: hemoglobin; TE: targeted echocardiography; MAP: mean airway pressure; PDA: patent ductus arteriosus; TOI: tissue oxygenation index; NIRS: near-infrared spectroscopy

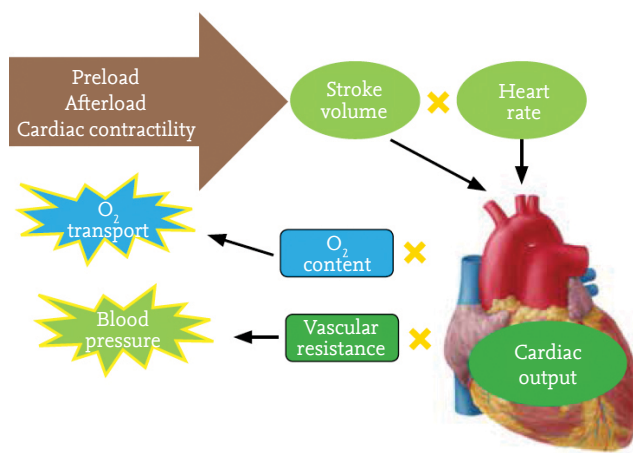


Figure 2. Organization of the cardiovascular system included in hemodynamic balance

and postnatal age. The mean BP after the postnatal 3rd day reaches ≥ 30 mm Hg in preterm babies and > 50 mm Hg in term babies. It is higher in female babies compared with male babies, and in babies born by cesarean section compared with those born by vaginal delivery; it is lower in asphyctic babies (9, 11). In the literature, there are various tables and graphs showing normal BP values in the

Table 1. Normal blood pressure values in the first day of life in newborns by birthweight*

Birthweight (g)	Systolic			Diastolic			Mean (Calculated)		
	Maximum	Median	Minimum	Maximum	Median	Minimum	Maximum	Median	Minimum
750	60	43	28	44	28	12	49	33	17
1000	62	46	30	45	30	14	51	35	19
1250	64	49	32	46	31	15	52	37	21
1500	66	50	34	48	32	16	54	38	22
1750	69	52	37	49	33	17	56	39	24
2000	71	55	39	50	34	18	57	40	25
2250	73	58	41	51	35	19	58	43	26
2500	76	60	43	52	37	21	60	45	28
2750	79	62	45	53	38	22	62	46	30
3000	80	64	48	54	39	23	63	47	31
3250	82	68	50	55	40	24	64	49	33
3500	85	70	52	56	41	25	66	51	34
3750	88	72	54	57	42	26	67	52	35
4000	90	74	56	58	43	28	69	53	37

*The highest and lowest values indicate 95% confidence interval (19)

neonatal period (9, 19-21). Table 1 and 2 show normal BP values as specified by Zubrow et al. (19).

2.2 Cardiac output:

Stroke volume is the amount of blood sent to the periphery by the heart in one pulse, and cardiac output is the amount of blood pumped to the periphery by the heart in one minute. Cardiac output is directly proportional to the heart rate and stroke volume (normal values: 150-350 mL/kg/min) (22).

Cardiac output = Heart rate X stroke volume

Reduced preload, reduced contractility, and increased afterload decrease cardiac output. Cardiac output in newborns is dependent on heart rate rather than stroke volume; therefore, cardiac output is disrupted in the event of very high (>180 pulses/min) or very low (<80 pulses/min) pulses persisting for a long-term.

Figure 3 shows the main conditions causing low cardiac output.

2.3 Systemic vascular resistance

Fetal circulation is characterized by low SVR and high pulmonary vascular resistance (PVR). Low resistance placental circulation is eliminated with cord clamping at

the time of delivery. Simultaneously, SVR increases with an increase in catecholamines and other hormones. The shunts during the fetal period (ductus arteriosus, ductus venosus, foramen ovale) start to close. Under normal conditions, SVR is controlled by vasoconstrictor and vasodilator factors (23). However, vasodilatation developing during acute events may lead to hypotension and shock. SVR decreases due to reduced afterload in hemodynamically significant PDA and due to cytokine-mediated peripheral vasodilation in sepsis and NEC. If appropriate treatment is not given, vasodilatation can not be compensated even if cardiac output is normal or increased and hypotension develops (4, 24, 25).

3. Tissue oxygenation

Blood flow (cardiac output), hemoglobin (Hb) level, and arterial blood oxygen content should be sufficient for tissue oxygenation (TO₂). Tissue oxygenation may also be disrupted with excessive consumption of tissues (e.g., septic shock). An anaerobic mechanism develops when the oxygen requirement of tissues is not met and lactic acid production increases. If this condition persists, the picture results in cell death and organ failure (4).

3.1 Calculation of tissue oxygenation

Tissue oxygenation can be calculated using cardiac output measured with echocardiography/catheterization,

Table 2. Normal blood pressure values in newborns by adjusted gestational week*

Gestational week	Systolic			Diastolic			Mean (Calculated)		
	Maximum	Median	Minimum	Maximum	Median	Minimum	Maximum	Median	Minimum
24	68	49	33	46	29	14	53	36	20
25	69	51	36	47	30	15	54	37	22
26	70	52	38	48	31	17	55	38	24
27	71	54	40	49	32	18	56	39	25
28	72	55	41	50	33	19	57	40	26
29	73	56	42	51	34	20	58	41	27
30	78	59	43	52	35	21	60	43	28
31	78	61	46	53	36	22	61	44	30
32	80	62	48	54	37	23	63	45	31
33	81	63	50	55	38	24	64	46	33
34	83	66	51	56	39	25	65	48	34
35	84	69	52	57	40	26	66	50	35
36	87	71	55	58	41	27	68	51	36
37	89	72	57	59	42	28	69	52	38
38	90	75	59	60	43	29	70	54	39
39	91	78	60	60	44	30	70	55	40
40	92	80	61	61	44	30	71	56	40
41	93	81	62	62	46	31	72	58	41
42	95	82	63	63	47	32	74	59	42
43	97	83	65	64	48	33	75	60	44
44	98	86	66	65	49	34	76	61	45
45	100	88	69	66	50	35	77	63	46
46	102	89	71	66	51	36	78	64	48

*The highest and lowest values indicate 95% confidence interval (19)

blood Hb level and arterial blood gases/pulse oxymeter oxygen saturation values.

$$TO_2 = \text{Cardiac output} \times \text{Arterial } O_2 \text{ content}$$

$$TO_2 = \text{Cardiac output} \times (\text{Hb-bound } O_2 + \text{released } O_2)$$

$$TO_2 = \text{Cardiac output} \times 1.34 \times \text{Hb} \times \text{SaO}_2 (\text{SpO}_2) + (\text{PaO}_2 \times 0.003^*)$$

*Released oxygen may be ignored.

Note: The oxygen binding capacity of Hb is 1.34. The Hb value is written in g/L and SpO₂ is written as a decimal (e.g., 95% → 0.95). Normal values: 20-40 mL/kg/min (26).

3.2 Calculation of tissue oxygen consumption

The difference between arterial and venous TO₂ yields the amount of tissue oxygen consumption (mL/kg/min) (normal values: 4-6 mL/kg/min) (26). Arterial (SaO₂) or saturation values (SpO₂) measured by pulse oxymeter should

be used when calculating arterial TO₂, and saturation values (SvO₂) measured by NIRS should be used when calculating venous TO₂.

Example: If pulse oxymeter SpO₂ is 95% (arterial O₂), cerebral NIRS SvO₂ (venous O₂) is 75%, Hb is 10 g/dL, and cardiac output by echocardiogram is 200 mL/kg/min in a baby born at the 30th gestational week with a birth weight of 1500 g:

$$\text{Arterial } TO_2 = 200 \times 1.34 \times 0.1 \times 0.95 = 25.5 \text{ mL/kg/min}$$

$$\text{Venous } TO_2 = 200 \times 1.34 \times 0.1 \times 0.75 = 20.1 \text{ mL/kg/min}$$

Tissue oxygen consumption: 25.5 (TO₂ arterial) – 20.1 (TO₂ venous) = 5.4 mL/kg/min O₂ is used by the brain (“cerebral O₂ consumption” within the normal limits).

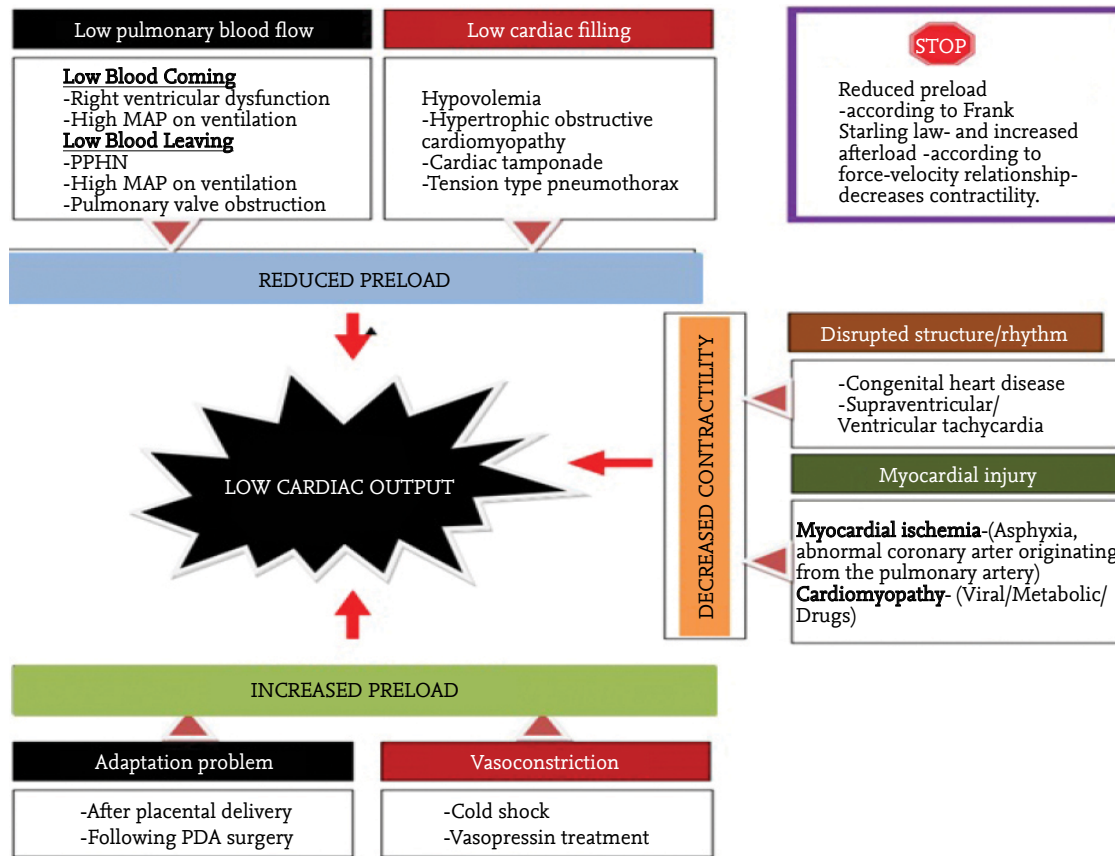


Figure 3. Conditions that lead to low cardiac output in newborns (4)

MAP: mean airway pressure; PDA: patent ductus arteriosus; PPHN: persistent pulmonary hypertension of the newborn

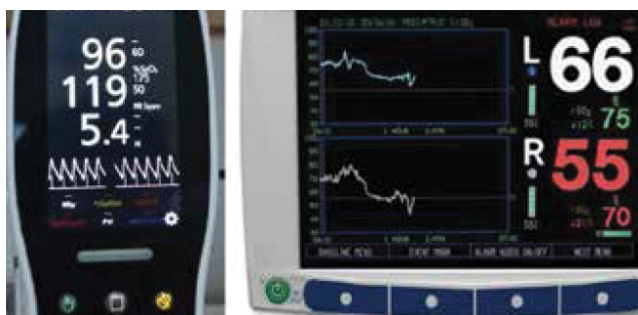


Figure 4. Tissue oxygen consumption: (SpO₂) 96%-(SvO₂) 66%=30%

The difference between arterial (pulse oxymeter-SpO₂) and venous (NIRS-TOI) saturations indicates the amount of oxygen consumed by tissues in percentages (normal values: 15-33%). In Figure 4, tissue oxygen consumption is calculated as SpO₂ (96%)-rSO₂ (SvO₂) (TOI) (66%)=30% (27).

3.3 Calculation of fractional oxygen extraction using near-infrared spectroscopy

Fractional oxygen extraction (FOE) indicates the percentage of oxygen removed by tissue. It is calculated according to the following formula: FOE= SaO₂-SvO₂/

SaO₂ (normal values: 0.15-0.22).

Fractional oxygen extraction changes depending on organ and organ activity. More active organs (brain, heart) are expected to remove a larger amount of oxygen from the blood. Tissues consume 15-33% of the transported oxygen (4, 27). When fractional oxygen extraction is 30%, venous oxygen saturation (NIRS-SvO₂) is 65-70%. An increase in oxygen extraction up to 65-70% results in reduction of venous oxygen saturation to 40-50%.

4. Autoregulation in target organs

The mechanism that regulates stable blood flow in an organ or region despite changes in blood pressure or perfusion is defined as autoregulation. Many defense mechanisms step in to prevent the development of tissue injury when blood flow is disrupted. The ability of autoregulation is limited in preterm babies (28). Munro et al. (29) reported the threshold BP value for cerebral autoregulation as 28-30 mm Hg in preterms.

Vasodilatation occurs in vital organs and vasoconstriction occurs in non-vital organs as a response to hypotension

Table 3. Pathophysiology and causes of systolic, diastolic and combined hypotension

Hypotension	Pathophysiology	Causes
Systolic BP <3 rd percentile	Left ventricular stroke volume is low	PPHN Septic (cold) shock Cardiogenic shock
Diastolic BP <3 rd percentile	Systemic vascular resistance is low	Systemic hypovolemia Septic (warm shock) PDA
Systolic and diastolic BP <3 rd percentile	Left ventricular stroke volume is low + Systemic vascular resistance is low +/- systolic function of the heart is disrupted	Previously systolic BP is ↓ PPHN Cardiogenic shock Previously diastolic BP is ↓ Hypovolemia or warm shock PDA

BP: blood pressure; PDA: Patent ductus arteriosus; PPHN: Neonatal persistent pulmonary hypertension

and inadequate perfusion. Primarily, more oxygen is removed from the blood. If this critical condition lasts for a long time, organ function/development is affected negatively. Anaerobic metabolism starts and tissues cannot extract oxygen. When vital cellular functions are disrupted, acute cell death occurs with necrosis and membrane potentials and integration cannot be maintained (4, 27, 30).

5. Causes of hemodynamic disruption in the neonatal period

Cardiovascular failure is an important cause of morbidity and mortality in the neonatal period. The frequency of hypotension is approximately 50% among very-low-birth-weight preterm babies internalized in the neonatal intensive care unit (NICU) (31, 32). Early-onset hypotension is generally related with abnormal peripheral vasoregulation, myocardial dysfunction, and hypovolemia (33).

Differences in the definition of hypotension are noted in the literature (19, 31-34). Therefore, it is difficult to give a single threshold value.

Definitions of hypotension:

- 1) A mean PB below the gestational week or at the <3rd (or 10th) percentile according to the gestational age;
- 2) A systolic, diastolic, and mean BP below the 95% confidence interval according to the gestational week;
- 3) A mean BP of <30 mm Hg in the first 72 hours in preterm babies with a gestational age of <32 weeks;
- 4) BP value at which organ blood flow autoregulation and tissue perfusion is disrupted.

Cardiac functions in newborns are different compared with older children and adults. In the early postnatal transmission period, complex vital changes are observed in all organs (29). In the myocardium of the newborn, noncontractile elements such as mitochondria are outnumbered, glucose-lactate production is excessive, calcium release is insufficient, and contractile reserve is low (35, 36). Therefore, sufficient response cannot be given in the event of increased need. Preload, myocardial contractility, and afterload are very important in the maintenance of hemodynamic balance. Blood pressure should be assessed separately as systolic and diastolic pressure and not only as mean BP. Table 3 shows the causes of hemodynamic disruption according to systolic, diastolic, and combined BP reduction.

5.1 Causes of hypotension/hemodynamic disruption in preterms (15, 33)

- a) Early postnatal transmission period;
- b) Hemodynamically significant PDA;
- c) Myocardial dysfunction;
- d) Perinatal depression;
- e) Sepsis and/or NEC;
- f) Hypovolemia;
- g) Relative adrenal insufficiency.

5.2 Causes of hemodynamic disruption in term newborns (15, 33, 37)

- 1 Hypovolemia
 - a) Placental bleeding, ablatio placenta, placenta previa;

- b) Feto-maternal bleeding;
- c) Birth trauma-subaponeurotic bleeding;
- d) Hepatic/splenic rupture;
- e) Massive pulmonary bleeding;
- f) Disseminated intravascular coagulation;
- g) Losses into the third space.

2 Cardiogenic shock

- a) Asphyxia;
- b) Arrhythmia;
- c) Congenital heart disease;
- d) Cardiomyopathy, myocarditis;

3 Air leakage syndromes

- a) Pneumothorax;
- b) Inappropriate positive end-expiratory pressure (PEEP).

4 Sepsis and septic shock

5 Endocrine causes:

- a) Adrenal hemorrhage;
- b) Adrenogenital syndrome;

6 Drug-associated hypotension

Pharmacologic treatment

Intavenous fluids, inotropics, vasopressors, and steroids are frequently used in the treatment of hypotension. The treatment approaches and vasoactive agents used show variance by clinics (38-40). Although the drugs are classified as inotropics and vasopressors, some (e.g., dopamine and adrenalin) show both effects according to the dose given. Differences in maturation according to gestational week and postnatal age change adrenergic (alpha and beta) and dopaminergic receptor expression and thus the cardiovascular response. Inotropics improve cardiac contraction by acting on the myocardium and increase cardiac output. Vasopressors lead to an increase in BP by way of vasoconstriction in the vascular bed. They basically act via the adrenergic system. Resuscitation guidelines recommend use of inotropics and/or vasopressors in hypotension that persists despite volume replacement (41). Which agent to be preferred in which newborn is still an issue of debate (2). There are insufficient clinical studies showing long-term results of treatment of hypotension in newborns. The most frequently used agents in the treatment of hypotension and hemodynamic disruption in newborns and their mechanisms of action are shown in Table 4 (42).

6.1 Pharmacologic treatment principles (12, 15, 38-40)

- a) Detailed clinical assessment should be performed before making a decision for treatment in presence of hypotension;
- b) It is recommended that the mean BP level should be kept above normal in very-low-birth-weight preterm babies (>gestational week or >30 mm Hg);
- c) In the treatment of hypotension, the first option should be dopamine if BP is desired to be increased. The initial dose should be 5 µg/kg/min and the dose should be increased up to a maximum dose of 15-20 µg/kg/min according to the hemodynamic responses, if necessary;
- d) Adding dobutamine (5-20 µg/kg/min) to the treatment may be helpful in hypotension that does not respond to volume expander and dopamine;
- e) When the effects of dopamine and dobutamine are compared, no difference is observed in morbidity and mortality rates, but dopamine has a stronger blood pressure-raising effect;
- f) If no response is obtained, although the dose of dopamine is increased to 10-15 µg/kg/min, assessment with TE may be directive in treatment;
- g) Increase in blood pressure does not necessarily mean that organ perfusion is improved;
- h) Milrinon and levosimendan act as inodilators; they should be used with caution in heat shock and in the presence of diastolic hypotension because they lead to peripheral vasodilatation;
- i) Adrenal insufficiency should be considered in hypotension that is irresponsive to high-dose inotropics, serum cortisol levels should be measured, and administration of hydrocortisone should be considered. The short-term and long-term adverse effects of steroids should be considered;
- j) It has been shown that adrenaline and vasopressors are effective in persistent hypotension.

Conclusion

The basis of treatment of hypotension in newborns is specifying and treating the underlying cause. The objective should be to correct organ perfusion rather than only obtaining a normal BP value (1-3, 33). Therefore, the patient should be intermittently assessed during the treatment period and at the end of treatment using clinical criteria, TE, tissue perfusion, and oxygenation. Figure 5a and 5b show a management algorithm in the presence of clinical circulatory failure.

In patients receiving multiple treatments (inotrope, va-

Table 4. Inotropics/vasopressors used in newborns and their mechanisms of action

Drug	Pharmacology	Physiological action	Dose	Practical information
Dopamine	D1, D2, alpha-1, beta-1	Increases contractility and vascular resistance Vasodilator at low doses (dopaminergic and beta receptor action), vasoconstrictor at high doses	5-20 µg/kg/min	Vasoconstriction; long intravenous access should be used, central venous access may be required.
Dobutamine	Alpha-1, beta-1, beta-2	Increases contractility without increasing vascular resistance. Strong beta receptor action: vasodilatation, tachycardia and chronotropy	5-20 µg/kg/min	May be administered by the peripheral access.
Epinephrine	Alpha-1, alpha-2, beta-1, beta-2 agonist	Increases contractility (increases vascular resistance at high doses), increases blood pressure by increasing heart rate and contractility, because its action on beta receptors is greater compared to alpha action. Dopamine and dobutamine are less potent compared to epinephrine and norepinephrine. They can all lead to tachycardia. Receptor insensitivity may develop at high doses.	0,01-0,3 µg/kg/min	Vasoconstriction; long intravenous access should be used, central venous access may be required.
Norepinephrine	Alpha-1, alpha-2, beta-1 agonist	Acts on alpha receptors, increases blood pressure by way of peripheral vasoconstriction.	Initial: 0,02-0,1 µg/kg/min Maximum: 1,0 µg/kg/min	Vasoconstriction; long or central venous access is required
Vasopressin	Antidiuretic hormone agonist in the renal tubules	Pulmonary vasodilatation, systemic vasoconstriction. It may increase basal vasopressin levels in presence of severe hypotension.	0,01-0,36 units/kg/hour	Hyponatremia, transaminitis. Vasoconstriction; long or central venous access is required
Terlipressin	Vasopressin analogu	Pulmonary vasodilatation, systemic vasoconstriction. It has greater affinity for V1 receptors rather than V2 receptors in comparison with vasopressin.	7 µg/kg/dose 12 hours apart, or 2 µg/kg/dose 4 hours apart.	Hyponatremia, transaminitis. Vasoconstriction; long or central venous access is required
Hydrocortisone	–	–	Loading (not mandatory): 2 mg/kg Maintenance: 0,5-1 mg/kg/dose, 6-8 hours apart, 3 or 5 days	It is not clear if it should be used for rescue treatment or primary treatment.
Milrinon	Phosphodiesterase III inh.	Increases myocardial contractility, leads to peripheral vasodilatation	Loading (not mandatory): 75 µg/kg Maintenance: 0,3-0,9 µg/kg/min	In warm shock, it may reduce blood pressure because it will lead to peripheral vasodilatation.
Levosimendan	Calcium sensitizier, phosphodiesterase III inh.	Increases nyocardial contractility, leads to peripheral vasodilatation	0,05-0,4 µg/kg/min, for 24-72 hours	In warm shock, it may reduce blood pressure because it will lead to peripheral vasodilatation

sopressor), the first drug to be reduced after obtaining hemodynamic stability depends on the underlying clinical picture. It should be evaluated as to whether the problem is related with myocardial performance, SVD or PVD. It is important that the patients' findings, de-

isions made, and applications performed are recorded at each step. An approach considering the newborn's physiologic characteristics and underlying pathophysiology seems to be rational in the management of hemodynamics.

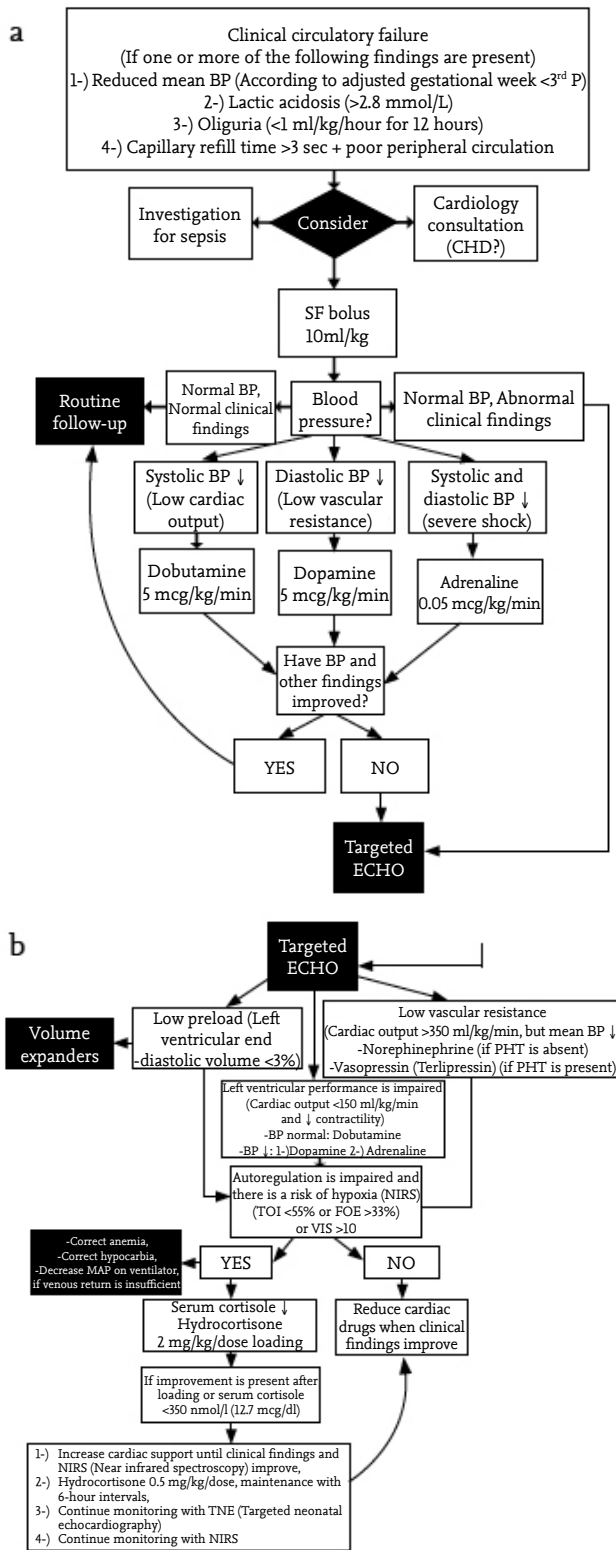


Figure 5. a, b. Clinical circulatory failure algorithm (12)

TOI: tissue oxygenation index; FOE: fractional oxygen extraction; BP: blood pressure; CHD: congenital heart disease; MAP: mean airway pressure; PH: pulmonary hypertension; NS: normal saline; VIS: vasoactive inotrope score; NIRS: near-infrared spectroscopy

See “Guideline for the Approach to Hemodynamics and Hypotension in the Neonatal Period” for detailed information about this subject (43).

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