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Management before the norwood procedure: correction of risk factors of unfavourable outcome

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ABSTRACT

Objective. To improve the outcomes in patients with single-ventricle physiology and obstructive systemic output via optimization of preoperative management.

Material and methods. A retrospective case-control study included 64 newborns for the period from 2005 to 2017.

Results. There were no significant differences in clinical and laboratory data between the patients of different age. Mortality was similar in groups with prenatal and postnatal diagnosis (p=0.472), as well as in patients born in various hospitals (p=0.956). Preoperative systemic hypoperfusion was associated with smaller aortic annulus or aortic atresia (p=0.020). We found that invasive pulmonary blood flow restriction is more effective than non-invasive measures (odds ratio 9.27, p=0.041). Serum lactate over 2.5 mmol/l indicates low success rate of non-invasive pulmonary blood flow restriction (p=0.000). Serum lactate over 21 mmol/l predicts preoperative mortality (p=0.000).

Conclusion. Prenatal diagnosis contributes to earlier admission to specialized hospital, but has no influence on the outcomes. Aortic atresia and higher serum lactate on admission indicate higher probability of preoperative systemic hypoperfusion. Invasive pulmonary blood flow restriction is more effective compared to non-invasive measures.

Keywords: *congenital heart disease, critical heart disease, hypoplastic left heart syndrome, bilateral pulmonary artery banding, prenatal diagnosis.*

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Background

Congenital cardiovascular disease is still a main cause of infant mortality [1]. Unfavorable outcomes are mainly associated with the most severe forms of congenital heart diseases (CHD) requiring treatment within a few days after birth. In particular these lesions include CHD with functional single ventricle (FSV) and obstructive systemic output [2].

Improvement of surgical technique reduced postoperative mortality. However, further improvement of treatment outcomes requires analysis of various preoperative risk factors [3].

The objective was to improve the outcomes in patients with single-ventricle physiology and obstructive systemic output via optimization of preoperative management.

Material and methods

The research was performed at the Department of Cardiology and Cardiovascular Surgery at the Samara State Medical University. This department is based on the Polyakov Samara Regional Cardiology Hospital. A retrospective case-control study has been carried out for the period 2005-2017. The main characteristics of patients are presented in **Table 1**. Quantitative data are shown as median, the 25th and the 75th quartiles.

Table 1. **Characteristics of patients**

Variable	Value
Demographic data	
Number of patients, *n* (%)	64 (100)
Boys, *n* (%)	44 (69)
Girls, *n* (%)	20 (31)
Gestational age, weeks	39 [38; 39]
Anthropometric data	
Body weight at birth, kg	3.21 [2,90; 3.53]
Height at birth, cm	53 [51; 55]
Body surface area (Haycock), m^2	0.22 [0.21; 0.23]
Single ventricle morphology	
Left or indeterminate morphology, *n* (%)	13 (20)
Right, *n* (%)	51 (80)

Statistical analysis

Mann-Whitney U-test was used for paired comparisons of independent samples. Assessment of binary classification implied ROC-analysis with area under curve and analysis of predictive values of the model (positive and negative results).

Odds ratio (OR) was applied to determine the correlation of certain risk factor with a particular outcome. The null statistical hypothesis was rejected at p-value <0.05.

Results

In 50 (78%) cases, CHD was detected at the prenatal stage. Patients with prenatal diagnosis admitted to a specialized hospital earlier. Median age at admission was 1.2 days [0.2; 2.2] vs. 5.8 days [2.2; 9.4] ($p = 0.000$).

Clinical and laboratory (including blood gases) data were similar in patients admitted at the age ⩽ 2 days and ⩾ 3 days.

Postoperative mortality after Norwood procedure was also similar in patients with and without prenatal diagnosis ($p = 0.472$). Moreover, we found no significant differences in mortality between the patients born in a hospital active pediatric cardiac surgery service and conventional obstetric facility ($p = 0.956$).

Upon admission, all patients were ensured with:

1. Vascular access and infusion of prostaglandins;
2. Sedation;
3. Loop diuretics (furosemide) and aldosterone antagonists (verospiron);
4. Inotropic support (dopamine 5-10 μg/kg/min);
5. Control of arterial and/or venous blood gases and acid-base state.

The criteria of low cardiac output syndrome caused by pulmonary hypervolemia included:

– saturation ⩾ 85% according to pulse oximetry data;
– serum lactate > 2.0 mmol/l;
– urine output rate < 1 ml / kg / h;
– tachycardia and tachypnea.

Demographic and clinical differences were insignificant between the patients with and without low cardiac output syndrome. Comparison of anatomical and laboratory parameters is summarized in **Table 2**.

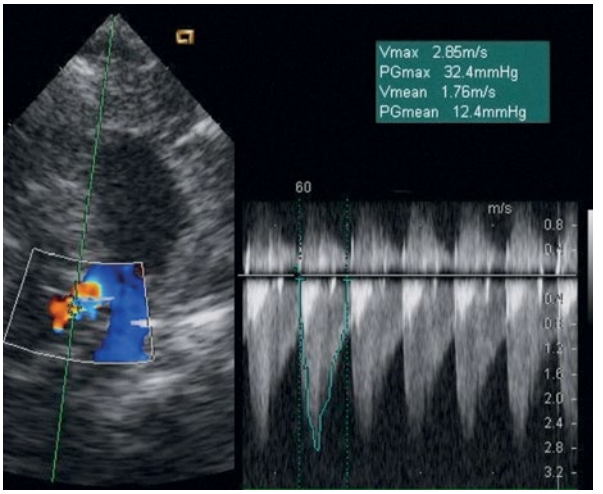


Fig. **Doppler mapping and spectral Doppler scanning after invasive pulmonary blood flow restriction.**
V_{max} — peak velocity, PG_{max} — peak pressure gradient, V_{mean} — mean velocity, PG_{mean} — mean pressure gradient.

Reduced aortic annulus (and, especially, aortic atresia) is significantly associated with the risk of low cardiac output syndrome (AUC = 0.670, [0.532; 0.807], $p = 0.020$). High concentration of serum lactate in venous blood is associated with advanced risk of systemic hypoperfusion (AUC = 0.677, [0.545; 0.810], $p = 0.015$). Considering AUC values, the quality of predictive models is moderate in both cases.

Low cardiac output syndrome was an indication for pulmonary blood flow restriction via mechanical hypoventilation to increase pulmonary vascular resistance and reduce pulmonary hypervolemia.

If non-invasive measures were ineffective within 48 hours, as well as in patients with contraindications for Norwood procedure within the next 7 days (severe concomitant extracardiac

Table 2. **Comparison of patients with and without systemic hypoperfusion upon admission**

Variable	No systemic hypoperfusion	Systemic hypoperfusion	*p-value*
	M (–95% — +95%) or Me (Q25%; Q75%)	M (–95% — +95%) or Me (Q25%; Q75%)	
	Anatomical features		
Z-score of aortic valve diameter	–34.70 (–52.25; –17.15)	–50.44 (–67.02; –33.85)	**0.020**
Z-score of ascending aorta diameter	–3.92 (–5.31; –2.54)	–5.02 (–6.14; –3.91)	0.130
Z-score of aortic arch diameter	–5.11 (–5.96; –4.27)	–4.49 (–5.04; –3.93)	0.279
Z-score of aortic isthmus diameter	–4.25 (–5.06; –3.44)	–3.57 (–4.10; –3.04)	0.156
Z– score of mitral valve diameter	–37.03 (–55.24; –18.83)	–37.00 (–53.48; –20.51)	0.187
	Laboratory data		
pH (vein)	7.34 (7.33; 7.36)	7.32 (7.26; 7.37)	0.957
pCO_2 (vein), mm Hg	40.61 (38.26; 42.96)	41.59 (36.59; 46.58)	0.772
pO_2 (venous blood), mm Hg	38.10 (34.97; 41.24)	39.56 (34.36; 44.75)	0.914
BE (venous blood), mmol/l	–2.81 (–4.21; –1.41)	–5.29 (–7.63; –2.96)	0.166
Lactate (venous blood), mmol/l	2.20 (1.94; 2.47)	4.03 (2.62; 5.44)	**0.015**
Saturation (venous blood), %	76.72 (73.16; 80.29)	72.47 (66.49; 78.44)	0.435

Table 3. **Preoperative measures and their effectiveness prior to the Norwood procedure**

Variable	Value
Non-invasive measures, *n* (%)	34 (53)
– successful	22 (65)
– unsuccessful	12 (35)
Pulmonary artery narrowing, *n* (%)	18 (28)
– successful	17 (94)
– unsuccessful	1 (6)
Inotropic support, *n* (%)	50 (78)
Mechanical ventilation, *n* (%)	36 (56)

diseases or multiple organ failure), we used invasive restriction of pulmonary circulation via bilateral narrowing of pulmonary arteries through median sternotomy.

Adequacy of pulmonary artery narrowing was assessed by daily monitoring of blood flow velocity through the narrowed segment of the artery (target range 2.5-3.0 m / s) **(Figure)**.

Preoperative measures before Norwood surgery and their effectiveness are summarized in **Table 3**.

Invasive approach was more effective compared to non-invasive approach (OR 9.27; 95% CI 1.10 — 78.50; $p = 0.041$).

We have compared the groups of patients to identify the risk factors of ineffective non-invasive measures for pulmonary hypervolemia. Demographic, anatomical and clinical data were similar in both groups. Differences in laboratory data are shown in **Table 4**.

Variables with significant differences were assessed in ROC analysis. Serum lactate (as a predictor of ineffective non-invasive measures) was characterized by excellent predictive quality with a cut-off value of 2.5 mmol/L **(Table 5)**. Good predictive quality was obtained for BE value. However, sensitivity, specificity and accuracy were unsatisfactory for the model with BE.

Other parameters (demographic, anthropometric, morphological, clinical and laboratory) were similar in all groups.

Considering these data, indications for primary bilateral pulmonary artery narrowing were anatomical variants with aortic atresia, serum lactate of venous blood over 2.5 mmol/L and need to postpone the first stage of hemodynamic correction.

Three 3 (5%) patients died before hemodynamic correction.

We have compared survivors and non-survivors to determine the risk factors and predictors of preoperative mortality **(Table 6)**. Significant differences in acid-base state were revealed (pH, BE, serum lactate). Demographic, clinical and anatomical characteristics of patients were similar.

ROC-analysis of predictive models included only significant predictors. Excellent quality was obtained for the model based on serum lactate in venous blood with a cut-off value of 21 mmol / L **(Table 7)**.

Table 4. **Characteristics of patients with successful and unsuccessful non-invasive pulmonary blood flow restriction**

Variable	Successful non-invasive measures	Unsuccessful non-invasive measures	*p-value*
	Me (Q25%; Q75%)	Me (Q25%; Q75%)	
pH (venous blood)	7.35 (7.33; 7.38)	7.23 (7.06; 7.40)	0.089
pCO_2 (venous blood), mm Hg	40.33 (37.33; 43.32)	43.77 (25.82; 61.71)	0.326
pO_2 (venous blood), mm Hg	39.57 (36.45; 42.69)	38.32 (19.52; 57.12)	0.079
BE (venous blood), mmol/l	−3.2 (−4.6; −1.84)	−10.3 (−17.4; −3.22)	**0.007**
Lactate (venous blood), mmol/l	2.52 (2.03; 3.0)	7.44 (3.07; 11.81)	**0.000**
Saturation (venous blood), %	77.01 (73.59; 80.43)	61.70 (42.46; 80.94)	0.108

Table 5. **ROC-analysis of serum lactate as a predictor of unsuccessful non-invasive measures**

Variable	Value	95% confidence interval	*p-value*
AUC	0.890	0.781—0.998	**0.000**
Sensitivity, %	61.8	43.6—77.8	—
Specificity, %	70.0	50.6—85.3	—
Positive predictive value, %	70.0	55.97—81.1	—
Negative predictive value, %	61.8	49.8—72.5	—
Accuracy, %	65.6	52.7—77.1	—
Odds ratio	2.06	1.12—3.78	**0.019**

Table 6. **Laboratory data in survivors and non-survivors prior to the Norwood procedure**

Variable	Survivors (*n*=61)	Non-survivors (*n*=3)	*p-value*
	Me (Q25%; Q75%)	Me (Q25%; Q75%)	
pH (venous blood)	7.34 [7.31; 7.38]	7.19 [7.01; 7.33]	**0.035**
pCO_2 (venous blood), mm Hg	41.11 [36.00; 45.50]	41.53 [19.60; 68.00]	0.703
pO_2 (venous blood), mm Hg	39.07 [32.70; 42.10]	34.93 [20.50; 45.60]	0.849
BE (venous blood), mmol/l	−3.78 [−5.20; −1.90]	−11.30 [−15.90; −5.80]	**0.013**
Lactate (venous blood), mmol/l	2.85 [1.80; 3.00]	9.77 [4.90; 15.00]	**0.007**
Saturation (venous blood), %	75.31 [73.60; 82.30]	57.13 [19.20; 79.80]	0.198

Table 7. **ROC-analysis of serum lactate as a predictor of mortality prior to stage-I surgery**

Variable	Value	95% confidence interval	*p-value*
AUC	0.967	0.920—1.000	**0.000**
Sensitivity, %	100	29.2—100	—
Specificity, %	98.4	91.2—99.96	—
Positive predictive value, %	75	30.0—95.5	—
Negative predictive value, %	100	42.1—100	—
Accuracy, %	98.4	91.6—99.96	—
Odds ratio	61.0	8.73—426.13	**0.000**

Discussion

Analysis of the actual results of staged hemodynamic correction of FSV and obstructive systemic output demonstrates improvement of survival of these patients [3–6].

To date, various surgical approaches have been developed in this group of patients. Nevertheless, only certain methods are equally widespread in Russian pediatric cardiac surgery. In many cases, the choice of preoperative and intraoperative management is based on predominant preferences and actual practical experience in certain hospital. Heterogeneity of these patients, small incidence of disease, complexity and expensiveness of treatment complicate randomized studies.

Scientists in various countries regularly discuss the influence of prenatal diagnosis on the outcomes of various congenital heart diseases [7–9]. We should emphasize contradictory nature of these data. Some authors report better postoperative outcomes following early specialized care [10]. Others emphasize no significant effect of prenatal diagnosis on the results of correction [11, 12]. Similarly, we found no significant positive effect of prenatal diagnosis on postoperative outcomes. This circumstance may be explained by higher importance of various intraoperative events for postoperative outcomes after Norwood procedure than prenatal diagnosis per se. Other essential aspects followed by higher survival regardless the age of diagnosis are wide distribution of prostaglandin drugs in various obstetric hospitals, as well as well-developed organization of patient transportation to specialized cardiac surgery hospitals.

Quantitative assessment of cardiac output in patients with FSV was mainly studied in relation to the course of postoperative period [13, 14]. However, severity of low cardiac output syndrome influenced the likelihood of unfavorable outcome even before surgical correction. In this regard, permanent monitoring of effectiveness of various measures is essential besides early medication and respiratory support.

Non-invasive and invasive measures are advisable for disproportionate pulmonary hypervolemia followed by systemic hypoperfusion [15, 16]. One should remember that non-invasive measures would be ineffective in some patients. Therefore, primary bilateral pulmonary artery narrowing is justified.

Conclusion

Although prenatal diagnosis contributes to earlier hospitalization of patients to a specialized hospital, it does not significantly affect the outcomes of stage-1 surgery. Aortic atresia and high serum lactate in venous blood upon admission indicate a high risk of preoperative systemic hypoperfusion. Invasive restriction of pulmonary circulation is more effective than non-invasive (conservative) measures.

Study limitations

This research was retrospective and all patients were treated at different times.

The authors declare no conflicts of interest.

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