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Anemia as a Risk Factor for Organ Dysfunctions in Patients Operated on Heart Valves

Aim	To study the effects of pre- and postoperative anemia on the risk and the structure of internal organ dysfunction in patients undergoing surgery for acquired heart diseases (AHD).
Material and methods	This was a retrospective cohort study including 610 primarily operated patients with AHD. A comparative analysis of the incidence and the structure of internal organ dysfunction was performed, and the likelihood of intraoperative hemotransfusion was determined for patients with preoperative anemia (Hb <130 g/l) and without it. The incidence and the nature of internal organ damage were compared in patients with postoperative Hb < 90 g/l and 90–130 g/l.
Results	The presence of postoperative anemia detected in 45% of patients at two days after the surgery 6-fold increased the risk of acute heart failure (odds ratio [OR], 5.75; 95% confidence interval [CI], 1.23–26.84; p=0.016), 4-fold increased the risk of multiorgan failure (MOF) (OR, 4.2; 95% CI, 1.16–15.64; p=0.03), and 5-fold increased the likelihood of hemotransfusion (OR, 4.74; 95% CI, 3.12–7.19; p<0.0001). Severe and moderate anemia (Hb <90 g/l) was observed in 11.2% of patients, which presence 6-fold increased the risk of brain dysfunction (OR, 5.72; 95% CI, 2.17–15.06; p=0.001) and MOF (OR, 5.97; 95% CI, 1.94–18.35; p=0.004) compared to patients with Hb 90–130 g/l.
Conclusion	In patients with AHD, postoperative anemia increases the risk of circulatory decompensation at two days after the surgery and of MOF and also increases the likelihood of intraoperative hemotransfusion; postoperative anemia with Hb <90 g/l increases the risk of brain damage and MOF.

Keywords	Anemia; internal organ dysfunction
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Anemia is a significant prognostic risk factor in postoperative complications and increased mortality after open-heart surgery [1]. According to the World Health Organization criteria, anemia is a fall in blood hemoglobin levels (Hb) less than 120 g/L in females and 130 g/L in males [2]. Low concentrations of hemoglobin before surgery negatively affect the early postoperative course for patients who have undergone surgery with a cardiopulmonary bypass (CPB). This can increasing the probability of acute kidney injury (AKI), cerebrovascular accident (CVA), and septic complications [3].

The most common causes of preoperative anemia may be iron deficiency and chronic kidney disease. Nosocomial anemia which can develop after invasive diagnostic procedures, such as coronary angiography, is also an important etiological factor [4]. Preoperative anemia causes high-probability intraoperative blood transfusion [5] and thus increases the risk of transfusion reactions [6, 7].

Despite strong evidence of the adverse effects of blood transfusion in critical anemic patients [8] and the safety of the restrictive management of patients operated under CPB [9], anemia is believed to have more adverse effects in cardiac patients than transfusion of blood components, so a free approach to their use is preferred [10-12]. According to Nakamura et al. [10], the restrictive management of transfusions for anemia in elderly patients undergoing heart surgery increases the risk of early postoperative cardiogenic shock. Garg et al. [11] found no difference in AKI incidence in cardiac patients between free or restrictive transfusion management. Moreover, according to Hajjar et al. [12], unlike the free approach, restrictive blood transfusion management does not reduce the 30-day mortality rate after open-heart surgery. The adverse effects of low blood hemoglobin levels in severe patients with concomitant heart disease were also shown in the meta-analysis by Cortés-Puch et al. [13]. Their study revealed a high incidence of acute coronary insufficiency in these patients with anemia compared to those without anemia.

Anemia is a common condition in patients undergoing cardiac surgery [1]. It is for this reason that its impact

on the early postoperative period requires careful study. Since reduced oxygen delivery in low cardiac output causes significant damaging effects on internal organs [14], reduced oxygen content in blood in anemia aggravates the imbalance between oxygen delivery and consumption, thus exacerbating the consequences of tissue hypoxia. Improved oxygen delivery by increasing cardiac performance is often challenging in patients undergoing surgery for acquired valve disease (AVD) due to myocardial failure [15, 16]. In this regard, low hemoglobin levels can have a further negative impact by aggravating the damage to internal organs.

Objective

To study the effects of preoperative and postoperative anemia on the risk of developing of internal organ failure and its structure in patients undergoing surgery for AVD.

Material and Methods

A retrospective cohort study of 610 cases of surgical treatment of patients with AVD above the age of 18 years was performed in 2019.

Exclusion criteria: repeated heart surgery; acute heart failure (AHF) in the intraoperative period and on day 1 after surgery; the use of deep hypothermic circulatory arrest. Patients underwent surgery under CPB for heart valve defects, including in combination with coronary artery bypass grafting or replacement of ascending aorta. The subjects received combined anesthesia with isoflurane MAC 0.7-1.1, propofol 4 mg/kg/h (during CPB), fentanyl 3 μg/kg/h, rocuronium bromide 0.5 mg/kg/hr. Extracorporeal perfusion was performed based on the blood flow velocity of 2.6 L/min/m2 under moderate hypothermia of 32°C. Cold-blood cardioplegia combined with Custodiol administration was used for cardiac arrest and myocardial protection.

The study was carried out in several stages. In stage 1, we studied the effects of preoperative anemia on the risk of developing organ and tissue failures in the early postoperative period. For this purpose, all patients, irrespective of sex, were divided into two groups depending on the preoperative levels of hemoglobin: patients with anemia (Hb <130 g/L) and patients without anemia (Hb>130 g/L). We performed a comparative analysis of the incidence of AHF on day 2 after surgery, brain dysfunction, liver dysfunction, hemostasis system failure pursuant to the criteria adopted in the National Medical Research Center of Cardiovascular Surgery n.a. A.N. Bakulev, acute respiratory distress syndrome [17], AKI stage 3 (Acute Kidney Injury Network) [18], and multiple organ failure (MOF) (Table 1). We also evaluated the effects of anemia on the risk of developing an organ or tissue failure and the likelihood of intraoperative blood transfusion.

At stage 2 of the study, we investigated the effects of the severity of postoperative anemia of the damage to internal organs. All patients who underwent surgery were divided into two groups depending on the severity of anemia: patients with Hb <90 g/L (moderate and severe anemia) and patients with Hb 90-130 g/L (mild anemia). We performed a comparative analysis of the incidence and structure of internal organ failure , as well as a risk assessment of the occurrence of internal organ damage, compared the duration of mechanical ventilation (MV) and time in the intensive care unit (ICU).

Stage 3 of the study included a comparative evaluation of the incidence and structure of internal organ failure in patients subjected to intraoperative red blood cell (RBC) suspension transfusions (BT group) and those who were not (no-BT group). The risk of internal organ damage was assessed depending on the intraoperative blood transfusion.

Statistical analysis of the data was performed using Microsoft Excel 2019 and StatPlus software suites. The values were expressed as the mean±standard deviation (SD) or the median (Me) and 25th and 75th percentiles [Q1; Q3]. The means were compared using the Mann–Whitney test. Odds ratio (OR) with 95% confidence intervals (95% CI) were calculated to assess the risks.

Table 1. Criteria of internal organ failure

Dysfunction	Diagnostic criteria
Acute heart failure	CVP> 14 mm Hg, PAWP> 18 mm Hg, CI <2.2 L/min/m^2, clinical signs of tissue hypoperfusion, blood adrenaline > 0.1 μg/kg/min
Kidney*	A threefold increase in blood creatinine, urine output <0.3 mL/kg/h for 24 hours, or anuria for 12 hours
Liver	Blood bilirubin > 34 μmol/L in combination with two-time elevated levels of AST, ALT, or ALP
Brain	The level of consciousness <15 according to the Glasgow score; convulsive disorder
Hemostasis system	D-dimer >2000 mg/L; INR >3; platelets <150*103/μL; fibrinogen <2 g/L
Acute respiratory distress syndrome#	• The onset of specific symptoms or exacerbation of existing signs of lung injury within one week after the exposure to damaging factor; • X-ray examination of the lungs: bilateral opacities (infiltration); • Absence of cardiogenic mechanisms of pulmonary edema or signs of fluid overload; • Impaired oxygenation (PaO_2/FiO_2 <300)

CVP, central venous pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; INR, international normalized ratio; PaO_2, arterial oxygen partial pressure; FiO_2, fraction of inspired oxygen; PaO 2/FiO_2, oxygenation index. * – Diagnostic criteria of acute kidney injury stage 3 (AKIN – Acute Kidney Injury Network) [17]; # – diagnostic criteria of acute respiratory distress syndrome (Berlin definition) [18].

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Results

Preoperative anemia was observed in 272 (45%) patients, and group Hb >130 g/L included 338 patients. All patients were similar in age, weight, Euroscore II risk of cardiac surgery, duration of CPB and aortic cross-clamping, and volume of intraoperative blood loss. There were no statistically significant differences in the duration of mechanical ventilation and time in ICU (Table 2).

Table 3 shows the incidence and structure of organ failure, implying that preoperative anemia was a risk factor of AHF on day 2 after surgery and MOF.

RBC suspension transfusion was performed in 37.5% of patients with Hb <130 g/L and 16.6% (p<0.0001) of patients without anemia, the preoperative anemia increased the likelihood of intraoperative transfusion more than four-fold (OR 4.75; 95% CI 3.28-6.68; p <0.05).

Postoperative anemia (Hb <130 g/L) was observed in 83% of patients. Patients with moderate to severe anemia (Hb <90 g/L) underwent longer CPB, aortic cross-clamping and had higher intraoperative blood loss (Table 4). Moreover, they had a longer duration of postoperative mechanical ventilation and time in ICU (Table 4).

Patients with postoperative hemoglobin levels less than 90 g/L had brain dysfunction and MOF more often, while moderate to severe anemia was a risk factor for these postoperative complications (Table 5).

RBC suspension transfusion in the intraoperative period was much more frequent in patients with moderate to severe postoperative anemia (63% vs. 26.2% in patients with postoperative levels of hemoglobin 90-130 g/L (p <0.0001).

Intraoperative BT was performed in 158 (25.9%) patients, 452 patients had no BT. Patients in both study groups were similar in age, weight, duration of CPB and aortic cross-clamping, intraoperative blood loss volume (Table 6). In the BT group, Euroscore II risk, duration of postoperative MV, and time in ICU were significantly higher (Table 6).

Patients who underwent intraoperative BT had a higher incidence of AHF on day 2 after surgery than patients without BT, and RBC suspension transfusion increased the risk of postoperative complications significantly (Table 7).

Discussion

In patients undergoing heart surgery the presence of preoperative anemia is associated with a high risk of internal organ failure in the early postoperative period [3] Decreased blood hemoglobin levels in low cardiac output or due to the limited compensatory possibilities of the heart in the intraoperative or early postoperative periods result in a significant reduction in oxygen delivery. This can cause the development of tissue hypoxia which is a significant pathophysiological aspect of visceral injury [14].

This study demonstrated the negative effects of preoperative anemia on the development of circulatory decompensation on day 2 after AVD correction manifested as AHF. The preoperative hemoglobin levels <130 g/L increased the risk of cardiac dysfunction almost sixfold on day 2 after surgery. Moreover, patients with preoperative hemoglobin levels <130 g/L are four times more likely to develop MOF when compared with patients without anemia. It should be noted that the patients in both

Table 2. Main patient characteristics (stage 1)

Parameter	Hb <130 g/L	Hb >130 g/L	p
Age, years	59±19	58±17	> 0.05
BMI, kg/m^2	26.83±5.18	26.79±4.67	> 0.05
Euroscore II, %	2.38 [1.67; 4.60]	2.44 [1.51; 4.54]	> 0.05
CPB time, min	140±52	137±57	> 0.05
Aortic cross-clamping time, min	85±35	84±36	> 0.05
Blood loss, mL	380±255	400±180	> 0.05
MV, h	16 [12; 21]	16 [12; 20]	> 0.05
Time in ICU, h	22 [19; 25]	21 [18; 24]	> 0.05

BMI, body mass index; CPB, cardiopulmonary bypass; here and in Tables 3, 4; 5:
Hb, hemoglobin; MV, mechanical ventilation; ICU, intensive care unit.

Table 3. Frequency and structure of internal organ failure (stage 1)

Parameter	Hb <130 g/L (n=272)	Hb >130 g/L (n=338)	p	OR; 95% CI
AHF on day 2 after surgery	3.3% (9)	0.6% (2)	0.016	5.75; 1.23–26.84
Brain dysfunction	3.3% (9)	2.7% (9)	> 0.05	1.25; 0.49–3.20
ARDS	0.7% (2)	0.3% (1)	> 0.05	2.5; 0.43–27.68
AKI	1.5% (4)	0.6% (2)	> 0.05	2.51; 0.46–13.79
Liver dysfunction	0%	0.3% (1)	> 0.05	–
MOF	3.7% (10)	0.9% (3)	0.03	4.2; 1.16–15.64
Mortality	2.9% (8)	0.9% (3)	> 0.05	3.38; 0.89–12.8

Table 4. Main patient characteristics (stage 2)

Parameter	Hb <90 g/L	Hb 90–130 g/L	p
Age, years	60±23	59±19	> 0.05
BMI, kg/m²	25.81±9.71	26.81±9.90	> 0.05
Euroscore II, %	4.81 [2.08; 11.93]	2.4 [1.72; 4.65]	0.02
CPB time, min.	161±73	140±52	0.002
Aortic cross-clamping time, min	93±45	85±35	0.04
Blood loss, mL	450±350	350±290	0.04
MV, h	21 [16; 54]	16 [12; 21]	<0.0001
Time in ICU, h	26 [22; 66]	22 [19; 24]	<0.0001

BMI, body mass index; CPB, cardiopulmonary bypass; MV, mechanical ventilation; ICU - intensive care unit.

Table 5. Frequency and structure (%) of internal organ failure (stage 2)

Parameter	Hb <90 g/L	Hb 90–130 g/L	p	OR; 95% CI
AHF on day 2 hours after surgery	4.4	1.8	> 0.05	2.49; 0.64–9.61
Brain dysfunction	11.8	2.3	0.001	5.72; 2.17–15.06
ARDS	1.5	0.5	> 0.05	3.26; 0.29–36.46
AKI	1.5	0.9	> 0.05	1.62; 0.18–14.74
Liver dysfunction	0	0.2	> 0.05	–
MOF	8.8	1.6	0.004	5.97; 1.94–18.35
Mortality	4.4	2.1	> 0.05	2.21; 0.58–8.36

AHF, acute heart failure; ARDS, acute respiratory distress syndrome;
AKI, acute kidney injury; MOF, multiple organ failure; OR, odds ratio; CI, confidence interval.

Table 6. Main patient characteristics (stage 3)

Parameter	BT	No BT	p
Age, years	60±16	57±20	> 0.05
BMI, kg/m²	25.91±8.30	27.08±10.17	> 0.05
Euroscore II, %	4.00 [2.07; 8.97]	2.27 [1.51; 4.38]	0.0002
CPB time, min.	147±62	139±52	> 0.05
Aortic cross-clamping time, min	81±40	85±35	> 0.05
Blood loss, mL	400±310	380±270	> 0.05
MV, h	18 [13; 28]	16 [12; 21]	0.003
Time in ICU, h	23 [20; 43]	21 [18; 24]	<0.0001

BT, blood transfusion; BMI, body mass index; CPB, cardiopulmonary bypass; MV, mechanical ventilation; ICU - intensive care unit.

Table 7. Frequency and structure of internal organ failure (stage 3)

Parameter	BT (n = 158)	No BT (n = 452)	p	OR; 95% CI
AHF on day 2 hours after surgery	4.4% (7)	0.9% (4)	0.01	5.19; 1.50–17.98
Brain dysfunction	4.4% (7)	2.7% (12)	> 0.05	1.7; 0.66–4.40
ARDS	1.3% (2)	0.2% (1)	> 0.05	5.78; 0.52–64.21
AKI	1.3% (2)	0.9% (4)	> 0.05	1.45; 0.26–8.02
Liver dysfunction	0	0.2% (1)	> 0.05	–
MOF	2.5% (4)	2.0% (9)	> 0.05	1.28; 0.39–4.21
Mortality	3.8% (6)	1.3% (6)	> 0.05	2.95; 0.94–9.28

BT, blood transfusion; AHF, acute heart failure; ARDS, acute respiratory distress syndrome;
AKI, acute kidney injury; MOF, multiple organ failure. OR, odds ratio; CI, confidence interval. The values are presented as % (n).

groups had no significant differences in age, weight, and intraoperative blood loss volume, duration of CPB and the period of myocardial anoxia. Thus ,these parameters have no effect on the development of internal organ failure. Preoperative anemia increased the likelihood of blood transfusion 4.7 times in patients undergoing

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surgery for AVD, but with no significant effect on mortality. Our findings are partially consistent with the retrospective observational study by Kim et al. [19] and meta-analyzes by Fowler et al. [5], Padmanabhan et al. [3], who demonstrated a higher frequency of internal organ damage, such as kidney, and an increased likelihood of intraoperative blood transfusions in patients subjected to CPB. However, patients with preoperative anemia when compared to patients without anemia before surgery had longer MV and time in ICU. Postoperative mortality was also higher [3, 5, 19] in the above works, unlike our study. According to our data, postoperative anemia was common among patients with AVD. The severity of anemia influenced the incidence and nature of internal organ failure. For example, patients with moderate to severe postoperative anemia had an almost sixfold likelihood of brain dysfunction and MOF when compared to patients with blood hemoglobin levels after surgery of 90-130 g/L. Moreover, all patients with postoperative hemoglobin <90 g/L underwent intraoperative blood transfusion three times more often. This fact could probably have influenced the development of internal organ failure due to a possible transfusion-mediated damage, as described by Tuinman et al. [20] and Müller et al. [21] in patients undergoing heart surgeries. These authors highlight the immunoinflammatory mechanism of internal organ failure. It should be noted that, patients with moderate to severe anemia underwent longer and more extensive surgeries than patients with postoperative hemoglobin levels within 90–130 g/L. This resulted in long-term CPB and aortic cross-clamping and greater volume of intraoperative blood loss. Such events could clearly contribute to visceral damage. However, in our opinion, an increased risk of internal organ failure is to a greater extent due to anemia during relatively extensive surgical intervention.

The detection of direct effect of the severity of postoperative anemia on the duration of MV and time in ICU after AVD correction was an important result of this study. According to our data, moderate to severe anemia (hemoglobin levels <90 g/L) after surgery increased the duration of MV by the mean of 5 hours and time in ICU by 4 hours compared to patients with blood hemoglobin levels varying from 90 to 130 g/L.

Since blood transfusion can directly influence visceral damage [6, 20, 21], it was necessary to evaluate its contribution to the development of internal organ failure in the study patients. Correlation between intraoperative RBC transfusion and circulatory decompensation on day 2 after

surgery was discovered. In our opinion, a fivefold increased risk of AHF on day 2 after surgery is not caused by blood transfusion but a condition that requires it. For example, patients who underwent intraoperative RBC suspension transfusion had more severe baseline heart defects and a higher risk of surgical intervention. This was reflected by a higher risk score (Euroscore II). Moreover, the severity of the underlying pathology and postoperative anemia, but not blood transfusion, had adverse effects on the duration of MV and time in ICU. We found no correlation between intraoperative blood transfusion and brain dysfunction, liver dysfunction, acute respiratory distress syndrome, AKI, MOF. Thus, anemia contributes the most to the development of organ failure in patients with AVD.

Conclusion

The presence of preoperative anemia (hemoglobin levels <130 g/L), compared to its absence, in patients undergoing surgery for acquired valve disease, leads to a 5.7-fold increase in the risk of circulatory decompensation on day 2 after surgery, 4.2-fold increase in the development of multiple organ failure, and 4.7-fold increase in the likelihood of intraoperative blood transfusion. Blood hemoglobin levels <90 g/L after valve disease correction increase six-fold the risk of brain dysfunction and organ failure. Moreover, moderate to severe anemia, when compared to mild anemia (hemoglobin levels 90-130 g/L), in patients after surgical intervention on heart valves increases the duration of mechanical ventilation and time in the intensive care unit. In patients with acquired valve defects, the need for intraoperative blood transfusion and extensive surgery leads to a 5.2-fold increase in the risk of circulatory decompensation on day 2 after surgery, while blood transfusion does not increase the likelihood of internal organ failure. The absence of adverse effects of intraoperative blood transfusion on the development of internal organ failure in the postoperative period may support the reasonability of restrictive transfusion management as adopted in the National Medical Research Center of Cardiovascular Surgery n.a. A.N. Bakulev.

No conflict of interest is reported.

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