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Impact of anemia on outcomes in on-pump coronary artery bypass surgery patients

Aim	To study the contribution of preoperative anemia to the prognosis of adverse clinical events (mortality, complications, transfusion) in patients with ischemic heart disease (IHD) after myocardial revascularization in the conditions of artificial circulation.
Material and Methods	This retrospective cohort study included 1133 patients with IHD who had undergone isolated myocardial revascularization in the conditions of artificial circulation in 2019. The primary endpoints were mortality and a composite endpoint that included, in addition to mortality, cases of acute coronary syndrome, heart, respiratory and renal failure, neurological deficit, and infectious complications. The secondary endpoints were duration of artificial ventilation of more than 12 h, duration of stay in the resuscitation and intensive care unit (RICU) of more than one day, and duration of postoperative inpatient treatment of more than 7 days.
Results	Preoperative anemia was found in 196 (17.3%) patients. The anemia was not associated with mortality but increased the risk of the composite endpoint, prolonged artificial ventilation, stay in RICU for more than one day, and red blood cell transfusion. Despite the absence of a relationship between red blood cell transfusion and mortality, the use of transfusion was associated with increased risks of the composite endpoint and prolonged stay in the RICU and hospital.
Conclusion	Preoperative anemia is a risk factor for adverse outcomes of myocardial revascularization in the conditions of artificial circulation. Timely treatment of preoperative anemia may improve outcomes of the treatment.

Keywords	Anemia; ischemic heart disease; coronary bypass; artificial circulation; transfusion
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Introduction

Preoperative anemia, blood loss, and transfusions comprise a triad of mortality in cardiac surgery [1]. However, the timely elimination of this negative factor in candidates for myocardial revascularization surgery has not been given sufficient attention until now. This is explained either by the low significance of more common mild anemia allegedly not requiring treatment or by the small volume of blood loss and good technical maturity of myocardial revascularization surgeries, which are wrongly considered as factors excluding postoperative anemia and allogeneic erythrocyte transfusion. The objective of the present work was to investigate the contribution of preoperative anemia to the prognosis of adverse events (mortality, complications, transfusions) in patients with coronary artery disease (CAD) who were subjected to myocardial revascularization under cardiopulmonary bypass.

Material and Methods

Study design

The retrospective cohort study included 1,133 patients with CAD who underwent isolated myocardial revascularization under cardiopulmonary bypass in 2019. Exclusions from the study comprised patients who underwent emergency surgeries, patients who had previously undergone heart surgeries, or patients who required additional interventions on top of myocardial revascularization (left ventricular aneurysm resection, valvular heart defect correction, etc.). The criterion for anemia was hemoglobin levels below 130 g/L in male patients and below 120 g/L in female patients.

The primary endpoint was mortality; the composite endpoint included mortality, acute coronary syndrome, heart failure, respiratory failure, kidney failure, neurologic deficit, and infectious complications. Secondary endpoints were time of artificial ventilation >12 hours, time in an intensive care unit (ICU) >24 hours, and time in hospital after surgery>7 days.

Characteristics of patients and surgery setting

Clinical characteristics of patients are presented in Table 1. Anemia was not treated prior to surgery. Myocardial revascularization was carried out under normothermic

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cardiopulmonary bypass with a median duration of 78.5 minutes. Aorta clamping was carried out in 77 (6.8%) cases with Custodiol cardioplegia. The number of bypasses ranged from 1 to 7 with a median of 3. There were no cases of bleeding requiring a review of cardiac and pericardial cavities. The volume of intraoperative and postoperative blood loss was 400 [400–500] mL and 50 [50–150] mL, respectively.

If hemoglobin levels were <70 g/L, allogeneic erythrocyte transfusion was indicated during cardiopulmonary bypass; if hemoglobin levels were <70 g/L in the absence of physiological triggers, allogeneic erythrocyte transfusion was indicated in the post-perfusion period; if hemoglobin levels were <80 g/L in the presence of physiological triggers, allogeneic erythrocyte transfusion was indicated (venous oxygen saturation <60%, venous partial oxygen pressure<32 mm Hg).

Statistical processing

Data analysis was performed using SPSS 26.0. The normality of distribution was evaluated using the Kolmogorov–Smirnov test. Quantitative variables are expressed as the median and interquartile range (Me [Q1 Q3]), and qualitative variables are represented as the absolute and relative values (n (%)). The comparison of two quantitative independent variables was carried out using the Mann-Whitney test; qualitative variables were compared using the χ^2criterion. Binary logistic regression analysis was performed for risk assessment purposes.

Results

Effects of preoperative anemia on treatment outcomes

Preoperative anemia was found in 196 (17.3%) patients: 149 (16.1%) male and 47 (21.5%) female patients. Although patients with anemia were slightly older and had higher EuroSCORE scores (Table 1), these variables had no prognostic value in terms of mortality and the composite endpoint (p=0.056 and p=0.187 for age, p=0.985, and p=0.961 for EuroSCORE scores, respectively). Anemia was more often combined with diabetes mellitus and chronic kidney disease (Table 1). However, these comorbidities did not show any impact on mortality and composite endpoint (p=0.056 and p=0.404 for diabetes mellitus and p=0.985 and p=0.512 for chronic kidney disease, respectively) in the multivariate (diabetes mellitus, chronic kidney disease, and anemia as predictors) of the binary logistics model with negative effects of anemia on the composite endpoint (odds ratio (OR) 1.944; 95% confidence interval (CI): 1.004–3.765; p=0.049). It is of note that the incidence of the postoperative acute coronary syndrome was high in patients with baseline anemia (5 (2.6%) versus 8 (0.9%), p=0.042).

Patients with preoperative anemia had significantly lower mean corpuscular diameter (MCD) and mean corpuscular hemoglobin (MCH). While all patients with comparable blood loss had anemia during the postoperative period, its severity was higher in patients with baseline anemia, which was combined with a greater need for ventilation and time in ICU (Table 2). As can be seen in Table 3, reoperative anemia increased the risks of composite endpoint (2-fold), long-term ventilation (1.6-fold), staying in ICU for more than 24 hours (1.9-fold), and the risk of erythrocyte transfusions (4-fold), but was not associated with mortality following myocardial revascularization under cardiopulmonary bypass.

Effects of erythrocyte transfusion on treatment outcomes

Transfusion of allogeneic erythrocytes required 225 (19.6%) patients: 82 (41.8%) and 143 (15.3%) patients with and without baseline anemia, respectively. The volume of transfusions was 343 [323–641] mL. The risk factors for erythrocyte transfusions in the multivariate binary logistics model were age (OR 1.079, 95% CI: 1.056–1.103; p<0.0001), history of chronic kidney disease (2.855–95% CI: 1.514–5.382, p=0.001), preoperative anemia (OR 4.0, 95% CI: 2.9–5.6, p<0.0001), duration of cardiopulmonary bypass (OR 1.013, 95% CI: 1.009–1.017, p<0.0001) and blood loss (OR 1.002, 95% CI: 1.001–1.009; p<0.0001).

Erythrocyte transfusion did not affect the probability of death (p=0.061), but increased the risk of achieving the composite endpoint in the multivariate binary logistic regression. The predictive value was reserved when including in the model the variables associated with transfusions and having significance in the univariate model predicting the composite endpoint (preoperative anemia (Table 3), duration of cardiopulmonary bypass (OR 1.017, 95% CI: 1.010–1.024, p<0.0001), blood loss (OR 1.001, 95% CI: 1.000–1.002, p=0.007) and erythrocyte transfusions (OR 3.407, 95% CI: 1.857–8.251; p<0.0001)) l, the duration of cardiopulmonary bypass (p<0.0001) and transfusion of allogeneic erythrocytes (p=0.022). The risk of staying in ICU for more than 24 hours was affected by blood loss (OR 1.001; 95% CI: 1.000–1.002, p=0.02) and erythrocyte transfusions (OR 3.179, 95% CI: 2.003–5.047; p<0.0001). The risk of long-term staying in hospital was affected only by erythrocyte transfusion (OR 2.263; 95% CI: 1.073–4.776; p=0.032). Adverse outcomes in patients after transfusions were due higher risk of acute coronary events (OR 4.8, 95% CI: 1.6–14.4, p<0.0001), respiratory failure (OR 4.1, 95% CI: 1.2–14.2, p=0.028), neurologic events (OR 4.1, 95% CI: 1.6–10.5, p=0.003) and infectious complications (OR 3.7, 95% CI: 1.5–9.2; p=0.005).

Discussion

Baseline anemia is common among cardiac surgical patients [2]. Preoperative anemia has intrinsic adverse

Table 1. Clinical and laboratory characteristics of patients

Parameters		All patients, n=1133, n (%), Me [Q1-Q3]	Group comparison		p
			Anemia +, n=196, n (%), Me [Q1-Q3]	Anemia –, n=937, n (%), Me [Q1-Q3]	
Sex	Male	915 (80.8)	149 (76)	766 (81.8)	0.064
	Female	218 (19.2)	47 (24)	171 (18.2)	
Age, years		63 [57–68]	66 [61–70]	62 [57–67]	0.0001
Body mass index, kg/m^2		28.7 [26.0–31.6]	28.7 [25.7–31.6]	28.7 [26.0–31.8]	0.310
Circulatory failure functional class		2 [2–3]	2 [2–3]	2 [2–3]	0.746
EuroScore		2.2 [1.5–3.3]	2.5 [1.7–5.0]	2 [1.5–3]	0.011
Diabetes mellitus		273 (23.8)	67 (34.2)	205 (21.9)	0.0001
Chronic kidney disease		42 (3.7)	14 (7.1)	26 (2.8)	0.005
History of stroke		64 (5.6)	10 (5.1)	51 (5.4)	0.848
Chronic obstructive pulmonary disease		130 (11.4)	20 (10.2)	104 (11.1)	0.712
Hypertensive heart disease		1043 (91.1)	179 (91.3)	853 (91)	0.896
Hemoglobin, g/L		140.8 [131.5–150.5]	119.8 [114–126.7]	144.8 [136.6–152.5]	0.0001
Erythrocytes, ×10^9/L		4.9 [4.6–5.2]	4.3 [4–4.6]	5 [4.7–5.3]	0.0001
MCV, fL		89.6 [86.5–92.4]	87.6 [84.2–91]	89.8 [87.1–92.6]	0.0001
MCH, pg		29 [27.8–30.1]	28.1 [26.3–29.8]	29.1 [28.0–30.1]	0.0001
Platelets, 10^9/L		242.7 [206.0–283.4]	245.8 [204–291]	241.5 [206.4–280.7]	0.359
Creatinine, μmol/L		84.4 [74.7–96.7]	84.6 [73.2–98.5]	84.4 [75–96.4]	0.949
APTT, sec		31.1 [29.3–33.8]	31.6 [29.1–34.1]	31.1 [29.4–33.7]	0.689
INR		1.03 [1.00–1.09]	1.04 [1.00–1.09]	1.03 [1.00–1.09]	0.573
Fibrinogen, g/L		4.3 [3.8–5]	4.54 [3.79–5.25]	4.35 [3.83–5.01]	0.076

p is the significance of differences between the patients with and without anemia.

Table 2. Changes in the levels of hemoglobin, blood loss, and duration of treatment of patients subject to the presence of preoperative anemia

Variable	Anemia +, n=196, Me [Q1-Q3]	Anemia –, n=937, Me [Q1-Q3]	p
Hemoglobin, day 1, g/L	96 [88.7–105.2]	111 [99.4–123.0]	0.0001
Hemoglobin, day 3, g/L	88.9 [78.3–100.9]	102.1 [90.3–112.4]	0.0001
Hemoglobin, day 5, g/L	95.5 [87.7–107.9]	110.8 [99.2–121.2]	0.0001
Intraoperative blood loss, mL	400 [400–500]	400 [400–500]	0.999
Postoperative blood loss, mL	0 [0.0–162.5]	0 [0–150]	0.531
Duration of cardiopulmonary bypass, min.	80 [60–105]	78 [60–101]	0.725
Duration of ventilation, hours	11 [7–17]	10 [7.0–13.5]	0.018
Time in ICU, days	0.8 [0.7–1.0]	0.8 [0.7–0.9]	0.024
Time in hospital, days	10 [8–13]	9 [8–12]	0.089

ICU – intensive care unit; p – significance of differences between patients with and without anemia.

Table 3. Anemia as an independent risk factor for adverse postoperative outcomes

Variable	Anemia +, n=196, n (%)	Anemia –, n=937, n (%)	OR	95% CI	p
Mortality	2 (1)	13 (1,4)	0,7	0,2–3,3	0,684
Composite endpoint	13 (6,6)	33 (3,5)	1,946	1,005–3,770	0,048
Ventilation>12 hours	75 (41,9)	253 (30,7)	1,63	1,17–2,27	0,004
Time in ICU>24 h	30 (15,5)	84 (9,0)	1,85	1,18–2,91	0,007
Time in hospital >7 days	182 (93,8)	869 (92,9)	1,2	0,6–2,2	0,663
RBC transfusion	82 (41,8)	143 (15,3)	4,0	2,9–5,6	0,0001

OR – odds ratio; CI – confidence interval; ICU - intensive care unit;
p – the significance of differences between patients with and without anemia.

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effects [3–5]. However, its severity after surgery is aggravated by intraoperative hemodilution, phlebotomy [6], surgical blood loss, inflammation. Trials performed in large patient cohorts with a history of coronary artery bypass grafting showed a fivefold increase in the risk of death and complications in patients with baseline anemia [7–9].

The unique feature of our study is the analysis of a relatively homogeneous group of patients in terms of baseline state and volume of surgical intervention. Despite the lack of correlation between baseline anemia and mortality, the former is associated with an increased number of complications and longer hospital time, as well as being a risk factor for erythrocyte transfusions. These results are even more disappointing considering that this factor can be modified at the preoperative stage, potentially allowing a significant proportion of postoperative complications to be prevented.

The microcytosis and hypochromia of erythrocytes observed in patients with baseline anemia indicate the predominant significance of iron deficiency in its development. It appears that baseline iron deficiency may cause a higher incidence of postoperative acute coronary events in patients with anemia, as iron plays a key role in energy processes, including in the maintenance of normal myocardial function [10, 11].

Due to the higher prevalence of anemia in patients over the age of 60 years with diabetes mellitus and chronic kidney disease, this category requires special attention when identifying and diagnosing the causes of anemia. In addition to iron deficiency, erythropoiesis disorders caused by bone marrow dysfunction or decreased erythropoietin secretion may be a negative factor leading to anemia in these categories of patients. The inhibition of erythropoiesis as a result of iron deficiency, reduced erythropoietin secretion, bone marrow dysfunction, and increased hepcidin secretion, requires timely pharmacological management for eliminating both anemia and its associated conditions.

Having combined various causes of anemia in cardiac surgical patients, we developed and introduced a protocol of preoperative preparation of candidates for surgery under cardiopulmonary bypass into routine clinical practice. The protocol included the main stages of diagnosis of anemia and evaluation of iron metabolism, principles of differential diagnosis of anemia, targeted therapy of anemia, and criteria of patient preparation effectiveness (Figure 1). Given the smaller volume of circulating blood in a female organism and the blood loss volume comparable with male patients, a higher baseline concentration of hemoglobin (at least 130 g/L) is desirable for female patients.

There is currently no reason to complain of insufficient time to prepare a patient for surgery. Although the optimal

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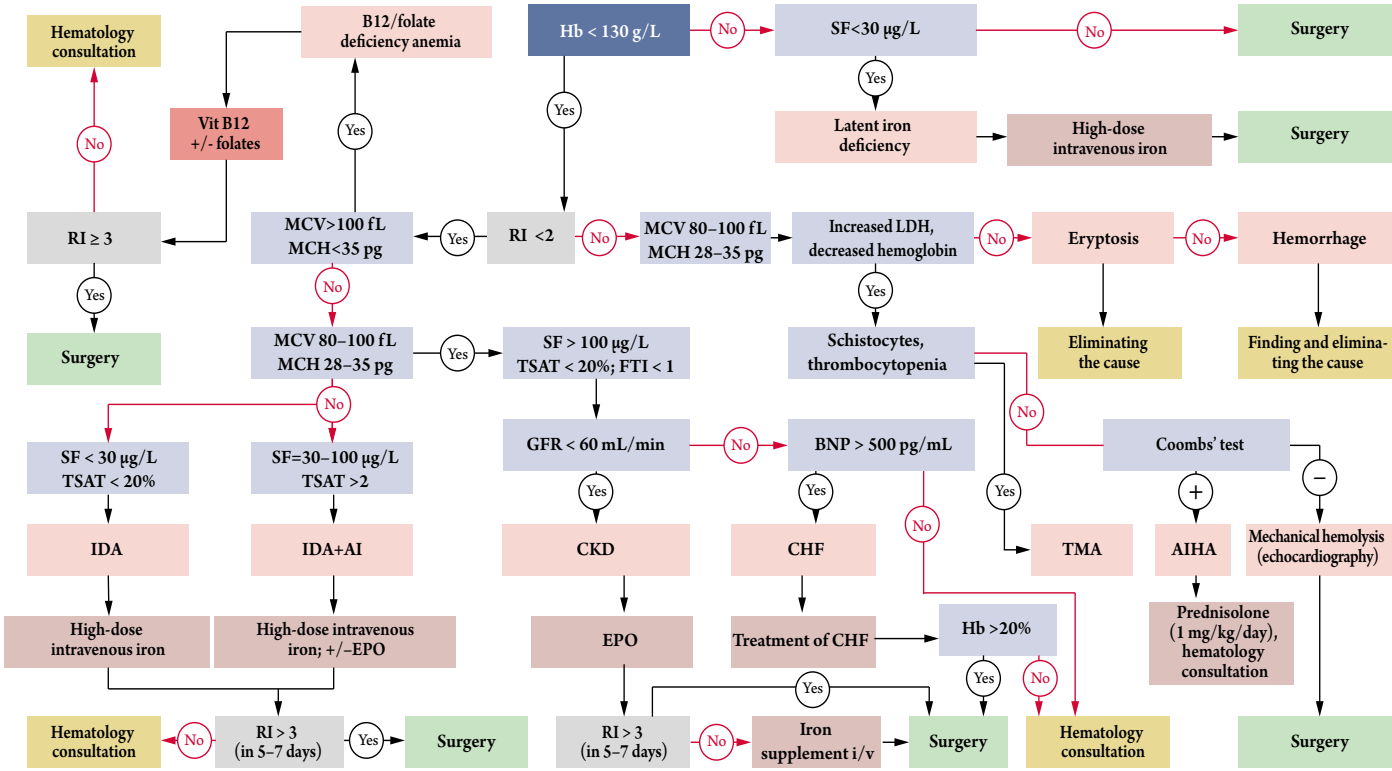
Figure 1. Correction algorithm for preoperative anemia and iron deficiency in cardiac surgery patients



Iron carboxymaltozate is a treatment of choice in iron deficiency combined with anemia and chronic heart failure.
Hb – hemoglobin; SF – serum ferritin; RI – reticulocyte index; LDH – lactate dehydrogenase; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; TSAT – transferrin saturation; BNP – B-type natriuretic peptide; FTI – ferrytin transferrin index (TSAT/logSF); GFR – glomerular filtration rate; TMA – thrombotic microangiopathy; AIHA – autoimmune hemolytic anemia; CHF – chronic heart failure; CKD – chronic kidney disease; IDA – iron deficiency anemia; AI – anemia of inflammation; EPO – erythropoietin.

duration of such preparation should be six weeks, this can be reduced to a few days (preoperative examination) or carried out on the eve of the surgery [12], meaning that it can be carried out in a 24-hour or day hospital. In other words, any action aimed at eliminating anemia is better than doing nothing but using allogeneic erythrocytes.

It is necessary to pay attention to the development of postoperative anemia in patients without baseline anemia since this cannot be explained by blood loss comparable to a donation volume. Under such conditions, the evident reason for a decrease in hemoglobin levels is not a decrease in its total mass but rather an increase in the volume of circulating blood due to hemodilution. While on the one hand, this fact can result in hyperdiagnosis of true postoperative anemia and unreasonable use of erythrocyte transfusions, on the other hand, it draws attention to excessive adherence to infusion therapy, whose usefulness is currently disputed.

Therapeutic use of allogeneic erythrocytes remains high despite precision surgical techniques, significant changes in transfusion management in cardiac surgery [13–16], and various blood-saving methods. While this may comprise an effective method in situations when immediate anemia correction is required, it is not so effective for etiological or pathogenetic treatment due to its failure to eliminate the causes of anemia and various potential adverse outcomes [17]. Comorbidities and duration of therapy increase many times after transfusion of allogeneic erythrocytes [18–22]. Increased hemoglobin levels after erythrocyte transfusion are associated with increased estimated oxygen delivery; however, the actual improvement of tissue oxygenation is not often observed [23, 24]. This may be due either to an imbalance between oxygen delivery and consumption not related to anemia, which means that erythrocyte transfusion was not caused by the clinical situation, was not indicated and therefore was ineffective, or else to possible changes in donor erythrocytes during harvesting, processing, and storage [25–32].

As expected, low preoperative hemoglobin levels are shown to be a predictor of blood transfusion. Allogeneic erythrocyte transfusion is mainly required following the loss of a large volume of blood, which determines the development and higher severity of postoperative anemia. Thus, the following three unrealized possibilities should be addressed: preoperative treatment of anemia; autoerythrocyte reinfusion at all stages of therapy; early stimulation of erythropoiesis (beginning from the first postoperative days).

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Interestingly, erythrocyte transfusions, which were also a consequence of preoperative anemia, had a greater influence on the endpoints. Therefore, transfusions should be used when there are no other options; hemoglobin levels cannot be considered as the only indication for erythrocyte transfusion, but physiological triggers should also be taken into account [33]. When considering transfusions in patients without baseline anemia, two potential causes should be addressed, namely blood loss and hemodilution. Here, it is necessary to clearly understand that deficient surgical hemostasis and resulting blood loss trigger a complex of pathological processes, of which anemia is the most innocuous, which cannot be eliminated (are rather aggravated) by transfusion of donor erythrocytes. Therefore, our study confirms the advantage of abandoning the ineffective tactic of «replacement of blood loss» using blood components and moving towards an approach characterized by «exclusion of blood loss». Similar close attention should be paid to excessive infusion therapy, which is often undertaken in patients with severe postoperative heart failure, whose increased preload results in vicious circles and worsened treatment prognosis. Thus, transfusions in patients without baseline anemia are treatment-induced and can be successfully prevented.

Conclusion

In conclusion, blood component transfusions in cardiac surgery serves as a criterion of quality of medical care since it reflects the inadequacy of patient preparation, the imprecision of surgical and anesthetic/perfusion techniques, as well as the severity of the postoperative course. Thus, coronary surgery carried out under conditions where blood component consumption tends to be zero should be considered the ideal. However, the achievability of this condition is subject to preoperative treatment of anemia and the exclusion of irreversible blood loss.

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