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RELATIONSHIP BETWEEN ALLOGRAFT PERFUSION PREPARATION VARIATIONS AND RATE OF ARTERIAL AND BILIARY COMPLICATIONS IN ORTHOTOPIC LIVER TRANSPLANTATION

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Objective: to evaluate the possible influence of different graft perfusion preparation variations on the incidence of biliary and vascular complications of orthotopic liver transplantation (OLT). **Materials and methods.** Data on 287 full-size liver transplants from donors with brain death and beating heart were processed. There were 262 and 25 primary and repeat OLTs, respectively. Before completion of portal anastomosis formation and inclusion into systemic blood flow, the graft was perfused with hypo- (group 2) and isotonic (group 4) saline in order to minimize hemodynamic disorders. **Results.** There was a statistically significant difference between groups 2 and 4 in the development of late ($p = 0.04$) and cumulative biliary complications ($p = 0.01$). The presence of these complications and the perfusion type were found to be associated (Fisher's exact test = 0.02). There were no differences in incidence of thrombosis in the studied groups. **Conclusion.** The conducted analysis suggests that it is inexpedient to use hypothermic solutions when preparing a liver transplant for perfusion before introducing it into systemic circulation.

Keywords: liver transplantation, post-transplant biliary complications, allograft preparation for perfusion.

INTRODUCTION

Liver transplantation (LT) is the only effective treatment for progressive liver failure and life-threatening complications of portal hypertension [1–3]. The pressing concern in transplantation, notwithstanding the high standards of surgical procedure, is to lower the rate of complications that result in graft dysfunction and loss. Prolonged hypotension in the donor during conditioning, the recipient's severe state at the time of transplantation, and a significant amount of intraoperative blood loss can be an adverse background for complications [4, 5]. Cold and warm ischemia time and the severity of allograft steatosis are proven factors in the development of graft dysfunction and complications [6–8].

Various methods of physical, chemical, therapeutic and other effects on the harvested organ are used, potentially reducing the negative impact of conservation stages. In several reports, there are different data on preliminary preparation of the transplant before introducing it into the systemic circulation. The benefitsof both normothermic and hypothermic machine perfusion are described with the purpose of "functional" preservation of the allograft in donor after cardiac death and reduction in the intensity of ischemia-reperfusion syndrome in recipients [9–11]. It is worth considering the assertion made by some authors that retrograde perfusion, unlike the classical technique in LT, lowers the concentration of toxic metabolites in the allograft that build up during the preservation process. This reduces the risks of significant hemodynamic disorders when the graft is introduced into systemic circulation in contrast to the classical OLT technique and the severity of reperfusion syndrome [12, 13].

No less significant are the elimination of technical flaws at all stages of transplantation, and peculiarities of the postoperative period, where the graft's adequate arterial blood supply is crucial. In this regard, minimizing negative factors that influence the development of arterial and biliary complications is one of the primary goals to preserve its full function, which determines the quality of life and prognosis in the recipient [14, 15]. Prevention of viral hepatitis recurrences in a significant proportion of recipients also remains an urgent task [16].

Methods of statistical processing of information

Pearson's chi-square test was used to establish regularities between categorical variables, and Fisher's exact test was used when the expected frequency of a characteristic was less than 10. Parametric Student's t test and non-parametric Mann–Whitney U test were used to determine the differences between two quantifiable independent variables. Kruskal–Wallis analysis of variance was used to compare the medians of independent samples from three or more groups. The Kaplan–Meier life table method was used to estimate survival rates. The arithmetic mean and standard deviation were used as measures of descriptive statistics, and for heterogene-

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ous data or small samples, the median and interquartile range (IQR) of 25–75% (in square brackets) were used.

MATERIALS AND METHODS

General Information

During the period from June 1998 to April 2023, 287 full-size liver transplants from donors with brain death and beating heart were performed at the Russian Research Center of Radiology and Surgical Technologies ("Research Center"). Indications for OLT were irreversible liver disease leading to predicted death within 6–12 months, with no effect from ongoing conservative treatment. Viral hepatitis resulting in cirrhosis and cholestatic diseases were the most common causes of disease that led to OLT. When preparing the liver transplant, its color, edge, density, presence of focal changes and fibrosis were evaluated. If steatosis was suspected, the suitability of the organ for transplantation was reevaluated after cold perfusion with Custodiol solution (Custodiol HTK, Kohler, Germany). Subsequently, express morphologic examination of the biopsy specimen was required in 37 (12.9%) cases. In our Research Center, LT with macrovesicular steatosis of more than 50%, diagnosed by express biopsy, was not performed. During routine examination of native biopsy specimens according to the degree of severity of macrovesicular steatosis (1–4) of the graft, distribution was performed in the following order: grade 1 (1–10%), grade 2 (11–30%), grade 3 (31–50%), grade 4 (>50%).

Primary and repeat OLT was performed in 262 and 25 cases, respectively (retransplantation was performed twice in 3 recipients). There were 116 (44.3%) men and 146 (55.7%) women who underwent transplantation. Their age ranged from 18 to 64 years, the mean was 45.1 ± 11.3, and median 46.8 years [IQR 38.8–53.9 years].

Surgical stages of transplantation

The main surgical stages were standard, including isolation of liver from the ligamentous apparatus and adhesions, arterial, portal, and venous devascularization followed by hepatectomy. Caval reconstruction variants are shown in Table 1.

Portal reconstruction was performed by end-to-end anastomosis. Before the final completion of portal anastomosis, the allograft was perfused (flushed) through the portal vein in 400–500 mL of blood with further inclusion of the liver into the systemic circulation (group 1, n = 83).

The retrograde liver perfusion variation was not performed in our Research Center in any case.

Table 1

Reconstruction variants of caval anastomoses

Anastomosis variant	Number of observations	%
Classic technique	45	15.7
Cavocavostomy	65	22.6
Piggyback	177	61.7
Total	287	100

Graft perfusion preparation

Significant hemodynamic complications – persistent hypotension, arrhythmia and asystole – were frequently encountered at the stage of organ incorporation into systemic circulation. The cause of these conditions was the entry into the blood of excess amount of ionized potassium, contained both in the perfusate (custodiol) and leaving the cytosol of hepatocytes in the process of preservation. Also, the factor of rapid one-time blood loss during the final flushing of the organ with portal blood played a major role in the genesis of these hemodynamic disorders.

In order to minimize or prevent hemodynamic disorders before the final flushing of the allograft through the portal vein, we started to perfuse the graft with 500–1500 mL of saline cooled to 2–4 °C (group 2, n = 85), and then with addition of 10% albumin solution in order to approach the osmotic and oncotic blood parameters (group 3, n = 61). The justification for the use of hypothermic solutions was based on the published printed works about the possibility of prolonging the optimal preservation of graft and its energy resources [17–18]. Preliminary perfusion of the organ was terminated when the amount of ionized potassium in the fluid passing from the liver through the inferior vena cava (IVC) reached a physiological or low level. Saline perfusion into the portal vein lasted for 5–15 minutes, the pressure of the injected fluid did not exceed physiologic parameters (10–12 mmHg).

As experience was gained with the use of preliminary perfusion of organs with solutions of different temperatures, operating surgeons began to note the peculiarities of the donor liver condition. After washing with hypothermic solutions, at the stage of inclusion into systemic circulation, palpatory irregular density increase, mosaic coloration of the organ parenchyma, as well as decrease in volumetric velocity of blood flow through graft arteries after arterial reconstruction and start-up were observed. At the same time, the patency of graft arterial bed before and after anastomosis, and adequate outflow through hepatic veins were preserved. This could indicate a disruption in intraorgan microcirculation and an increase in peripheral vascular resistance. The abovementioned changes prompted us to abandon hypothermic perfusion in favor of isothermal perfusion.

We started perfusing the organ with saline at a temperature of 20–24 °C; the amount of fluid varied from 500 to 2000 mL. Following the commencement of portal blood flow in the transplant, 200–250 mL of blood were used for extra "flushing" of the liver through the IVC

subhepatic segment. This was followed by suturing of the "window" in the vein (group 4, n = 58) and inclusion of the transplanted organ into systemic circulation.

In order to evaluate the influence of the temperature factor and to correctly compare the perfusion preparation variations in the comparison groups, we used perfusion variation 2 (n = 85), where 500–1500 mL saline cooled to 2–4 °C was used, and perfusion variation 4 (n = 58), where saline with a 20–24 °C temperature was used, and the fluid volume varied from 500–2000 mL.

Groups 1 and 3 were not included in the comparative analysis due to different perfusion variations: no saline solution was injected into the group 1 graft, albumin was added in group 3.

Arterial reconstruction

Further, arterial reconstruction with standard anatomy was performed in most cases by forming an anastomosis with the donor's proper hepatic artery (PHA) (Table 2).

Arterial reconstruction with donor's proper hepatic artery (PHA) was performed in 70.4% (n = 202); in 57 of 202 cases, a common site with the donor's gastroduodenal artery was formed to match the diameters of the vessels being sutured. The second most frequent variant was anastomosis with the donor's common hepatic artery – 16.4% (n = 47). Separate anastomoses were used in 8.7% of cases (n = 25). This was due to the branching of the substitute right hepatic artery (RHA) of the donor organ by a separate trunk (from the superior mesenteric artery) or the presence of a significant accessory left hepatic artery (LHA). In these cases, reconstruction was most often performed by anastomosing with the recipient's RHA and LHA, respectively. Most arterial anastomoses were formed by continuous sutures (using the parachute technique) with Prolene 6/0 suture. A small number of anastomoses were formed by separate interrupted sutures using Prolene 7/0–8/0 suture. In 13 recipients (4.5%), the graft arteries were sutured directly to the aorta using a vascular graft. In 9 out of 13 cases, this technique was used in liver retransplantation due to severe scar adhesions in the subhepatic space.

Table 2

Reconstruction variants of arterial anastomosis

Reconstruction variant	n	%
PHA (d) – vessels (p)	202	70.4
CHA (d) – vessels (p)	47	16.4
Split anastomosis	25	8.7
Aortic anastomosis	13	4.5
Total	287	100

Note: PHA, proper hepatic artery; CHA, common hepatic artery.

Table 3

Biliary reconstruction variants

Biliary reconstruction variant	n	%
BBA with external drainage	161	56.1
BBA on lost drainage	39	13.6
BBA without drainage	53	18.5
HPA	28	9.7
Cholangiostomy	4	1.4
Other	2	0.7
Total	287	100

Note: BBA, biliobiliary anastomosis; HPA, hepatic portoenteroanastomosis.

Biliary reconstruction

Biliobiliary anastomosis was formed in the vast majority of transplantations, including repeat transplants, when the recipient's bile duct was identified (Table 3). At the beginning of the practice, biliodigestive anastomosis on the loop of small intestine disconnected by Roux was performed in recipients with primary sclerosing cholangitis and at retransplantations. However, with our own experience, we concluded that primary biliodigestive anastomosis is applicable only in cases of "absence" of normal anatomy of the recipient's common bile duct, patency of its lumen after revision of hepatoduodenal ligament elements, less often in case of repeat OLT.

When transecting the graft bile duct, the degree of adequacy of blood supply at its incision was assessed; if necessary the duct was dissected proximally. When forming a biliobiliary anastomosis, we used absorbable suture material (PDS 6/0, less often 5/0), a separate interrupted suture. If there was obvious mismatch between the diameters of the ducts to be sutured (small diameter of the donor part), we resorted to combining the hepatic and cystic ducts into one site. Different drainage variants were resorted to in the event that reconstruction proved problematic or the course was expected to be complicated (presence of cholangitis, pancreatitis, sludge syndrome). Since 2019, almost no external drainage has been done.

Hypothesis and justification for its possible causes

The reason for the study was the differences in the incidence of postoperative biliary complications for different variations of transplant perfusion preparation (Table 4).

To analyze possible factors that are directly or indirectly influencing biliary complications, the following were evaluated:

1. Cold and warm time,
2. Duration of anhepatic phase,
3. Arterial reconstruction time (before its start),
4. Intraoperative blood loss (estimated by the volume of exchange transfusion),

5. Severity of patient's condition according to the MELD score at the time of transplantation (data before 2007 were considered retrospectively).

Evaluating the influence of the severity of allograft macrovesicular steatosis on the development of post-transplant complications, a study of biopsies of the "native" liver was conducted in 141 (98.6%) of 143 recipients (perfusion variations 2 and 4). No biopsy was performed in 2 cases.

The correlation of problems of arterial blood supply to the graft with the development of postoperative biliary complications was analyzed. Taking into account the leading role of arterial insufficiency in biliary complications, we also carried out the statistical processing of preservation parameters and intraoperative indicators of the problems of arterial blood supply of the graft. We took into account all the facts of its surgical and x-ray endovascular correction performed intraoperatively, as well as in the early and late periods after liver transplantation.

RESULTS

When analyzing the incidence of biliary complications in the comparison groups with perfusion variations 2 and 4, the following results were obtained (Table 5).

There was a statistically significant difference between groups 2 and 4 in the development of late* (p = 0.04) and all* biliary complications (p = 0.01).

In terms of severity of graft steatosis, the perfusion variations 2 and 4 groups, who subsequently had early biliary complications, were comparable (Cochran–Armitage test for trend p = 0.130).

In recipients (perfusion variations 2 and 4) with late biliary complications, the following results were obtained (Cochran–Armitage test for trend, p = 0.026), Table 6.

Thus, the majority of allografts of both study groups had grade 1 steatosis (1–10%), and did not statistically differ from each other (p = 0.063) in the development

Table 4

Frequency of biliary complications

Perfusion variation	Number of early complications (n/%)	Number of late complications	Total
1 (n = 83)	2 (2.4%)	7 (8.4%)	9 (10.8%)
2 (n = 85)	15 (17.6%)	14* (16.5%)	29* (34.1%)
3 (n = 61)	5 (8.2%)	8 (13.1%)	13 (21.3%)
4 (n = 58)	6 (10.3%)	3* (5.2%)	9* (15.5%)
Total (n = 287)	28 (9.8%)	32 (11.1%)	60 (20.9%)

Note: *, p < 0.05.

Table 5

Frequency of biliary complications in groups 2 and 4

Perfusion variation	Number of early complications (n/%)	Number of late complications	Total
2 (n = 85)	15 (17.6%)	14* (16.5%)	29* (34.1%)
4 (n = 58)	6 (10.3%)	3* (5.2%)	9* (15.5%)
p (CI <95%)	0.23	0.4	0.01
Total (n = 143)	21 (14.7%)	17 (11.9%)	38 (26.6%)

Note: *, p < 0.05.

Table 6

Distribution of recipients by degree of macrovesicular steatosis

Degree of steatosis	Complications (perfusion variation 2)		P (CI <95%)
	No	Yes	
1 (1–10%)	52 (61.2%)	13 (15.3%)	0.811
2 (11–30%)	1 (1.2%)	1 (1.2%)	0.293
3 (31–50%)	1 (1.2%)	0	0.614
4 (>50%)	1 (1.2%)	0	0.614
Degree of steatosis	Complications (perfusion variation 4)		P (CI <95%)
	No	Yes	
1 (1–10%)	40 (69%)	3 (5.2%)	0.446
2 (11–30%)	7 (12.1%)	0	0.481
3 (31–50%)	1 (1.7%)	0	0.803

of complications. It is worth noting the relatively small sample of steatosis grade 2 and higher in both groups. However, its severity with and without complications in recipients was not significantly different in both study groups.

The indicators of the studied factors of late complications (Table 7), in their absence (Table 8), as well as generalized data (Table 9) are presented below.

Table 7 shows that there is a two-fold difference between median duration of arterial reconstruction and of

Table 7

Analyzed indicators in recipients with late biliary complications

Parameters/ perfusion		Medians				
	CI (min)	WI (min)	AHP (min)	Art.Rec (min)	MELD	ET (mL)
2	355 [253.8–426.3]	50 [38.8–60]	82.5 [65–98.8]	32.5 [25–48.80]	17 [16–20]	846.5 [401–1631.8]
4	275 [275–282.5]	50 [40–70]	115 [80–120]	62.5 [40–73.8]	17 [12–18]	1660 [828–2387]
p (CI <95%)	0.432	0.676	0.768	0.264	0.953	0.3

Test Statistics[a]

	ET (mL)	MELD	CI (min)	WI (min)	AHP (min)	Art.Rec (min)
Mann–Whitney U	12.000	20.000	14.000	17.000	18.000	5.000
Wilcoxon W	117.000	26.000	20.000	122.000	123.000	83.000
Z	–1.134	–0.129	–0.885	–0.509	–0.379	–1.287
Asymp. Sig. (2-tailed)	0.257	0.897	0.376	0.611	0.705	0.198
Exact Sig. [2*(1-tailed Sig.)]	0.3	0.953	0.432	0.676	0.768	0.264

Note: WI, warm ischemia; CI, cold ischemia; AHP, anhepatic phase; Art.Rec, arterial reconstruction duration; MELD, Model of End-stage Liver Disease; ET, exchange transfusion; *, $p < 0.05$.

Table 8

Analyzed indicators in recipients without biliary complications

Parameters/ perfusion		Medians				
	CI (min)	WI (min)	AHP (min)	Art.Rec (min)	MELD	ET (mL)
2	330 [281.3–402.5]	45 [40–55]	75 [65–93.8]	30 [23.8–42.5]	17.5 [13–21]	842 [406–1973]
4	325 [262.5–397.5]	60 [45–65]	85 [70–105]	40 [30–53.8]	19 [15.5–22]	1817 [817.3–2400]
p (CI <95%)	0.321	0.001*	0.017*	0.035*	0.1	0.003*

Test Statistics[a]

	ET (mL)	MELD	CI (min)	WI (min)	AHP (min)	Art.Rec (min)
Mann–Whitney U	896.000	1121.500	1217.500	864.000	1003.000	749.500
Wilcoxon W	2492.000	2717.500	2442.500	2460.000	2599.000	1652.500
Z	–2.921	–1.614	–0.993	–3.284	–2.377	–2.106
Asymp. Sig. (2-tailed)	0.003*	0.107	0.321	0.001*	0.017*	0.035*

Note: WI, warm ischemia; CI, cold ischemia; AHP, anhepatic phase; Art.Rec, arterial reconstruction duration; MELD, Model of End-stage Liver Disease; ET, exchange transfusion; *, $p < 0.05$.

Table 9

Analyzed parameters of all recipients with perfusion variations 2 and 4

Parameters/ perfusion		Medians				
	CI (min)	WI (min)	AHP (min)	Art.Rec (min)	MELD	ET (mL)
2	330 [270–410]	45 [40–55]	75 [62.5–92.5]	30 [25–55]	17 [14–20.5]	931 [431–1742.5]
4	295 [263.8–386.25]	55 [45–65]	85 [70–105]	40 [25–50]	18.5 [17.8–23]	1759 [765–2387]
p (CI <95%)	0.199	0.001*	0.006*	0.207	0.1	0.004*

Test Statistics[a]

	ET (mL)	MELD	CI (min)	WI (min)	AHP (min)	Art.Rec (min)
Mann–Whitney U	1738.500	2067.000	2153.000	1671.500	1797.500	1654.500
Wilcoxon W	5393.500	5722.000	3864.000	5326.500	5452.500	4000.500
Z	–2.847	–1.641	–1.283	–3.282	–2.752	–1.261
Asymp. Sig. (2-tailed)	0.004*	0.101	0.199	0.001*	0.006*	0.207

Note: *, $p < 0.05$.

exchange transfusion. Nevertheless, in all parameters examined, there was no statistically significant difference between the groups with perfusion variations 2 and 4.

When analyzing the parameters (Table 8), there was a statistically significant difference in warm ischemia time, anhepatic phase duration, arterial reconstruction and volume of exchange transfusion (more in group 4).

In all patients from the analyzed groups (2 and 4), there was a statistically significant difference in warm ischemia time, anhepatic phase duration, and exchange transfusion volume, which prevailed in group 4.

In order to determine the influence of the transplant perfusion preparation variations (groups 2 and 4), the following statistical processing was performed (Table 10).

Estimating the odds ratios and relative risk, the chances of complications with variation 2 perfusion are 2.819 times higher than with variation 4.

Regression analysis models were used to identify the possible impact of the analyzed parameters (as risk factors) on the incidence of biliary complications. Preliminary testing showed that distributions in the sample of features, except for MELD, were significantly different

Table 10

Analysis of correlation of biliary complications with perfusion variations

Complications * Perfusion Cross Tabulation (a)

			Perfusion		Total
			2	4	
Complications	No	Count	56_a	49_b	105
		% within	65.9%	84.5%	73.4%
	Early	Count	15_a	6_a	21
		% within	17.6%	10.3%	14.7%
	Late	Count	14_a	3_b	17
		% within	16.5%	5.2%	11.9%
Total		Count	85	58	143
		% within	100.0%	100.0%	100.0%

The results demonstrate that there were no complications in 65.9% cases of variation 2 perfusion and in 84.5% cases of variation 4 perfusion. Late complications were more frequent in perfusion 2 (16.5%) than in perfusion 4 (5.2%), $p < 0.05$.

Complications Perfusion Cross Tabulation (b)

			Perfusion		Total
			2	4	
Complications	No	Count	56_a	49_b	105
		% within	65.9%	84.5%	73.4%
	Yes	Count	29_a	9_b	38
		% within	34.1%	15.5%	26.6%
Total		Count	85	58	143
		% within	100.0%	100.0%	100.0%

According to general processed data for groups 2 and 4, it was noted that complications appeared significantly more frequently in variation 2 perfusion (34.1%) than in variation 4 (15.5%).

Chi-Square calculation for the table by five methods (c)

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6.113[a]	1	0.013		
Continuity Correction	5.197	1	0.023		
Likelihood Ratio	6.414	1	0.011		
Fisher's Exact Test				0.020	0.010
Linear-by-Linear Association	6.070	1	0.014		
N of Valid Cases	143				

Fisher's exact test ($p = 0.02$) is presented for the processed data.

Risk Estimate (d)

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Perfusion (2 / 4)	2.819	1.217	6.534
For cohort Compl_b = 1	2.199	1.126	4.293
For cohort Compl_b = 2	0.780	0.646	0.942
N of Valid Cases	143		

from normal, and statistical significance at preliminary testing was insignificant ($p > 0.05$).

Analysis of transplant arterial insufficiency

Proceeding from the proven association between transplant arterial insufficiency and biliary complications, an analysis of factors potentially influencing the development of intraoperative, early and late thrombosis and graft arterial insufficiency was done (generally – transplant arterial insufficiency, Table 11).

Analyzing the data in Table 11, we obtained a significant difference in the frequency of intra- and postoperative complications. However, there were no significant difference when comparing cumulative complications between groups 2 and 4 ($p = 0.96$).

Direct ultrasound flowmetry and duplex scanning of liver vessels in all recipients were used to assess the arterial volumetric blood flow velocity.

Intraoperative thrombosis of the hepatic artery trunk or its lobular branches, which required repeated reconstruction, was observed in 4 cases (2.8%), of which 3 recipients underwent separate lobular arterial anastomosis. Early and late postoperative thrombosis developed in 5 (3.5%) and 2 (1.4%) cases, respectively. In 6 (4.2%) cases, arterial blood supply in the graft was restored by means of X-ray endovascular techniques, only in one case was open thrombectomy performed (Table 12).

As follows from Table 12, there was no significant difference in the incidence of thrombosis in perfusion groups 2 and 4.

After conducting a statistical analysis of the factors under investigation, we found that groups 2 and 4 differed significantly in terms of volume of exchange transfusion required for all cases of thrombosis and the severity of the condition (MELD) in intraoperative thrombosis cases (Table 13).

In 3 (3.5%) cases from group 2, intraoperative correction of graft arterial blood supply was performed due to anastomosis deformity, kinking or doubts about arterial patency. This situation was more often observed when anastomosis was formed separately with the lobar arteries. Anastomoses were revised using a Fogarty catheter, the vascular bed was heparinized, and if there were no improvements, repeated arterial reconstruction was carried out. In one case, arterial inflow was corrected endovascularly.

Transplant arterial insufficiency was assumed on the basis of a decrease in volumetric velocity of blood flow through the hepatic artery to less than 100 mL/min (according to intraoperative flowmetry), provided that there were no palpatory and visual signs of anastomotic

Table 11

Frequency of liver transplant arterial insufficiency in different periods

Group (n)	Intraoperative (n/%)	Postoperative (n/%)		Total (n/%)
		Early	Late	
2 (n = 85)	15/17.6	5/5.9	9/10.6	29/34.1
4 (n = 58)	1/1.7	18/31	1/1.7	20/34.4
p (CI 95%)	0.003*	0.001*	0.04*	0.96
Total: 143 OLT	16/11.2	23/16.1	10/7	49/34.3

Note: *, $p < 0.05$.

Table 12

Frequency of arterial thrombosis in OLT

Group (n)	Intraoperative thrombosis (n/%)	Postoperative thrombosis (n/%)		Total (n/%)
		Early	Late	
2 (n = 85)	3/3.5	4/4.7	2/2.4	9/10.6
4 (n = 58)	1/1.7	1/1.7	–	2/3.4
p (CI 95%)	0.52	0.34	0.24	0.12
Total: 143 OLT	4/2.8	5/3.5	2/1.4	11/7.7

Table 13

Differences in the studied parameters

Parameters	ET medians (mL, all thromboses)	MELD medians (intraoperative thrombosis)
Group 2	1193 [566.5–2202]	15 [11–19]
Group 4	1759 [800–2395]	18.5 [16–22.5]
p (CI 95%)	<0.05	<0.05

Table 14

Correlation between vascular and biliary complications in early and late postoperative period

Perfusion variation	Arterial insufficiency / number of early complications (n (%))	Arterial insufficiency / number of late complications (n (%))	Total
1 (n = 83)	0/2	3/7 (42.8%)	3/7 (42.8%)
2 (n = 85)	13/15 (86.7%)	7/14 (50%)	20/29 (69%)
3 (n = 61)	4/5 (80%)	3/8 (37.5%)	7/13 (53.8%)
4 (n = 58)	6/6 (100%)	1/3 (33.3%)	7/9 (77.8%)
Total (n = 287)/60	23/28 (82.1%)	14/32 (43.8%)	37/60 (61.7%)

obstruction, and blood pressure level was not lower than 100 mmHg.

In order to correct the volumetric velocity of blood flow through the hepatic artery in 8 cases (9.4%) from group 2, we skeletonized the main arteries supplying the liver, including ligation of the gastroduodenal and splenic arteries (in one case, the left gastric artery was ligated). This resulted in a significant increase in arterial contribution to hepatic blood flow. Overall, hepatic artery skeletonization to increase volumetric blood flow velocity was performed in 31 cases. However, in the early and late postoperative periods, these patients developed biliary complications in 3 and 1 cases, respectively.

When analyzing the possible causes of early transplant arterial insufficiency, we found a statistically significant difference in warm ischemia time. In groups 2 and 4, the medians were 45 [40–60] and 55 [45–65] minutes, respectively ($p < 0.05$). There was a difference in exchange transfusion volume – 750 [401–1618] vs 1718 [2398–6497] mL in groups 2 and 4, respectively ($p < 0.05$).

When analyzing the correlation between pre-existing transplant arterial insufficiency and biliary complications, the following data were obtained for different periods (Table 14).

According to Table 14, pre-existing transplant arterial insufficiency was highly likely to be the cause of early biliary complications.

DISCUSSION

It is known that shortening the preservation stage prevents graft dysfunction in OLT and reduces the risk of early and late postoperative complications [19]. The desire to maximize preservation of allograft from expanded criteria donors (and donors after cardiac death) divided the researchers into two camps, explaining the advantages of both hypothermic and normothermic machine perfusion. According to reports, the hypothermic option allows prolonging allograft safety in the process of preservation, while the use of the normothermic method is recommended when using a suboptimal graft [20–23].

The methods of perfusion with hypothermic solutions used suggest a reduction in expenditure of liver energy reserves in the allograft preservation process; nonetheless, considering the other resulting effects, they remain a matter of debate. Summaries from randomized controlled trials in published works are scarce. To lessen the adverse effects of warm ischemia, we prepared the graft using cooled solutions due to our lack of experience with retrograde and machine perfusion. Prevention of acute cardiovascular diseases due to ionized potassium inflow into systemic circulation and one-time blood loss during graft flushing with portal blood was also considered important.

Perfusion with hypothermic solutions against the background of warm ischemia may aggravate endothelial cell damage (most significantly in sinusoidal veins). This could compromise microcirculation within the graft. We did not use retrograde caval reperfusion. The rationale for this technique is provided in published works – when the graft is introduced into systemic circulation, there is no rapid entry of excess ionized potassium or anaerobic metabolic products into the graft. Together with a decrease in the concentration of vasoactive substances, this reduces the severity of reperfusion syndrome manifestations [24]. However, the liver transplant reperfusion experience across various centers prevents us from giving preference to a clear-cut technique for its implementation [25].

As the number of transplantations increased, we gained more experience in vascular and biliary complications in OLT, which became the most frequent and significant causes of graft dysfunction and graft loss in the postoperative period [26]. Analysis of biliary complications seemed to be the easiest and most informative to process. A significant difference was obtained in the development of late (16.5 *vs.* 5.2%) and cumulative (34.1 *vs.* 15.5%) biliary complications in groups 2 and 4 ($p < 0.05$). This necessitated a comparison of preservation parameters, intraoperative data and severity of condition (MELD) in the studied groups.

In recipients of the analyzed groups with complications, there was no statistically significant difference in the analyzed characteristics. In cases without biliary complications, there was a significant excess in warm ischemia time, anhepatic phase, arterial reconstruction and exchange transfusion volume in group 4 ($p < 0.05$).

In the groups (2 and 4), there were significant differences ($p < 0.05$) in warm ischemia time, anhepatic phase, and exchange transfusion volume. Moreover, despite

the unfavorable background in group 4, complications developed less frequently.

The analysis established the comparability of groups with different perfusion variations in terms of severity of steatosis. A possible drawback in information processing is the small sample size for steatosis of grade 2 or more. But this is retrospective.

Fisher's exact test was used to determine the possible correlation between biliary complications and perfusion variations (2 and 4); the result was $p = 0.02$. It cannot always be calculated, but if it exists, then you need to focus on it. Thus, there is a relationship between complications and perfusion type. In our study, perfusion with hypothermic solutions against the background of warm ischemia could aggravate endothelial cell injury (most significantly in the sinusoidal veins), and as a result, lead to impaired microcirculation in the graft.

When calculating the odds ratio and relative risk, complications with variation 2 perfusion are 2.819 times higher than with variation 4; variation 2 is 2.819 times higher than variation 4. There is also a confidence interval to this odds ratio. For the cohort of patients with biliary complications, the odds of belonging to perfusion 2 are 2.199 times higher than perfusion 4. Stated differently, perfusion 2 has a 2.199-fold higher risk of getting complications than perfusion 4 ($p < 0.05$). With the regression analysis models used, we were unable to determine how the examined parameters affected the frequency of biliary complications. Similarity between groups 2 and 4 in terms of preservation and steatosis severity, as well as abnormal distribution in the samples, could be one reason for this.

Considering the results obtained in recipients with transplant arterial insufficiency, intraoperative and late disorders were predominant in group 2 ($p < 0.05$), while early disorders predominated in group 4 ($p < 0.05$).

There was a significant predominance of medians in group 4 with regard to exchange transfusion volume for all thromboses, and severity (MELD) of intraoperative thrombosis, although no difference in the incidence of thrombosis was found among the studied groups.

In the early postoperative period, after routine doppler ultrasound of the graft, splenic artery steal syndrome was ruled out in cases of suspected hepatic ischemia (without signs of impaired mechanical patency), low peak systolic velocity and diastolic component, high resistance (RI >0.80), abnormal dynamics of blood biochemical parameters (bilirubin, transaminases, INR). The diameter of the splenic artery exceeded the hepatic artery 1.5 times or more; there was severe splenomegaly and portal hyperperfusion (Fig. 1–3). This was considered an indication for direct angiography, which confirmed low volumetric blood flow. In our observations, the median resistive index in these patients with variation 4 perfusion was 0.86 [0.835–0.955].

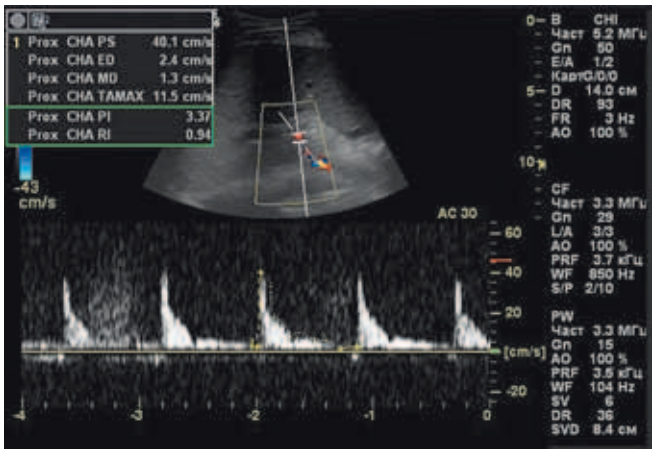

Fig. 1. Low-velocity blood flow in hepatic artery with high intravascular resistance (RI = 0.94)

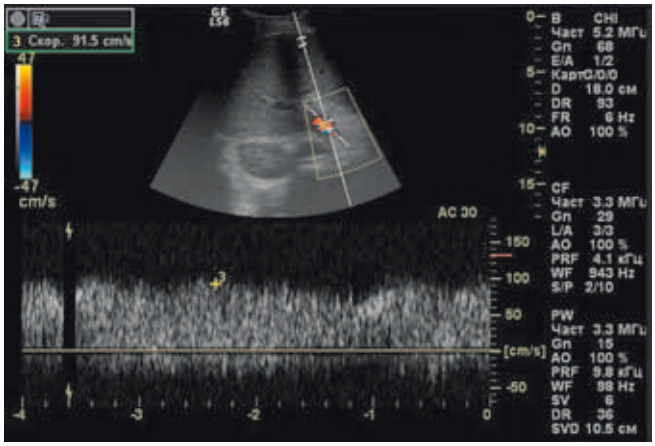

Fig. 2. Accelerated blood flow in the portal vein and hyperperfusion

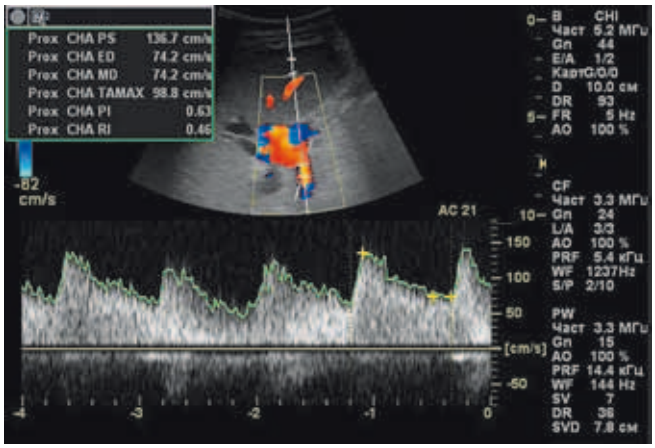

Fig. 3. Hyperdynamic blood flow in splenic artery

The syndrome of splenic artery stealing was confirmed by angiography. Blood supply of the graft was improved by splenic artery embolization (Fig. 4, 5).

In this regard, active management tactics for recipients with suspected transplant arterial insufficiency in

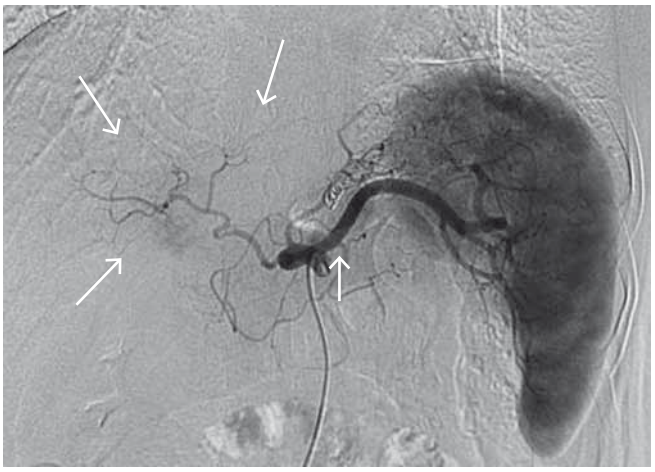

Fig. 4. Celiacography. Diameter of the splenic artery is 11 mm and hepatic artery is 4 mm. Impoverishment of hepatic arterial architectonics at the segmental level (arrows)

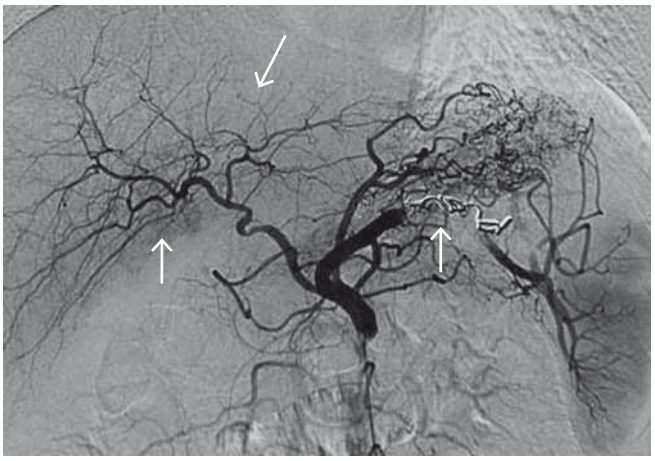

Fig. 5. Redistribution embolization of the splenic artery trunk. Restoration of hepatic arterial architectonics at the segmental level (arrows)

group 4 in the early postoperative period can explain the high rates presented in Table 11. It is possible that this subsequently resulted in reduced incidence of biliary complications after OLT.

Assessing the relationship between the incidence of early biliary complications and pre-existing transplant arterial insufficiency in the graft, in most cases there was a correlation with arterial insufficiency.

CONCLUSION

Group 4 exhibited a significantly longer warm ischemia and anhepatic phase, as well as a higher exchange transfusion volume. However, this unfavorable background did not lead to increased number of biliary complications in comparison with the group where hypothermic graft perfusion was performed. In terms of severity of graft steatosis, perfusion regimens 2 and 4, which subsequently had biliary complications, were comparable. Statistical analysis revealed a correlation between incidence of biliary complications and specific perfusion type. These findings suggest that it is inappropriate to use hypothermic solutions in perfusion preparation of a liver transplant before introducing it into systemic circulation.

The authors declare no conflict of interest.

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